ORIGINAL RESEARCH PAPER

Paediatrics

COMPARISON OF CORD LIPID PROFILE BETWEEN TERM AND PRETERM NEONATES IN INDIAN POPULATION.

KEY WORDS: Lipid profile, Hypercholesterolemia, Term, Preterm,Neonate, CVD

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ABSTRACT

Cardiovascular diseases are known to cause mortality and morbidity in large number worldwide. Modern serenditary lifestyle, eating habits, smoking ,alcohol, obesity are all modifiable well known factors to cause CVD. Relationship between genetics and maternal factors like nutrition, hypercholesterolemia, mode of delivery, preeclampsia with cord blood lipids and lipoprotiens can not be ignored. Studies are now emerging showing prematurity as a risk factor causing altered lipid profile and predesposition to CVDs earlier in life. We are further adding up the results via this study. Also we have compared the lipid profile between AGA's and SGA's from both preterm and term neonates.

INTRODUCTION

Worldwide CVD's are the largest contributor to the mortality. Atherosclerosis has the most serious consequences.[1] Atherosclerosis results in cardiac ischemia, cardiac infarction and stroke which is a big health nuisance for people all over the world.[2] As per the Global Burden of Disease Study age-standardized estimates (2010) around 25% of all deaths in India are attributable to CVD.[3]

Modern serenditary lifestyle, feeding habits, smoking, use of alcohol, obesity, diabetes, HTN are all well known factors causing CVD.[4] There is rise in trend of early presentation of CVD's, patients diagnosed CVD in thier 30s are commonly seen. Many of these illnesses may have originated in early childhood and in fetal environment. Maternal smoking, use of alcohol, poor nutrition and placental insufficiency may incite the injury in early antenatal period resulting in CVD's later in life. Low birth weight and small for gestation indicates poor fetal nutrition and/or antenatal fetal injury.

Atherosclerosis is a process that begins early in life progresses silently over decades. Lipid metabolism disorder specially increased serum cholesterol, favours atherosclerotic changes. There are evidences available supporting relationship between both genetic and maternal factors like nutrition, hypercholesterolemia, mode of delivery, gestation & preeclampsia with the cord blood lipids & lipoprotein profiles. [5]

Fetal origin hypothesis states that fetus adapts to malnutrition by altering cell programming eventually causing systemic organ dysfunction. There is vascular endothelial dysfunction, activation of fetal remin-angiotensin system among IUGRs; ed renal function, Insulin resistance, deficiency at ILGF, all causes rise in systolic blood pressure, abnormal glucose metabolism & elevated lipid profile.[6]

At birth, cord sera contain low levels of VLDL & LDL cholesterol which with age continues to achieve adult pattern of relatively high LDL cholesterol.[7] Cord sera contain all characterized adult lipoprotein & apolipoproteins. Fetal growth restriction is associated with atherogenic lipoprotein metabolism.[8] Apolipo AI, apolip-B & their ratio are considered as markers for development of CVDs. Detection of these markers in umbilical cord blood of newborns could identity neonates at higher risk for CVD's.[9,10]

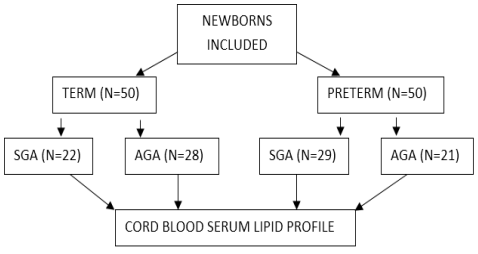
Earliest possible intervention like lifestyle modification including diet & exercise, avoidance of tobacco, alcohol, improvement of lipid profile using drugs eg. statins may result in healthy outcome and can help in lowering the disease burden.

METHODS:

From 100 neonates delivered at our institute in over 12 months period, we collected umbilical cord blood of newborns immediately and analyzed it for lipid profile. This study was approved by local ethical committee.

Neonates meeting the following criteria were included- term gestation (37 – 41 weeks), preterm (32- 36 weeks), one minute Apgar score > 7, absence of congenital heart disease in newborn, absence of diabetes, hypertension, CVD, thyroid and obesity in mother, absence of hypoxia, RDS, sepsis, MAS, PPH in newborn. Mothers on any medication except for iron, vitamins were excluded. Information of antenatal events, drugs & complications were obtained from mother on pre designed performa. Informed consent was taken from the parents of newborns included in the study.

Following delivery either vaginally or through CS, 5ml of blood was collected from the placental end of umbilical cord immediately under full aseptic precaution. Collected blood was immediately sent to laboratory where it was centrifuged, serum obtained was stored at – 20°C until analysed. Estimation of total cholesterol, LDL, HDC, VLDL, TG's was done by photometry on the unicel DxC 800 analyzer of Beckman carter. Serum cholesterol & triglyceride was measured using enzymatic method, HDL using timed end point homogenous detergent assay and Apolipoproteins by nephelometry. Data was collected using SPSS version 20 (SPSS, Inc, USA). T test was used for quantitative data. Qualitative data was expressed in terms of frequency & percentage. Corelation of co-efficient was used to check the statistical significance of data at 0.05 level significance.



RESULTS

The present study includes 100 newborns. Comprising of 50 term (50%) and 50 preterm (50%) neonates. Umbilical cord blood lipid profile was studied and compare in these two groups. Out of the 100 neonates, 43 (43%) neonates were males and 53 (57%) were females. Male:female ratio was 3:4. There were a total of 100 neonates in the study, 50 (50%) were term and the rest 50 (50%) were preterm. Of the 100 neonates including in the study 62

(62%) were normal vaginal delivered, while the rest 38 (38%) through caesarian section. Among the 50 term neonates, 28 (28%) were term AGA and 22 neonates (22%) were term SGA. Among the 50 preterm neonates, 21 (21%) were preterm AGA and 29 (29%) neonates were preterm SGA.

Table 1: Distribution of neonates (n=100)

Characteristics	No. of cases	Percentage
Male	43	43%
Female	57	57%
LSCS	38	38%
NVD	62	62%
Term	50	50%
Preterm	50	50%
Term AGA	28	28%
Pre term AGA	21	21%
Term SGA	22	22%
Pre term SGA	29	29%

Table 2 shows lipid and lipoprotein levels in term and preterm neonates. TC, TG, LDL, VLDL, APO B and APO B/ APO A-I were higher in preterm neonates compared to term neonates and they were statistically significant (p<0.05).

Table 2: Lipid and lipoprotein levels (mg/dl) in term and preterm neonates (n=100)

	Term (n=50)	Preterm (n=50)	P value
TC	72.6±22.20	96.22±27.00	0.001
TG	51.10±6.95	79.66±7.01	0.001
HDL	29.90±12.06	31.02±6.70	0.568
LDL	32.48±15.35	49.26±23.59	0.001
VLDL	10.22±1.39	15.93±1.40	0.001
LDL/HDL	1.23±0.87	1.58±0.74	0.999
TC/HDL	2.63±0.98	3.13±0.75	0.005
Apo A-I	87.86±7.87	86±16.48	0.473
Apo B	54.06±12.85	64.12±16.12	0.001
APO B/APO A-I	0.62±0.16	0.78±0.26	0.001

Table 3 shows lipid and lipoprotein levels in term and preterm AGA neonates. TC, TG, LDL, VLDL, TC/HDL and APO B and APO B/ APO A-I were higher in preterm AGA neonates compared to term AGA neonates and they were statistically significant (p<0.05**)**.

Table 3: Lipid and lipoprotein levels (mg/dl) in term and preterm AGA neonates (n=100)

	Term AGA (n=28)	Preterm AGA (n=21)	P value
TC	76.42±25.40	100.76±26.70	0.001
TG	50.82±7.90	81.28±5.45	0.001
HDL	30.89±13.84	34.19±6.53	0.318
LDL	35.37±15.80	56.31±24.67	0.001
VLDL	10.16±1.58	16.25±1.09	0.001
LDL/HDL	1.26±0.64	1.67±0.72	0.373
TC/HDL	2.64±0.71	3.16±0.75	0.018
Apo A-I	85.39±6.47	90.19±13.05	0.097
Apo B	63.35±8.08	53±14.93	0.003
APO B/APO A-I	0.74±0.09	0.60±0.21	0.005

Table 4 shows lipid and lipoprotein levels in term and preterm SGA neonates. TC, TG, LDL, VLDL, TC/HDL and APO B and APO B/ APO A-I were higher in SGA neonates compared to term SGA neonates and they were statistically significant (p<0.05) .

Table 4: Lipid and lipoprotein levels (mg/dl) in term and preterm SGA neonates (n=100)

	Term SGA (n=22)	Preterm SG (n=29)	P value
TC	67.72±16.62	88.58±24.96	0.001
TG	51.45±5.69	78.48±7.84	0.001
HDL	28.63±9.49	28.72±5.93	0.968
LDL	28.8±14.27	44.16±21.80	0.035
VLDL	10.29±1.13	15.69±1.56	0.001
LDL/HDL	1.20±1.11	1.52±0.76	0.507
TC/HDL	2.61±1.26	3.10±0.76	0.088
Apo A-I	91±8.51	82.96±18.19	0.061
Apo B	42.22±6.31	72.17±11.64	0.001
APO B/APO A-I	0.46±0.08	0.90±0.21	0.001

Table 5 shows lipid and lipoprotein levels in term AGA and SGA neonates. ApoA-1 levels were high in SGA neonates compared to those of AGA and that was statistically significant. Apo B and Apo B/Apo A-1 were more in AGA neonates and the values were statistically significant(p<0.01).

Table 5: Lipid and lipoprotein levels (mg/dl) in term AGA and term SGA neonates (n=100)

	Term AGA (n=28)	Term SGA (n=22)	P value
TC	76.42±25.40	67.72±16.62	0.171
TG	50.82±7.90	51.45±5.69	0.753
HDL	30.89±13.84	28.63±9.49	0.517
LDL	35.37±15.80	28.8±14.27	0.357
VLDL	10.16±1.58	10.29±1.13	0.753
LDL/HDL	1.26±0.64	1.20±1.11	0.256
TC/HDL	2.64±0.71	2.61±1.26	0.892
Apo A-I	85.39±6.47	91±8.51	0.011
Apo B	63.35±8.08	42.22±6.31	0.001
APO B/APO A-I	0.74±0.09	0.46±0.08	0.001

Table 6 shows lipid and lipoprotein levels in preterm AGA and preterm SGA neonates. TC levels were higher in preterm AGA and was statistically significant (p<0.05). Apo B and Apo B/Apo A-I were more in preterm SGA neonates and were statistically significant (p<0.01).

Table 6: Lipid and lipoprotein levels (mg/dl) in preterm AGA and preterm SGA neonates

	Preterm AGA (n=21)	Preterm SGA (n=29)	P value
TC	100.76±26.70	88.58±24.96	0.017
TG	81.28±5.45	78.48±7.84	0.165
HDL	34.19±6.53	28.72±5.93	0.003
LDL	56.31±24.67	44.16±21.80	0.141
VLDL	16.25±1.09	15.69±1.56	0.165
LDL/HDL	1.67±0.72	1.52±0.76	0.884
TC/HDL	3.16±0.75	3.10±0.76	0.785
Apo A-I	90.19±13.05	82.96±18.19	0.127
Apo B	53±14.93	72.17±11.64	0.001
APO B/APO A-I	0.60±0.21	0.90±0.21	0.001

Table 7 represents relationship of cord blood lipid profile with birth weight. TG, VLDL and TC/HDL and APO B/APO A-I had significant inverse correlation with birth weight (p<0.05).

Table 7: Correlation coefficient between lipid profile and Birth weight

	Correlation coefficient	P value
Birth weight vs TC	-0.187	0.063
Birth weight vs TG	-0.625	0.001
Birth weight vs HDL	0.062	0.539
Birth weight vs LDL	-0.176	0.080
Birth weight vs VLDL	-0.625	0.001
Birth weight vs LDL/HDL	-0.137	0.174
Birth weight vs TC/HDL	-0.212	0.034
Birth weight vs Apo A-I	0.023	0.817
Birth weight vs Apo B	-0.183	0.069
Birth weight vs APO B/APO A-I	-0.208	0.038

Table 8. represents relationship of cord blood lipid profile with gestational age. TC, TG, LDL, VLDL, TC/HDL and LDL/HDL, Apo B

and APO B/APO A-I had significant inverse correlation with gestational age ($p<0.05$).

Table 8: Correlation coefficient between lipid profile and Gestational age

	Correlation coefficient	P value
Gestational Age vs TC	-0.377	0.001
Gestational Age vs TG	-0.801	0.001
Gestational Age vs HDL	-0.076	0.451
Gestational Age vs LDL	-0.311	0.002
Gestational Age vs VLDL	-0.801	0.001
Gestational Age vs LDL/HDL	-0.218	0.029
Gestational Age vs TC/HDL	-0.200	0.046
Gestational Age vs Apo A-I	0.057	0.571
Gestational Age vs Apo B	-0.302	0.002
Gestational Age vs APO B/APO A-I	-0.315	0.001

Discussion

In this study we have compared the umbilical cord lipid profile in preterm & term neonates of AGA & SGA group. Since total cholesterol increases after birth, it might be presumed that the total cholesterol levels in preterm are lower than or similar to the term neonates. However our results has shown that cholesterol levels of premature neonates are significantly higher than the term counterpart, various studies done previously had shown similar results.

We found that total cholesterol levels were higher in preterm AGA compared to preterm SGA and to term neonates both AGA and SGA. This was similar to the result observed by Prado, Jain R & Diaz.[11,12,13] Cholesterol is synthesized either de novo or obtained from maternal source. It is required in large amount for growth and development of fetus as a component in each & every cellular structure, especially nervous system. Key regulator of cholesterol bio-synth is SPEBP-2 protein.[14] In adults activation of this protein is regulated by cholesterol content inside a cell. In fetus there is lack of regulation of SREBP – 2 protein and there is continuous cholesterol synthesis which is required for the rapidly developing fetus.[15] When the gestation reaches near term, neonate starts developing SREBP-2 mediated cholesterol feedback regulation & cholesterol synthesis gets regulated resulting in low cholesterol level. Fetal liver & biliary system is immature in early & mid gestation, excretion of cholesterol via biliary system is not well developed in preterm in response, the level of cholesterol are found higher in preterms.[16]

Cholesterol transports in form of lipoproteins majority being LDL & VLDL and to small extent via HDL. LDL-C is a circulatory form of cholesterol excreted from liver. Cholesterol decreases with increase in gestation due to maturation of LDL receptors activity in growing fetus.[17] In our study VLDL & LDL both were found higher in preterm AGA & SGA in comparison to term AGA & SGA. HDL cholesterol level were found same in both groups. Since HDL is produced in circulation & not synthesised from liver it could be the possible reason that HDL level was found same. Out of the apoproteins, type B (Apo B) is most strongly associated with CVD.[18] In our study we found the Apo B level higher in preterm neonates compared to the term neonates. Although the concentrations of Apolip-A-I were not different in both group.

Preterm birth & low birth weight has been described as risk factors in various studies for CVD in later life. Our findings demonstrate that total cholesterol, LDL, VLDL & apolip B are significantly higher in preterm neonates compared with term. There are few studies (ref 7, 19) showing no relationship between serum cholesterol level & gestation.[18,19]

We further augment the available data with our results, however more studies are required with large sample sizes to establish the relationship. Considering the results of this study and previous available data, we should focus primarily on strategies promoting fetal growth to prevent the consequenses. In cases of premature births early diagnosis, dietary intervention and drug therapy can be started initially to prevent CVD in later life.

CONCLUSION.

This study again potentiate the link between cord blood lipid profile and prenatal factors. In this study we found significantly unhealthy lipid profile among preterms, with the values observed we can say that preterms are exposed to more atherogenic enviornment. This opens up scope for further research to see natural trend of lipid values as neonate grows and to see cardiovascular complications later in life.

REFERENCES

1. World Health Organization. World health statistics 2009. WHO; 2009.
2. Pac-Kozuchowska E. Evaluation of lipids, lipoproteins and apolipoproteins concentrations in cord blood serum of newborns from rural and urban environments. Ann Agric Environ Med. 2007; 14: 25-9.
3. Dorairaj Prabhakaran, Panniyammakal Jeemon and Ambuj Roy Cardiovascular Diseases in India Current Epidemiology and Future Directions. Circulation. 2016;133:1605-1620.
4. Rifai N, Bachorik PS, Albers JJ. Lipids, lipoproteins and apolipoproteins. In: Carl AB, Edward RA, editors. Teitz Textbook of Clinical Chemistry. 3rd ed. USA: WB Saunders; 1999. p. 826-30.
5. Cohen MS. Fetal and childhood onset of adult cardiovascular diseases. Ped Clin North Am. 2004; 51(6):1697-719.
6. Fřnnebř V, Dahl L, Moe P, Ingebretsen O. Does VLDL-LDL-Cholesterol in Cord Serum Predict Future Level of Lipoproteins?. Acta Paediatrica. 1991; 80(8-9):780-85.
7. Barker D. Fetal and infant origins of adult disease. Monatsschrift Kinderheilkunde. 2001; 149(0):S2-S6.
8. Barker D. The intrauterine origins of cardiovascular disease. Acta Paediatrica. 1993; 82(s392):93-99.
9. MC Conathy WJ, Lane DM. Studies on the apolipoproteins and lipoproteins of cord serum. Pediatr Res 1980; 14: 757-61.
10. Casanueva V, Cid X, Chiang MT, Molina M, Ferrada MC, Perez R & Casanueva P. Serum lipids, lipoprotein and apolipoprotein levels in normal Chilean newborns. Revista Medica de Chile. 1998; 126: 1073.
11. Jain R, Tripathi VN, Singh RD, Pandey K. Lipid Profile & Apolipoproteins in Neonates in relation to Birth Weight and Gestational Maturity. Journal of Pediatric Sciences. 2011; 3 (2):2-7.
12. Pardo IM, Geloneze B, Tambascia MA, Barros-Filho AA. Atherogenic lipid profile of Brazilian near-term newborns. Braz J Med Biol Res. 2005; 38(5):755-60.
13. Diaz M, Leal C, Ramon Y, Cajal J, Jiminez MD, Martinez H, Pocovi M, Grande F. Cord blood lipoprotein-cholesterol relationship with birth weight and gestational age of newborns. Metabolism. 1989; 38: 435 –8.
14. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J. Clin. Invest. 2002;109:1125-1131.
15. Carr BR, Simpson ER. Cholesterol synthesis by human fetal hepatocytes: Effect of lipoproteins. Am J. Obstet. Gynecol. 1984;150:551-557.
16. Cai HJ, Xie CL, Chen Q, Chen XY, Chen YH. The relationship between hepatic low-density lipoprotein receptor activity and serum cholesterol level in the human fetus. Hepatology 1991;13:852-857.
17. Nagano N, Okada T, Yonezawa R, Yoshikawa K, Fujita H, Usukura Y, et al. Early postnatal changes of lipoprotein subclass profile in later preterm infants. Clin. Chim. Acta 2011;413:109-112.
18. Wang XL, Wilcken DEL and Dudman NPB. Apolipoproteins A-1 and B and the B/A-1 ratio in the first year of life. Pediatric Research. 1991; 30: 544-9.
19. Kelishadi R, Badiee Z, Adeli K. Cord blood lipid profile and associated factors baseline data of a birth cohort study. Ped. Peri. Epidem. 2007;21:513-526.
20. Ahn E-M, Cho S-C, Lee MG, Cha Y-S. Serum carnitine, triglyceride and cholesterol profiles in Korean neonates. Br. J. Nutr. 2007;98:373-379.