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Study of Umbilical Cord Blood Lipid Profile in Relation to Gestational Age and Neonatal Birth Weight

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ABSTRACT

BACKGROUND-*Atherosclerotic cardiovascular disease is the major cause of death in adulthood and has become a significant problem in our society. Increasing awareness about the origin of the atherosclerosis in early life has renewed interest in determination of various lipid fractions in paediatric age group and it is well documented that atherosclerosis may originate during fetal period.*

This study was undertaken with the aim to find out the correlation of gestational age and birth weight with cord blood lipid profile in neoantes.

OBJECTIVE- *To estimate and compare the cord blood lipid profile in term and preterm neonates, small for gestational age(SGA) and appropriate for gestational age (AGA)neonates.*

METHOD-It was a hospital based cross sectional observational study. Cord blood lipid profile of 150 neonates were studied at a tertiary care centre. After written and informed consent of parents cord blood was collected at birth and sent for lipid profile analysis. Lipid profile was compared between preterm and term neonates, SGA and AGA neonates. statistical analysis was done using unpaired t-test. $p<0.05$ was considered significant

RESULTS- *A total of 150 neonates were studied of which 80 were term neonates and 70 were preterm. Among them 88 were AGA and 62 were SGA. Preterm neonates had higher values of TC (96.6±18.6), TG (80.03±16.36), LDL (53.66±1.04), compared to Term neonates and values were statistically significant ($p<0.05$). Cord blood Lipid profile values for TG (85.41±16.86) was significantly higher ($P<0.05$) and HDL (22.24±7.87) level was significantly lower ($p<0.05$) in the SGA neonates compared to AGA neonates*

CONCLUSION-*Preterm neonates had significantly higher cord lipid profile compared to term neonates.SGA neonates had significantly higher values of TGL and significantly lower values of HDL compared to AGA neonates. Cord lipid profile value does not have significant correlation with gender. Key words-lipid profile, small for gestational age, preterm.*

INTRODUCTION

Cardiovascular disease is the primary cause of morbidity and mortality in developed and developing countries. The incidence of coronary artery disease depends on the prevalence of genetic and environmental risk factors[1]. Recent animal experiments and human studies have shown the influence of the intrauterine environment on the development of risk factors for cardiovascular disease.[1]Unhealthy lifestyle practices and behaviours are well accepted as contributing factors, but the true origins of these diseases may actually be found in utero.[2]

These findings have led to the " fetal origin of cardiovascular disease hypothesis "which suggests that an adverse intrauterine environment during a critical period of development could program or imprint the development of fetal tissues and organs, and permanently determine responses that produce later dysfunction and disease.[2] It is known that premature and growth restricted newborns have lost the chance to complete their energy deposits in later part of pregnancy. Thus, many times these growth restricted neonate needs to use these endogenous reserves, there by activating lipid metabolism that generates energy and promotes gluconeogenesis, and also due to the limited supply of the nutrients, the development of essential organs is favoured when compared to non essential organs, such as kidney (nephron mass) and pancreas (beta cell mass). The long-term consequences of these metabolic adaptations will lead on to an increased prevalence of cardiovascular diseases, hypertension and type 2 diabetes mellitus in this group of babies.[3,4] Lipid profile is a marker of an underlying cardiovascular status. Lipid profile includes measurement of cholesterol and its derivatives and various atherogenic indices. Studies have shown that SGA babies had abnormal lipid profile compared to AGA babies. [5-8]

There are many studies showing the direct relationship between the abnormalities in lipid profile among the SGA babies and occurrence of cardiovascular diseases. The present study was undertaken for early detection of abnormalities in the lipid profile at the earliest (at birth), especially in the SGA babies, so that these high risk babies can be under vigilant monitoring in future.[9-11] Early diagnosis followed by prudent dietary supplementation and drug therapy in these high risk neonates may provide an opportunity for long range primary amelioration of risk factors that contribute to development of cardiovascular diseases in adult life.

The Barker Hypothesis

David Barker (M.D. Ph.D. FRS)a Physician and Professor in the Department of Cardiovascular Medicine at the Oregon Health and Science University, US , Twenty years ago showed for the first time that people who had low birth weight are at greater risk of developing coronary heart disease. In 1995, the British Medical Journal named this the "Barker Hypothesis." and is now widely accepted.

Barker proposed the concept of a 'fetal origin of coronary heart disease'. In essence this model proposes that in response to malnutrition during gestation that includes macronutrients and micronutrients causes intrauterine adaptation of the fetus for survival despite adversity by conserving energy supply at the expense of growth, ensuring a reduced fetal demand, resulting in a small baby. These adaptations generate a *thrifty phenotype* which persists after birth. With the availability of nutrients after birth, catch up growth occurs which tends to increase deposition of white adipose tissue resulting in adiposity;a rearrangement of skeletal muscle mitochondria; and increased oxidative injury . These changes set the stage for metabolic syndrome, diabetes mellits, and coronary artery disease in adulthood.

MATERIALS AND METHODS

This hospital based cross sectional observational study was conducted from November 2014 to October 2016 on 150 neonates in an educational hospital in western Maharashtra, India. Ethics Committee approval was taken before the start of the study. After taking written informed consent from the parents, cord blood was collected immediately after delivery and sent for lipid profile analysis by auto analyser.

Inclusion criteria was all neonates who are born at KIMS hospital via normal vaginal delivery.

Exclusion criteria: Neonates with any congenital malformation, born to mother with any maternal illness like gestational diabetes mellitus, tuberculosis, asthma, pregnancy induced hypertension and thyroid disease, family history of coronary heart disease, any maternal medication, except vitamins and iron supplements, instrumental delivery including extraction, neonates born by LSCS ,5 minute Apgar score <7.

Neonates were examined and relevant anthropo-metric variables recorded. They were classified into preterm (<37 weeks) and term (>37 weeks) based on new Ballard scoring and as AGA and SGA neonates based on AIIMS intrauterine growth charts and ponderal index. *Ponderal Index (PI) = Weight (GM)/Length (CM)^3 x 100.*

Ponderal index values of < 2.0 between 29 and 37 weeks and <2.25 beyond 37 weeks are indicative of intrauterine fetal malnutrition. SGA is defined as having birth weight that is more than two standard deviations below the mean or less than 10th percentile of a population specific birth weight vs. gestational age plot or having Ponderal index less than 50th percentile for the respective gestational age. Lipid profile was compared between the above groups.

Data was entered in Microsoft Excel 2016 & analysed using Graph Pad Instat 4.0.Qualitative data was expressed as percentage, frequencies & ratios and expressed using graphs. Quantitative data was expressed as Mean±SD. Non-parametric test was applied using Unpaired t-test. P<0.05 was significant.

RESULT

Sex-wise Distribution of Term & Pre-Term Neonates-

Gender of Babies:	Term Babies:	Pre-term Babies:
Male	44	37
Female	36	33
Total (n=150)	80 (53.3%)	70 (46.67%)

In the present study males were 82 and females were 68.

Demographic Characteristics of Term & Pre-Term Neonates:

Neonatal parameter	Pre-Term	Term	p value
Weight (kg)	2.23±0.38	2.52±0.51	<0.01
Length (cms)	46.02±1.56	47.42±1.22	<0.02
Head circumference (cms)	32.42±1.15	33.56±1.14	<0.0001
PI (gm/cm3)	1.87±0.34	2.35±0.37	<0.0001
GA(weeks)	35.78±2.15	37.2±2.34	<0.0001

The demographic characteristics like weight, length, head circumference, ponderal index & gestational age of term neonates is significantly higher compared to pre-term neonates (Since p<0.05).

Distribution of Neonates as per Ponderal Index:

Ponderal Index (PI):	SGA	Percentage (%)
≤2	45	72.58%
>2	17	27.42%
Total	62	100%

Total number of small for gestational age neonates were 62, out of which 45 had ponderal index < 2 ,hence were asymmetric IUGR neonates and 17 had ponderal index > 2 which signifies they were symmetric IUGR.

Demographic Characteristics of SGA & AGA Neonates:

Neonatal parameter	SGA	AGA	p value
Weight (kg)	1.76±0.35	2.52±0.51	<0.0001
Length (cms)	45.88±1.86	47.03±1.36	<0.0001
Head circumference (cms)	32.32±1.37	33.66±1.04	<0.0001
PI (gm/cm3)	1.83±0.23	2.4±0.39	<0.0001
GA(weeks)	36.78±2.09	36.55±2.79	**0.6381**

The demographic characteristics like weight, length, head circumference & ponderal index of term neonates is significantly higher compared to preterm neonates. The only exception is Gestational Age as it is expected to be in the same range (p>0.05).

Lipid Profile Comparisons of Term & Pre-Term Neonates:

Neonatal parameter	Term	Pre-Term	p value
	Mean +/- SD	Mean +/- SD	
Total Cholesterol	82.94±20.2	96.6±18.6	**<0.001**
Triglycerides	70.88±1.86	80.03±16.36	**<0.01**
HDL	27.26±8.51	25.46±6.75	0.43
LDL	42.32±1.37	53.66±1.04	**<0.0001**
VLDL	9.78±3.32	9.21±4.8	0.72

Total Cholesterol, Triglyceride & LDL Cholesterol levels are significantly higher in Pre-Term Neonates compared to Term Neonates in our population ($p<0.05$).

Lipid Profile Comparisons of SGA & AGA Neonates:

Neonatal parameter	SGA	AGA	p value
	Mean +/- SD	Mean +/- SD	
Total Cholesterol	88.44±18.2	83.6±16.6	0.085
Triglycerides	85.41±16.86	71.63±18.36	**<0.001**
HDL	22.24±7.87	29.96±4.77	**<0.001**
LDL	38.11±9.08	34.24±14.10	0.078
VLDL	8.88±2.36	9.84±6.8	0.10

Triglyceride level is significantly higher in SGA Neonates compared to AGA Neonates in our population ($p<0.05$) while reverse is true in the case of HDL Cholesterol.

Lipid Profile Comparisons of Term SGA & Pre-Term SGA Neonate

Neonatal parameter	Term SGA	Pre-Term SGA	p value
	Mean +/- SD	Mean +/- SD	
Total Cholesterol	71.70±21.25	105.82±27.21	**0.001**
Triglycerides	66.28±19.95	77.50±24.69	**<0.05**
HDL	41.32±9.49	27.95±5.34	**<0.001**
LDL	34.26±16.05	60.10±24.01	**0.001**
VLDL	13.24±03.98	15.50±04.53	**0.01**

Total Cholesterol level, Triglyceride level, LDL & VLDL is significantly higher in Pre-term AGA Neonates compared to Term AGA Neonates in our population ($p<0.05$) while reverse is true in the case of HDL Cholesterol level. This supports the fact that small for gestational age babies are predisposed to dyslipidemia even if they are term deliveries.

DISCUSSION

Recently interest in cord lipids has increased because serum lipid disorders have their roots in childhood and atherogenic changes are postulated to originate early in life.

Levels of Lipids and Lipoproteins in the cord sera should be a reflection of the status of plasma lipid metabolism in the infant at birth because most fetal Lipids are synthesized de novo through the conversion of glucose to various fatty acid containing compounds. Only part of it is derived from placental circulation, so measurement of cord blood Lipid profile will be like measuring Lipid metabolism during fetal life and at birth.[1-4]

Among various factors theorised in the development of atherosclerosis, increased plasma levels of cholesterol and/or triglycerides are considered to be most important. Furthermore a number of investigators now consider only LDL and HDL as major risk factors on the development and progression of atherosclerotic vascular diseases. Hence determinations of cord lipid profile becomes a useful tool in the earlier detection of babies at a higher risk, since several investigators believe that the atherosclerotic lesions may have its genesis in childhood.[7,8]

Pre-Term v/s Term Neonates

N.Haridas and P.T. Acharya et al. in their study concluded that Preterm neonates have higher TG and TC levels but statistically significant difference was found only in TC ($p<0.001$) levels.[13]

Mathur et al. in their study concluded that in preterms TC value was significantly high ($p<0.001$).[14]

Jane Oba et al. in their study concluded that TC, LDL, HDL values were significantly higher in Preterm neonates ($p<0.0001$), TG value was significantly lower in preterm neonates ($p<0.01$).[15]

Pardo et al. in their study concluded that TC, LDL, HDL were higher in Preterm neonates compared to term neonates with statistically significant difference in TC and LDL ($p<0.001$) levels, but HDL had no statistically significant difference.[16]

A K Kalra et al. in their study concluded that all Cord lipid profile values were lower in Preterm neonates compared to term neonates but statistically significant difference was found with TC levels ($p <0.001$) and no statistically significant difference was found with HDL and LDL levels.[17]

Jagadish Singh et al. in their study concluded that Term neonates had higher TC compared to Preterm neonates with statistically significant difference ($p<0.05$).[6]

P.K Mishra et al. in their study concluded that TG levels were more in term compared to term with no statistically significant difference.[18]

In our study higher cord lipid levels in preterm babies could be explained by the fact that preterm babies lack both hepatic carbohydrate and subcutaneous adipose stores, with a result that circulating fuel are low and may run out. Rise in cord blood cholesterol levels may reflect the metabolic adaptation to provide adequate energy, especially to organs like brain.

SGA v/s AGA Neonates

In present study cord blood Triglycerides level was significantly elevated, and HDL-C levels were significantly decreased with p values of $p<0.01$. This can be explained on the fact that Triglyceride is the major constituent of chylomicrons and VLDL (synthesized in liver), its synthesis is increased in SGA babies and also its metabolism is decreased due to decreased activity of lipoprotein lipase. Similarly all other studies showed significant elevation in the Triglyceride levels compared to present study, and Daniel et al. study[19] had the closest similarity with the present study for elevation of triglyceride level with value of 85.6 mg/dl.

In the present study cord blood lipid profile values in Pre-Term SGA neonates compared to were elevated when compared to Term SGA neonates, except for HDL-C, the reason is that, there is lack of glucose as fuel in SGA babies, so these babies use alternative source as a fuel (amino acid and lipids) and generate glucose (gluconeogenesis), where by activating lipid and other metabolism, so there will be increased hepatic generation of lipids (particularly VLDL and chylomicrons) also there is decreased peripheral utilization of lipids because of decreased activity of lipoprotein lipase enzyme in growth restricted babies, these two facts explain higher concentration of plasma lipids in SGA babies.[5-7]

SUMMARY AND CONCLUSION

1. Total Cholesterol, Triglyceride & LDL Cholesterol levels are significantly higher in Pre-Term Neonates compared to Term Neonates in our population ($p<0.05$)
2. Triglyceride level is significantly higher in SGA Neonates compared to Term Neonates in our population ($p<0.05$) while reverse is true in the case of HDL Cholesterol.
3. Total Cholesterol level, Triglyceride level, LDL & VLDL is significantly higher in Pre-term AGA Neonates compared to Term AGA Neonates in our population ($p<0.05$) while reverse is true in the case of HDL Cholesterol level. This supports the fact that small for gestational age babies are predisposed to dyslipidemia even if they are term deliveries.

4. Total Cholesterol level, Triglyceride level, HDL, LDL & VLDL levels are all comparable in both Term AGA Neonates & Pre-Term AGA Neonates in our population ($p>0.05$).
5. In our study higher cord lipid levels in preterm babies could be explained by the fact that preterm babies lack both hepatic carbohydrate and subcutaneous adipose stores, with a result that circulating fuel are low and may run out. Rise in cord blood cholesterol levels may reflect the metabolic adaptation to provide adequate energy, especially to organs like brain.
6. Cord blood Triglycerides level was significantly elevated in SGA neonates, and HDL-C levels were significantly decreased with p values of $p<0.01$. This can be explained on the fact that Triglyceride is the major constituent of chylomicrons and VLDL (synthesized in liver), its synthesis is increased in SGA babies and also its metabolism is decreased due to decreased activity of lipoprotein lipase.
7. Apolipoprotein-A could have given us more insight into this condition, but it wasn't done as part of the routine lipid profile in this study. This is an important limitation of our study as Apolipoprotein-A is used in recent studies as a surrogate endpoint, but the reliability of this test when it is used in neonates is not yet proved adequately.

Implications of this study-Maternal weight gain during pregnancy is a sensitive indicator of fetal growth restriction. Serial weight recording during pregnancy should be given due importance, if found abnormal these pregnancies should be carefully monitored for intra uterine growth restriction.

Maternal anemia and PIH are still the major causes for SGA babies. Early detection and treatment of these complications may reduce the incidence of SGA babies. optimal and good quality antenatal care shall be provided to all pregnant women. Measurement of lipid profile in the cord blood should be done routinely, especially for the babies with birth weight of <3rd percentile for respective gestational age or Ponderal index <10th percentile, so that we can have baseline values for further follow up.Babies with abnormal cord blood lipid profile values require regular monitoring of lipid profile in future along with proper dietary advice and drug therapy.

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