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Original Article

Neonatology Section

Study on Serum Lipoprotein Profile of Exclusive Breast Fed, Mixed Fed and Formula Fed Preterm Infants

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ABSTRACT

Introduction: Breast feeding is protective for atherosclerotic cardiovascular disease, obesity, Diabetes Mellitus (DM) and hypertension. Serum lipoprotein is principal risk factor for atherosclerosis. There is growing evidence that risk of Coronary Heart Disease (CHD) begins to emerge from infancy. Lipoprotein level is affected by different feeding pattern during infancy.

Aim: To compare serum lipoprotein profile of exclusively breast fed, mixed fed and formula fed preterm infant.

Materials and Methods: A total of two fifty preterm newborn were recruited at birth and divided into three groups. Group A were Exclusively Breast Fed (EBF), Group B were Mixed Fed (MF) and Group C were Formula/bovine milk Fed (FF) infants. Preterm newborns with severe sepsis, hypoglycemia, Hypoxic Ischemic Encephalopathy (HIE) stage II and III, meconium stained amniotic fluid, pathological jaundice, Hyaline Membrane Disease (HMD), less than 28 weeks gestation, with major congenital anomaly and infants born to mothers with DM, gestational diabetes, hypertension, pre-eclampsia, eclampsia or on long term medications were excluded from the study. Lipoprotein profile estimation was done at four weeks and again at 16 weeks of age.

Results: At four weeks of age, Total Cholesterol (TC), Triglyceride (TG), Low Density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL) were higher in EBF infants as compared to MF and FF infants. For TC, difference was significant between EBF vs. MF ($p<0.001$), EBF vs. FF ($p<0.001$) and MF vs. FF ($p=0.005$) infants. At 16 weeks also, TC and HDL were higher in EBF infants as compared to MF and FF infants. For TC, this difference was significant between EBF vs. MF ($p<0.001$) and EBF vs. FF ($p<0.001$) infants. When infants were followed up to 16 weeks of age, TC and LDL level fell significantly ($p<0.001$) in EBF and MF group, a significant ($p<0.05$) rise for TC was seen in FF group. At 16 weeks of age, there was no significant rise in HDL in EBF infants, but significant fall was seen in MF ($p=0.0001$) and in FF ($p=0.001$) infants.

Conclusion: Breastfeeding, even MF is beneficial in preterm infants as compared to FF in terms of lipoprotein profile which is protective for atherosclerosis.

Keywords: Exclusive breast feeding, Formula feeding, Mixed feeding

INTRODUCTION

Breast milk is an optimal feed for infant, both for full term and preterm, as suggested in international and national guidelines [1,2]. Breast milk, not only provides all the nutrients in proper amount to the infant, but it has other beneficial effects to both infant and mother. Long term benefits associated with breast feeding are better cognitive development in childhood and lower risk of obesity, diabetes mellitus, high blood pressure and atherosclerotic cardiovascular disease [3-8].

Increase in serum concentration of LDL is a principal risk factor for atherosclerosis and thus a major cause of cardiovascular disease [9]. There is growing evidence that risk of CHD begins to emerge from infancy. Animal and epidemiological evidence suggest that exposures acting in early life may play a role in cardiovascular disease risk. In humans also, early nutritional exposures during infantile period modify cardiovascular risk, including blood cholesterol concentrations in later life [10,11]. It has been seen that infants on different feeding regimens, have different lipoprotein profiles [12]. In exclusively breast fed infants the lipid profile is higher than the formula fed infants [12,13].

Concentrations of the cord blood lipoprotein subtypes are influenced by fetal malnutrition and prematurity while after birth it is affected by the type of feed taken by infant [14]. Cord blood lipoprotein profile in preterm infant is higher than full term infant [15,16] and young adults born preterm have higher risk for cardiovascular disease than those born term [17,18].

With this background, an attempt is made to compare the lipoprotein profile in EBF, MF and FF preterm infants, as there is paucity of studies regarding comparison of lipoprotein profile in EBF, MF and FF preterm infants. Majority of studies have compared this in EBF infants with FF infants [19,20].

MATERIALS AND METHODS

The present prospective cohort study was carried out in the Department of Paediatrics, BRD Medical College, Gorakhpur from June 2010 to May 2011. The study protocol was approved by the Institutional Ethics Committee. Well informed written consent in local language was taken from mothers/guardians of each infant, ensuring their full confidentiality.

Sample size was calculated using G Power Version 3.1.9.2 with mean difference between three groups and standard deviation was calculated from a previous study [20]. Mean difference between breast milk and MF was chosen for sample size calculation. Since, its mean difference was lowest i.e., 12.46±6.72 in breast milk feeding and 18.5±9.48 in mixed feeding group, the calculated effect size was 0.73. Calculated sample size with α error of 5% and power of 95%, was 150 (50 in each group). Assuming 10% of drop out and the possibility of change in feeding pattern during study period, the sample size taken was 200.

A total of 3020 preterm newborn screened from Neonatal unit of Department of Paediatrics, Department of Gynaecology and Obstetrics of BRD Medical College, Gorakhpur and outside deliveries were referred on same day. Two hundred fifty preterm infants with known gestation of <37 weeks (determined by date of last menstrual

period, corrected by ultrasound, if necessary) and apparently healthy, along with their mothers, were recruited on first day of birth. Subjects were recruited consecutively during operational working period irrespective of sex, race, religion and socioeconomic status. Preterm infants having severe sepsis, hypoglycaemia, HIE stage II and III, meconium stained amniotic fluid, pathological jaundice, HMD, less than 28 weeks gestation or with major congenital anomaly were excluded from the study. Also, infants born to mothers with DM, gestational diabetes, hypertension, pre-eclampsia, eclampsia or on long term medications were excluded from the study. Infants whose feeding patters changed during study period were also excluded. Mothers of every infant taken under the study were first counselled to start exclusive breast feeding, because it is the hospital's policy to advice for exclusive breast feeding to all infants. Few working mothers and some non working mothers decided to give artificial milk to their infants because they thought that their infants will not grow properly only by breast feeding. After the mothers had taken the decision, infants were divided in three groups:

Group A: Exclusively breast fed from birth onwards.

Group B: Mixed fed infants, given breast feeding and bovine milk/ commercial preterm milk.

Group C: Formula fed infants (commercial preterm milk)/bovine milk.

Infant Data

After inclusion in the study, preterm infants were admitted in Neonatal unit of Paediatric Department and their sex, period of gestation, birth weight, birth length and head circumference were recorded. Sick preterm infants were excluded from the study but they were admitted in NICU and appropriate treatment was given. Weight was taken using electronic weighing scale with an accuracy of 10 gm. Length was measured by infantometer to the nearest of 1 mm and head circumference was taken by a fibreglass tape to the nearest of 1 mm. Counselling for feeding was done by staff nurse trained in Infant and Young Child Feeding (IYCF). Newborn care was given according to "Departmental Management Protocol" of preterm newborn care.

Maternal Data

Maternal data like age, parity, education status and her breast feeding knowledge was recorded on predesigned proforma. Maternal weight, waist circumference and height were recorded and Body Mass Index (BMI) was calculated. Mothers of infants of Group A were educated for proper positioning and attachment. Mothers of infants of Group B and Group C were counselled for the hygienically preparation of artificial feed in proper amount.

Follow up

Infants were followed up with their mothers, initially weekly for four weeks and then fortnightly up to 16 weeks of age. At each visit we enquired about their feeding method, amount of artificial feed given and hygiene for preparing feed. Venous blood sample was taken for lipoprotein profile estimation. Minor ailments of infants were treated and mothers were advised for vaccination of their infants.

Lipoprotein Profile Estimation

Around 3-4 ml venous blood was taken from mother at the time of recruitment. Infant's sample was taken under all aseptic precautions, two hours before the next feed. First sample was taken at the time of birth, second at four weeks and third sample at 16 weeks of age. Serum was separated and stored at -20ºC.

Serum was analysed for lipoprotein profile estimation by auto analyser (Thyrocare technologies limited, Mumbai). Analysis was done for:

Cholesterol: CHOD POD Method [21];

High Density Lipoprotein (HDL): Selective Immune Precipitation method;

Triglycerides: Enzymatic Calorimetric Method (GPO);

Low Density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL) were calculated by formula-

LDL: TC-(HDL-C+VLDL-C)

VLDL: TG/5

Total Cholesterol/HDL ratio and HDL/LDL ratio was also calculated.

Precision and accuracy of the measured parameters (Cholesterol Estimation) at laboratory are as follows:

Within run	Level 1	Level 2
n=40		
Mean (mg/dl)	235	102.8
SD (mg/dl)	7.5	2.9
CV (%)	3.2	2.84

Total n=40 (10 days/2 runs per day/2 replicates per run)

Mean (mg/dl)	235	102.8
SD (mg/dl)	7.2	3.2
CV (%)	2.7	3.01

Level 1- Person of high cholesterol level was chosen and test was run (n=40) for 40 times, to calculate the mean and SD of cholesterol level.

Level 2- Similarly person of low cholesterol level was chosen to perform the same test.

STATISTICAL ANALYSIS

SPSS version 16 was used for statistical calculation. Unpaired (two-tailed) t-test was applied to differentiate means of various parameters between the two groups. Paired t-test was used to calculate difference in mean value of various parameters at different period of time within two groups. Categorial variables were compared by Chi-square test. One way ANOVA was used to compare three variables. A p-value of <0.05 was taken as significant.

RESULTS

Two fifty infants were enrolled for the study and followed up to the age of 16 weeks. Out of these, 23 infants lost for follow up and 22 infants changed their feeding pattern during the study, therefore analysis was done on 205 infants. At 16 weeks of age there were 80, 80 and 45 infants in groups A, B and C respectively. At 16 weeks in Groups A, B and C, male:female ratio was 1.7:1, 1.9:1 and 2:1 respectively.

Baseline data included infantile characteristics, maternal charac-

Infantile Characteristics	Group A (EBF) n=80	Group B (MF) n=80	Group C (FF) n=45	p-value
Weight (Kg)	1.5642±28.06*	1.3321±34.21*	1.2921±30.19*	p=0.998
Length (cm)	44.54±4.63*	44.14±3.80*	43.12±3.44*	p=0.174
HC (cm)	32.11±2.19*	31.7±3.42*	31.30±2.90*	p=0.3088
Gestational Age				
28-30 weeks	20	32	18	χ^2=4.643 df=3 p>0.05
31-32 weeks	30	33	12	
33-34 weeks	25	20	11	
35-36 weeks	25	15	09	
Lipoprotein Profile				
TC	149.27±31.67*	144.08±44.59*	141.35±38.14*	p=0.499
HDL	45.66±13.06*	48.16±19.80*	48.36±20.17*	p=0.818
TG	136.85±49.88*	132.0±44.20*	145.79±45.00*	p=0.658
Total	80	80	45	

[Table/Fig-1]: Baseline characteristics of infant.
HC-Head Circumference, TC-Total Cholesterol, HDL-High Density Lipoprotein, TG-Triglyceride
*mean±SD,
χ^2=Chi square test

teristics and at birth lipoprotein levels in mother and infant [Table/Fig-1,2]. Baseline characteristics were comparable in three groups.

At four weeks of age TC, TG, LDL and VLDL were higher in EBF infants as compared to MF and FF infants [Table/Fig-3]. On statistical analysis for TC, the difference was significant between EBF vs. MF (p<0.001), EBF vs. FF (p<0.001) and MF vs. FF (p=0.005) infants. On statistical analysis for LDL, this difference was significant between EBF vs. MF (p=0.040) and EBF vs. FF (p=0.026) infants. For TG and VLDL the difference was statistically significant between EBF and FF (p=0.031) infants. HDL level was lower in EBF infants as compared to other groups. There was no difference in TC/HDL-C and HDL/LDL ratio in three groups.

At 16 weeks of age [Table/Fig-4] TC and HDL were higher in EBF infants as compared to MF and FF infants. On statistical analysis for TC and HDL, this difference was significant between EBF vs. MF (p<0.001) and EBF vs. FF (p<0.001) infants. On statistical analysis for LDL, this difference was significant between EBF vs. FF (p=0.009) and MF vs. FF (p<0.05) infants. For TG and VLDL, the difference was statistically significant between EBF and MF (p<0.05) infants. HDL/LDL ratio was also showing statistically significant difference between EBF vs. MF (p<0.001), EBF vs. FF (p<0.05) and MF vs. FF (p<0.05) infants.

[Table/Fig-5] shows lipoprotein profile at birth, four weeks and 16 weeks of age. Changes in lipoprotein levels over a period from four to 16 weeks in three groups were analysed. In EBF infants TC, LDL, VLDL and TG levels fell significantly (p<0.001) from four weeks to 16 weeks. In MF group statistically significant (p<0.001) fall was seen for TC and LDL level and in FF group statistically significant (p<0.05) rise was seen for TC level. HDL level increased in EBF infants from four weeks (46.90±12.93 mg/dl) to 16 weeks (48.54±10.60 mg/dl), although this difference was not statistically significant (p>0.05). Instead the HDL level fell from four weeks to 16 weeks in MF (p<0.001) and in FF (p=0.001) groups.

Maternal Characteristics	Group A (EBF) n=80	Group B (MF) n=80	Group C (FF) n=45	p-value
Weight (Kg)	50.34±6.90*	51.74±6.26*	50.43±6.21*	p=0.342
Waist circumference (cm)	81.831±3.70*	82.081±5.42*	82.981±4.22*	p=0.388
BMI (Kg/M^2)	20.46±3.36*	21.20±2.29*	20.86±1.66*	p=0.214
Breast Feeding Knowledge				
Adequate	53	46	21	χ^2=1.883 df=2 p>0.05
Inadequate	47	54	29	
Age				
<25 yrs	56	68	30	χ^2=3.11 df=2 p>0.05
>25 yrs	44	32	20	
Parity				
<2	51	46	26	χ^2=0.535 df=2 p>0.05
>2	49	54	24	
Smoking/Drinking				
Yes	8	9	4	χ^2=0.773 df=2 p>0.05
No	92	91	46	
Lipoprotein Profile				
TC	159.37±29.63*	155.99±24.81*	148.74±23.16*	p=0.100
HDL	42.26±11.12*	44.72±11.84*	43.88±9.44*	p=0.366
TG	149.65±45.58*	159.45±42.33*	163.17±33.57*	p=0.162
Total	80	80	45	

[Table/Fig-2]: Baseline characteristics of mother.
BMI-Body Mass Index, *mean±SD
χ^2=Chi square test

DISCUSSION

This study was carried out in a tertiary care hospital to compare the lipoprotein profile in EBF, MF and FF preterm infants. We found that at four weeks TC, TG, LDL and VLDL were higher in EBF infants as compared to MF and FF infants. But at 16 weeks TC, TG, LDL and VLDL level decreased and HDL level increased in EBF infants. At the end of 16 weeks TC levels decreased in MF infants but increased in the FF ones. HDL level decreased at 16 weeks of age in both MF and FF infants.

LDL profile of cord blood represents the maturational status of infant, because adrenal gland and liver are the major organs that utilise cholesterol for the development. After birth, LDL profile is affected by type of milk feed taken by infant [22].

In our study, the level of TC and LDL at four weeks of age and only TC at 16 weeks of age, were significantly higher in EBF infants as compared to MF and FF infants. TG and VLDL levels were significantly higher in EBF infants than in FF infants at four weeks and higher than MF infants at 16 weeks.

Other researchers had also shown that both TC and LDL cholesterol concentrations are higher in breast fed infants as compared to formula fed infants [13,23].

Lipoprotein Profile	Group A (EBF) n=80 mean±SD	Group B (MF) n=80 mean±SD	Group C (FF) n=45 mean±SD	p-value (EBF-MF)	p-value (EBF-FF)	p-value (MF-FF)
TC (mg/dl)	167.62±26.29	143.38±26.44	126.38±26.43	p<0.001	p<0.001	0.0052
HDL (mg/dl)	46.90±12.93	47.25±11.00	48.84±12.61	0.8539	0.4182	0.4634
TG (mg/dl)	162.00±57.76	144.91±52.14	139.53±51.07	0.0512	0.0316	0.5780
LDL (mg/dl)	107.70±1.05	83.15±5.01	68.64±3.59	0.0403	0.0264	0.1016
VLDL (mg/dl)	32.40±11.55	28.98±10.42	27.90±10.21	0.0510	0.0313	0.5088
TC/HDL	4.545±406.62	4.322±360.90	4.243±360.45	0.9697	0.9666	0.9901
HDL/LDL	0.531±1.40	0.703±2.19	0.63±0.55	0.5548	0.6503	0.8267

[Table/Fig-3]: Lipid profile of the infants at four weeks in Group A, B and C.
TC-Total Cholesterol, HDL-High Density Lipoprotein, TG-Triglyceride, LDL-Low Density Lipoprotein, VLDL-Very Low Density Lipoprotein.

Lipoprotein Profile	Group A (EBF) n=80 mean±SD	Group B (MF) n=80 mean±SD	Group C (FF) n=45 mean±SD	p-value (EBF-MF)	p-value (EBF-FF)	p-value (MF-FF)
TC (mg/dl)	140.29±30.95	109.84±24.68	138.61±26.40	p<0.001	p<0.001	0.7123
HDL (mg/dl)	48.54±10.60	39.42±11.58	40.34±11.67	p<0.001	p<0.001	0.6730
TG (mg/dl)	114.99±75.24	133.54±34.85	129.73±24.04	0.0471	0.2043	0.5115
LDL (mg/dl)	68.76±5.09	66.12±18.57	72.32±9.91	0.2219	0.0090	0.0399
VLDL (mg/dl)	22.99±15.26	26.70±6.99	25.95±4.82	0.0493	0.2085	0.5197
TC/HDL	4.545±406.62	4.322±360.90	4.243±360.45	0.9697	0.9666	0.9901
HDL/LDL	0.705±2.08	0.596±0.623	0.557±1.177	p<0.001	0.0410	0.0383

[Table/Fig-4]: Lipoprotein profile of the infants at 16 weeks in Group A, B and C.

Group A (n=80)	At Birth mean±SD	Four Weeks mean±SD	16 Weeks mean±SD	p-value
TC (mg/dl)	169.27±31.67	167.62±26.29	140.29±30.95	0.0001
LDL mg/dl)	96.24±8.64	88.32±1.88	68.76±5.09	0.0001
VLDL mg/dl)	27.37±9.97	32.04±11.55	22.99±15.26	0.0001
HDL (mg/dl)	45.66±13.06	46.90±12.93	48.54±10.60	0.3816
TG (mg/dl)	136.85±49.88	162.0±57.76	114.99±75.24	0.0001
HDL/LDL	0.47±1.51	0.531±2.04	0.705±2.08	0.9318
Group B (n=80)				
TC (mg/dl)	144.08±44.59	143.38±26.44	109.84±24.68	0.0001
LDL mg/dl)	69.52±15.95	76.23±5.02	66.12±18.57	0.0001
VLDL mg/dl)	26.4±8.84	28.98±10.42	26.70±6.99	0.1061
HDL mg/dl)	48.16±19.80	47.25±11.0	39.42±11.58	0.0001
TG (mg/dl)	132.0±44.20	144.91±52.14	133.54±34.85	0.1069
HDL/LDL	0.69±1.24	0.703±2.19	0.596±0.623	0.6749
Group C (n=45)				
TC (mg/dl)	141.35±38.14	126.38±26.43	138.61±26.40	0.0307
LDL (mg/dl)	63.84±8.97	76.74±22.82	72.32±9.91	0.2366
VLDL(mg/dl)	29.15±9.00	27.90±10.21	25.95±4.82	0.2498
HDL (mg/dl)	48.36±20.17	48.84±12.61	40.34±11.67	0.0013
TG (mg/dl)	145.79±45.00	139.53±51.07	129.73±24.04	0.2473
HDL/LDL	0.75±2.24	0.636±0.552	0.557±1.177	0.6845

[Table/Fig-5]: Lipoprotein profile of infant at four and 16 weeks of age in Group A, B and C.

High level of TC and LDL is a known risk factor for atherosclerosis, which was found in EBF infants, but it is a well known fact that the breast feeding is protective to atherosclerosis [24]. Explanation for this could be "Nutritional Programming" of infants for cholesterol metabolism [13,25]. The lower blood cholesterol concentrations observed in adult life in exclusively breast fed infants raise the possibility that exposure to breast milk may have long term effects on blood cholesterol concentrations later in life [26]. Early enteral exposure to the high cholesterol content of breast milk in infancy reduces the endogenous synthesis of cholesterol, probably by down regulation of hepatic hydroxymethylglutaryl coenzyme A reductase, which is seen even in adult life [19,27]. Hence, higher cholesterol levels in infants in first few months of life may prime them for lower cholesterol production later in life.

A second explanation could be a "Behavioral Programming" of infant; according to this theory early exposure to breast milk contents like immunoglobulins, nucleotides and hormones specially leptin has an effect on dietary behavior in later life [28]. Breast feeding affects acquisition of taste preferences in infancy and therefore, there is possibility that breastfed infants simply have "healthier" dietary patterns in later life [29-31]. Breast feeding exposes infants to volatile flavour compounds from the maternal diet and this may have a significant impact on flavour learning in infancy, which has some experimental evidences [32-34] also.

When infants were followed up to the age of 16 weeks, the TC level decreased and HDL level increased in EBF. In MF group TC was decreased but HDL also decreased. But in FF group both TC increased and HDL level was also decreased. This finding indicates that even MF is beneficial as compared to FF in terms of lipoprotein profile.

At four weeks the HDL level was less in EBF infants as compared to MF and FF infants, but the difference was not statistically significant. But at 16 weeks HDL level was significantly higher ($p<0.001$) in exclusively breast fed infants as compared to other groups. This demonstrated that a healthy lipoprotein profile which is protective to cardiovascular disease has started from early in life. High HDL level might be because of the increased concentration of lipoprotein lipase, hepatic lipase and lecithin-cholesterol acyl transferase enzymes which is responsible for increased degradation of TG.

It was observed that sickness episodes like diarrhoea, ARI, pneumonia, sepsis were less in EBF preterm infants as compared to MF and FF infants. Hospitalisations were also less in EBF group as compared to MF and FF ones. This may be because of benefits of breast feeding, health education given to all mothers during each follow up visit and other measures like discouraging bottle feeds.

LIMITATION

The main limitation of our study is its short term follow up. Future longitudinal studies with long term follow up are necessary to determine whether the effect of feeding pattern on LDL level persists into adulthood or changes with age, as observed in TC concentrations in breast fed adults and to know the clinical implications of the these findings. Furthermore, mother's diets and the subsequent effect on composition in breast milk should also be investigated to assess infant's serum lipoprotein profile and its long term effect.

CONCLUSION

We concluded that in early few months of life the exclusive breast feeding is beneficial as compared to mixed and formula feeding in terms of healthy lipoprotein profile. Even mixed feeding is beneficial to formula feeding because in MF group TC was decreased but in FF group both TC was increased and HDL was decreased at 16 weeks of age.

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