Research Article

Title: "Serum Lipid Profile In Newborns With Intrauterine Growth Retardation And Its Comparison With Appropriate For Gestation Age Newborns"

Abstract

Background: Newborns with intrauterine growth retardation (IUGR) are known to permanently change their physiology and metabolism to adapt to limited supply of nutrients in utero. These programmed changes can later be the cause for the origin of diseases like coronary artery disease, diabetes mellitus and hypertension. If the premature development of cardiovascular risk factors can be anticipated during childhood, future events can be prevented effectively by taking appropriate measures.

Objective of the study: To study serum lipid profile of newborns with IUGR and Appropriate for Gestation Age(AGA) newborns and compare them.

Methodology: This cross sectional study was conducted from February 2018 to September 2018 in the department of Neonatology, BSMMU, Dhaka, Bangladesh. Newborn who met the inclusion criteria, information regarding antenatal, natal and postnatal history were recorded in a data collection form after taking consent from the parents/guardians. Weight, length, OFC were taken along with other clinical examination. Serum samples of infant with intrauterine growth retardation and matched group of Appropriate for Gestation Age newborns were collected within 24 hours of postnatal age before starting feed and sent to Biochemistry laboratory of BSMMU and analyzed for lipid profile which included serum cholesterol, Triglyceride, Low Density Lipoprotein(LDL) and High Density Lipoprotein (HDL).All data were recorded in a preformed questionnaire and data was analyzed by statistical package for social sciences (SPSS) version 20. Quantitative data were expressed as mean± SD and categorical data were presented as proportion. All quantitative variables were compared by unpaired*t*-test; categorical variables were compared by Chi-square test or Fisher's exact test. $P < 0.05$ was considered as significant. Pearson correlation was done to see the correlation between gestation age and lipid profile in both IUGR and AGA newborns.

Results: Total population included 43 IUGR newborns and 43 AGA newborns who were matched by gestational age and sex. No significant difference was seen among both the groups based on demography except for birth weight which was lower in IUGR newborns than AGA newborns (1398.02±307.14 vs 1777.91±551.2 , p=<0.001). It was observed that serum triglyceride level in IUGR group was significantly higher

than those in AGA group (90.23 ± 48.16 vs. 70.13 ± 27.76, p=0.020). Serum HDL-c level was found to be significantly lower in IUGR group as compared to AGA group (20.62± 8.88 vs. 26.95 ±7.91, p=0.001). There was a significant negative correlation between gestation age and serum LDL-c level in IUGR infants(r = -0.334).

Conclusion: As compared to AGA newborns, IUGR infants had significantly higher levels of triglyceride and lower levels of HDL-c. Significant negative correlation was observed between gestation age LDL-c in IUGR newborns.

Keywords: Serum Lipid Profile, Newborn, IUGR, Gestation Age.

Introduction

Birth weight has long been identified as an important indicator for survival and future quality of life. Low birth weight babies are likely to have higher risk of morbidity and mortality. Low birth weight can be caused by preterm delivery, intrauterine growth restriction or a combination of the two. Intrauterine growth retardation (IUGR) affects 7-10% of all pregnancies [1], and is defined as under achievement of the genetic growth potential in the fetus. It is one of the principle burning public health issues in developing countries. Infants with IUGR have a perinatal morbidity and mortality5–30 times than that of infants with higher weights [2]. IUGR is associated with an increased risk of adverse perinatal outcome and long term fetal programming in the form of cardiovascular disease, metabolic syndrome and neurological deficits [3]. In the fetal period, from nine weeks after conception onwards, there begins the phase of rapid growth that continues until after birth. The main feature of fetal growth is cell division. Different tissues of the body grow during periods of rapid cell division. Growth depends on nutrients and oxygen, and the fetus's main adaptation to lack of these is to slow its rate of cell division. Disproportionate growth can occur because different tissues have critical periods of growth at different times [4]. The first priority for a developing fetus is survival, and this is achieved by reduced rate of growth. Small size at birth and disproportion in head size, length and weight are markers of lack of nutrients or oxygen at particular stages of gestation. They reflect adaptations that fetus made to sustain its development which may be permanent. A number of epidemiological studies in different races and ethnic groups have shown a consistent association between low birth weight and hypertension, coronary artery disease, type 2 diabetes mellitus [5, 6]. These findings have led to the "fetal origins hypothesis" which suggests that an adverse intrauterine environment during a critical period of development could program the development of fetal tissues and organs, and permanently determine responses that produce later dysfunction and disease [7]. This is termed as "programming" a process by which developmental stress leads

to disease [8]. It is generally assumed that lower insulin sensitivity in IUGR newborns may explain the association with dyslipidemia [9]. Hyperinsulinemiais known to enhance hepatic very low density lipoprotein synthesis, which may contribute to increased plasma triglycerides and LDL levels [10]. Resistance to action of insulin on lipoprotein lipase in peripheral tissues in IUGR newborns may also contribute to elevated triglyceride level [11]. Intrauterine growth also influences cholesterylester transferase protein (CETP). High Triglyceride (TG) and low High Density Lipoprotein (HDL) levels which may be found in infants with Intrauterine Growth retardation might result from increase cholesterol ester transfer and may in part explain the increased risk of Coronary Heart Disease in IUGR babies in later life [12].

Materials And Methods

Study design: Cross sectional study.

Place of study: Department of Neonatology, BSMMU, Dhaka, Bangladesh.

Study period: February 2018 to September 2018.

Study population: All IUGR infants admitted in the department of neonatology, BSMMU, Dhaka, Bangladesh during study period.

Inclusion criteria:

1. All Inborn IUGR neonates admitted in NICU who were diagnosed sonographically in the womb and/or by clinical examination after birth whichever was well matched.
2. AGA group –was taken by matching gestation age and sex.

Exclusion Criteria:

1. Perinatal asphyxia.
2. Major congenital anomalies.
3. Parents refused to participate in the study.

After taking informed written consent from the parents / guardians of eligible newborn, face-to-face interview was taken regarding thorough history. Mother's medical records were also reviewed and recorded in a data collection form. IUGR neonates were diagnosed on the basis of suggestive antenatal sonography and/or by postnatal anthropometry (Birth weight, length, OFC less than 10^{th}centile or birth weight less than 10^{th} centile). Anthropometry like weight, length, and head circumference were measured at birth by researcher. Newborn's gestational age was calculated on the basis of New Ballard scoring. The newborn infants weight were taken by researcher without clothing soon after birth on an electronic scale with a precision of 10 g [Model 914, SALTER]. The lengths were taken by infant meter & OFC

were measured by measuring tape, expressed in centimeter (cm).Newborn babies whose mother received complete antenatal corticosteroids were distributed into Complete ACS (Antenatal corticosteroids) group. Newborn babies whose mother did not receive antenatal corticosteroids or received single dose were distributed into incomplete/ No ACS group. Mother's weight was taken within 48-72 hours of postpartum period by an electronic scale (model: SALTER) and height was measured by stadiometer in the postpartum period between 48 to 72 hours. BMI was calculated and expressed in kg/m².Taking all aseptic precautions 2ml of venous blood sample was collected in EDTA vials from both IUGR and AGA newborns during sampling for other investigations. Blood sampling was done within 24 hours of postnatal age before starting feed and was sent to Department of Biochemistry, BSMMU for analysis. In biochemistry laboratory sample was first centrifuged at a rate of 4000 rpm for 5 minutes for preparation of serum. About 10μL of serum was taken and then sample was kept on the operation area of automated computerized biochemical analyzer. Unit of measurement of lipid profile was mg/dl. Estimation of lipid profile were carried out by automated analyzer: Architect Plus ci 8200 which was first designed in the United Stated in year 2003.

Statistical Analysis: After collection, data was entered into a personal computer and was edited, analyzed, and plotted in tables. Comparisons were performed by chi-square test for categorical variables, independent t-test for quantitative variables. P value less than 0.05 was considered statistically significant. Pearson correlation was done to see linear correlation between the variables. The Data was analyzed using the statistical package for social sciences (SPSS) version 20.0.

Results

During the study period, there were total 54 eligible infants. Among these 54 infants, 3 were excluded due to perinatal asphyxia , 3 infants were excluded for major congenital abnormality , 5 patients were excluded as no blood sampling was done within 24 hours of age (Figure-1).

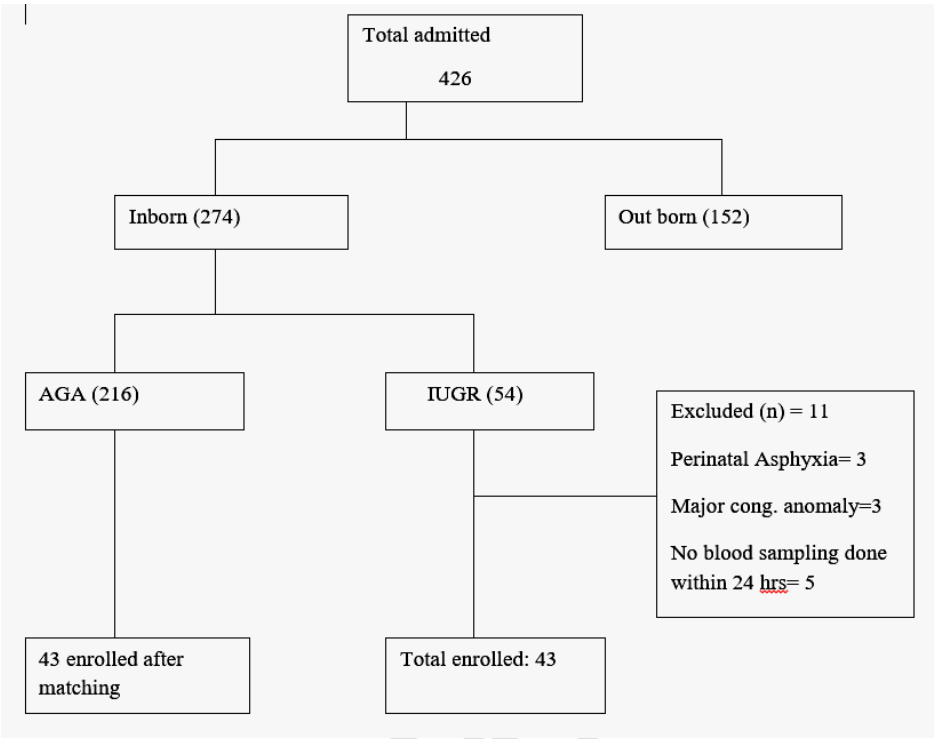

Figure 1: Flow chart of participants in the study.

Regarding the baseline characteristics of the studied infants, mean gestational age of IUGR and AGA infants were34.26±1.96 weeks and 33.37±2.20 weeks, mean birth weight were 1398.02±307.14gand 1777.91±551.2g, respectively and the difference of birth weight was statistically significant ($p< 0.001$)(table-1). 32(74.4%) IUGR infants and 35(81.4%) AGA infants were delivered by LUCS respectively. Gender distribution reflects male predominance in both groups ;22(51.2%) and 25(58.1%)male infant in IUGR and AGA groups respectively. Based on socioeconomic status most belonged to middle socioeconomic class, 34(79.1%) in IUGR group and 36(83.7%) in AGA group respectively. 25(58.1%) among IUGR group received complete dose of antenatal corticosteroid as compared to 22(51.2%) in AGA group. Maternal Hypertension was present in 23(53.5%) IUGR infants as compared to 14(32.6%) in AGA group, however the difference was not statistically significant ($p=0.081$). 7(16.3%) mothers had diabetes mellitus in IUGR group and 9(20.9%) mothers had diabetes mellitus among AGA infants. Postpartum Maternal BMI was <25 kg/m² in 28(65.1%) mothers in IUGR group and 23(53.5%) in AGA group respectively.

Table-1: Baseline characteristics of enrolled infants (N=86)

Characteristics	IUGR (n=43)	AGA (n=43)	p-value
Mode of delivery, n (%) NVD LUCS	 11(25.6%) 32(74.4%)	 8(18.6%) 35(81.4%)	0.604 NS
Sex distribution, n (%) Male Female	 22(51.2%) 21(48.8%)	 25(58.1%) 18(41.9%)	0.516 NS
Socioeconomic status, n (%) Low Middle High	 6(14.0%) 34(79.1%) 3(7.0%)	 4(9.3%) 36(83.7%) 3(7.0%)	0.79 NS
Gestational age(wk),mean±SD	34.26±1.96	33.37±2.20	0.053 NS
Birth weight(g),mean±SD	1398.02±307.14	1777.91±551.2	<0.001 S
Antenatal corticosteroid, n (%) Yes No	 25(58.1%) 18(41.9%)	 22(51.2%) 21(48.8%)	0.516 NS
Multiple gestation, n (%) Yes No	 4(9.3%) 39(90.7%)	 2(4.7%) 41(95.3%)	0.397 NS

Contd.

Table-2: Baseline characteristics of enrolled infants (N=86)

Characteristics	IUGR(n=43)	AGA(n=43)	p-value
Maternal diabetes, n (%) Yes No	 7(16.3%) 36(83.7%)	 9(20.9%) 34(79.1%)	0.397 NS
Maternal Hypertension, n (%) Yes No	 23(53.5%) 20(46.5%)	 14(32.6%) 29(67.4%)	0.081 NS
Maternal BMI (kg/m²), n (%) <25 kg/m² ≥25 kg/m²	 28(65.1%) 15(34.9%)	 23(53.5%) 20(46.5%)	0.380 NS

Continuous data are presented as mean±SD and categorical data as percentage (%)

NS: not significant, S: Significant

Statistical test: Independent Sample t test and Chi square test

Among 43 IUGR infants 18 (41.9%) and 25 (58.1%) belonged to 28-<34 weeks and ≥34 weeks respectively. Among 43 AGA infants 23(53.5%) and 20(46.5%) belonged to 28-<34 weeks and ≥34 weeks respectively (Figure 2).

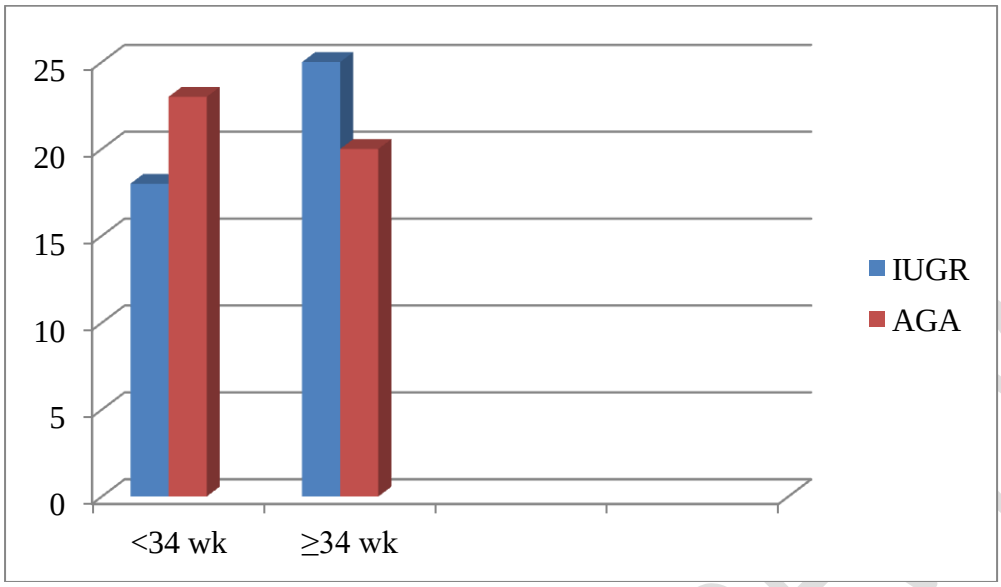

Figure 2- Distribution of gestational age among the enrolled infants.

About 4.7% of IUGR infants were extremely low birth weight, 53.5% were very low birth weight and 41.9% were low birth weight. Approximately 4.7% of AGA infants were extremely low birth weight, 25.6% were very low birth weight, 58.1% were low birth weight and 11.6% had normal birth weight (Figure 3).

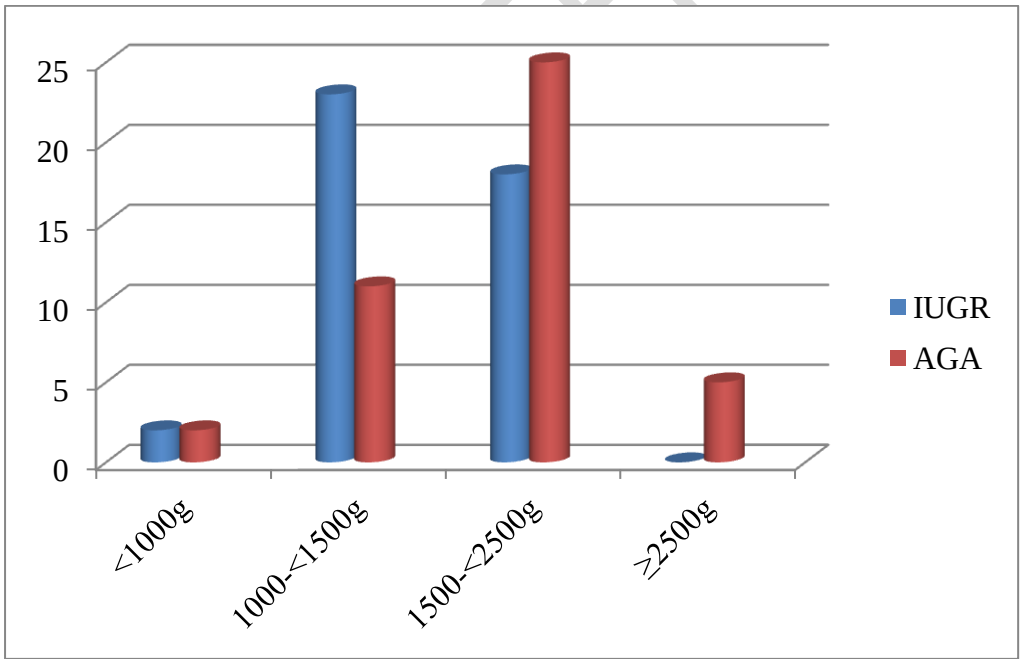

Figure 3: Distribution of birth weight among the enrolled infants.

The mean serum levels of Total cholesterol, Triglyceride, HDL-c and LDL-c were compared in both IUGR and AGA groups (Table 2). The mean value of Total Cholesterol was 67.62±37.58 in IUGR group and 75.65± 27.55 in AGA group. There was a significant difference between both the groups in terms of serum Triglyceride

and HDL levels. Serum Triglyceride level was higher in IUGR group i.e. 90.23±48.16 as compared to AGA group which was 70.13±27.76 (p=0.020). Serum HDL-c level in IUGR group was 20.62±8.88 and AGA group was 26.95±7.91 which was significantly lower in IUGR group(p=0.001). Serum LDL-c level in IUGR group was 31.47±30.12 and in AGA group was 42.52±22.59 , however the difference was not statistically significant (0.058).

Table-3: Comparison of lipid profile in study groups (N=86)

Characteristics	**IUGR (n=43) mean±SD**	**AGA (n=43) mean±SD**	**p-value**
Total cholesterol	67.62± 37.58	75.65± 27.55	0.262 NS
Triglyceride	90.23 ± 48.16	70.13 ± 27.76	0.020 S
HDL-c	20.62± 8.88	26.95 ± 7.91	0.001 S
LDL-c	31.47± 30.12	42.52± 22.59	0.262 NS

S: significant
NS: not significant

Statistical test: Independent Sample t-test

Mean levels of all lipid parameters were measured based on gestational age in IUGR group (Table 3). No significant difference of lipid parameters was found between two groups of gestational age. It was observed that mean value of Total cholesterol in IUGR infants born between 28-<34 weeks was 80.00±52.03 and 58.72±18.87 in those born ≥34 wk. Mean value of Triglyceride in IUGR infants born between 28-<34 weeks was 90.83±53.25 and in ≥34 wk infants was 89.80±45.27. Mean value of HDL-c in IUGR infants born between 28-<34 weeks was 21.50±10.58 and in ≥34wk was 20.40±7.63 .Mean value of LDL-c in IUGR infants was 41.16±32.43 and 24.49±13.83 among those born between 28-<34 weeks and ≥34wk respectively.

Table-4: Comparison of lipid profile among IUGR infants according to gestational age (N=86)

Characteristics	**28-<34wk (n=18) mean±SD**	**≥34 wk (n=25) mean±SD**	**p-value**
Total cholesterol	80.00±52.03	58.72±18.87	0.066 NS
Triglyceride	90.83±53.25	89.80±45.27	0.946 NS
HDL-c	21.50±10.58	20.40±7.63	0.694 NS
LDL-c	41.16±32.43	24.49±13.83	0.073 NS

S: significant
NS: not significant
Statistical test: Independent Sample t-test

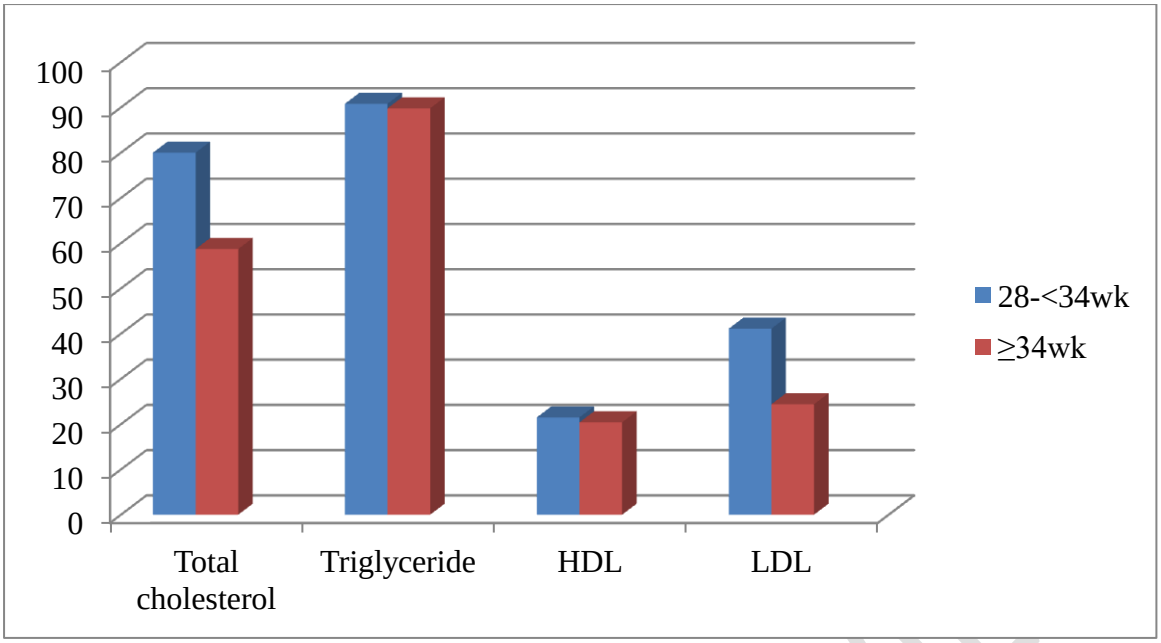

Figure 4: Comparison of mean values of lipid profile in IUGR newborns according to the Gestational age category.

Correlations of lipid parameters with gestational age was done in both IUGR and AGA groups by pearson correlation. Significant negative relationship was seen between gestational age and LDL-c levels in IUGR newborns ,r= -0.334**(Figure-5). There was significant positive relationship (r= 0.430**) between gestational age and Triglyceride levels in AGA newborns(Figure-6).

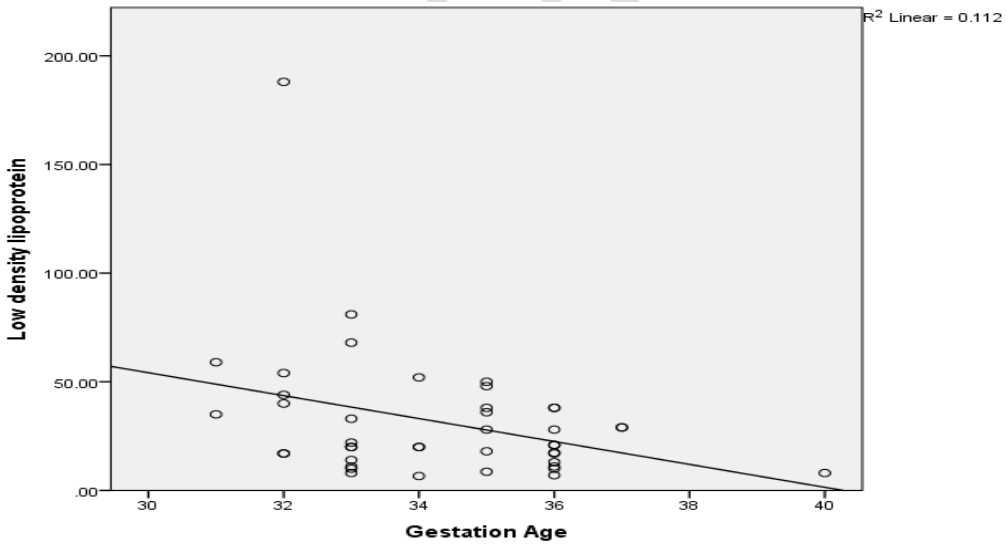

Figure 5: Scatter diagram showed significant negative relationship (r= -0.334**) between gestational age and LDL-c levels in IUGR newborns.

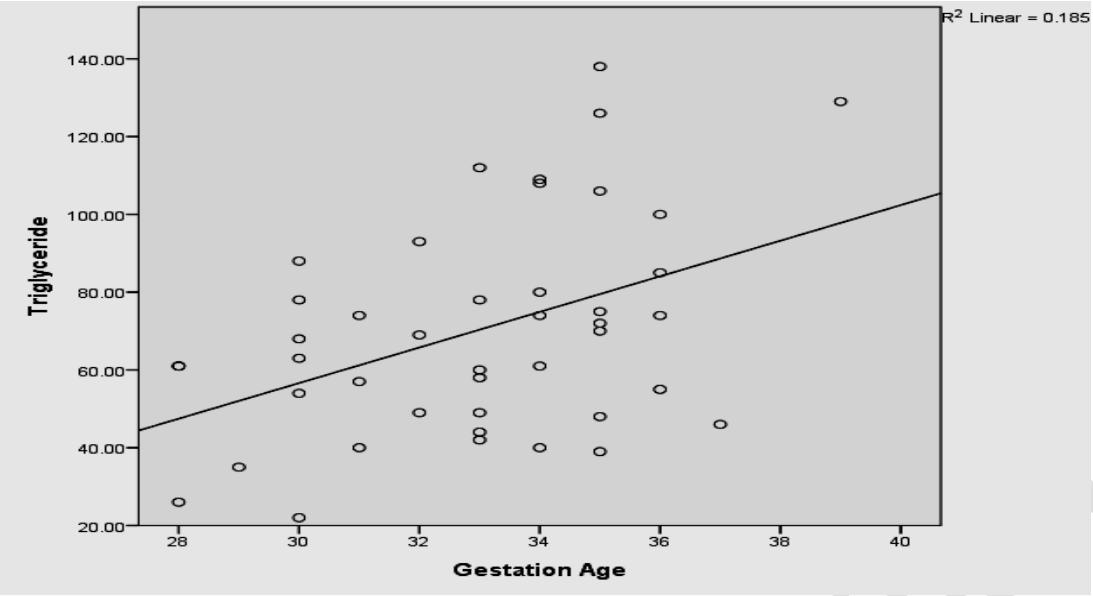

Figure 6: Scatter diagram showed significant positive relationship (r= 0.430**) between gestational age and Triglyceride levels in AGA newborns.

Discussion

This study was done to determine whether lipid metabolism is affected by undernourishment in utero. This cross sectional study was done in the Neonatology department, BSMMU, Dhaka, Bangladesh. Total population included 43 IUGR newborns and 43 AGA newborns who were matched by gestational age and sex. It was observed that IUGR newborns had higher level of serum triglyceride level and lower level of HDL-c as compared to AGA newborns which was statistically significant. It is known that high values of serum triglyceride and low level of HDL-c are associated with increased risk of coronary artery disease. Hence it can be said that IUGR newborns are more prone to develop coronary artery disease in adulthood.

Total serum cholesterol:

In this study it was observed that total serum cholesterol in IUGR group was lower than those in AGA groups (67.62± 37.58 vs. 75.65± 27.55 , p= 0.262) , however the difference was not statistically significant. This finding was similar with study done by Jadhaoet al. [18] Katragaddaet al. [19] and Pecks et al [20]. In IUGR fetuses there maybe alteration of cholesterol acceptor concentration or functionality and a disturbed interaction with reverse cholesterol transport mechanisms (RCT) at the placental interface. Reduction in cholesterol efflux acceptor capacity appears to diminish cholesterol availability and trans-placental cholesterol transport to IUGR fetuses by Peckset et al [21].

Serum Triglyceride:

In this study it was observed that serum triglyceride level in IUGR group was significantly higher than those in AGA group (90.23 ± 48.16 vs. 70.13 ± 27.76, p=0.020).This finding was in agreement with Khalid et al., [12] Katragadda et al., [19] and Hossain et al., [22] Khalid et al., [12] reported triglyceride level of 101.14±28.26 in IUGR newborns as compared to 74.33±13.15 in AGA newborns($p<0.05$). Higher concentration of triglyceride in plasma of IUGR neonates might be due to increased secretion of TG-rich lipoproteins by the liver or decreased lipolysis or reuptake of TG-rich lipoproteins. In state of undernourishment, there may be impaired clearance of TG-rich lipoproteins rather than increased secretion of TG-rich lipoproteins contribute to higher level of triglyceride in IUGR newborns by Kaser et al [23]. Resistance to the action of insulin on lipoprotein lipase in peripheral tissues may also contribute to elevated triglyceride level in IUGR newborns.

Serum HDL-cholesterol:

Serum HDL-c level was found to be significantly lower in IUGR group as compared to AGA group (20.62± 8.88 vs. 26.95 ± 7.91 , p=0.001) which was in agreement with Jadhao et al [18]. They reported HDL-c level in 11.72±0.36 in IUGR group as compared to 13.66±0.31 in AGA group ($p<0.001$). In study done by Inazu A et al., [24] they had concluded that subjects homozygous for Cholesteryl Ester Transfer Protein (CETP) deficiency had markedly increased levels of HDL cholesterol by Kaseret et al., [23] found a lower mass of CETP but high CE- transfer among the IUGR newborns. High rate of CE- transfer results in low HDL-c which partly explains high risk of chronic heart disease in IUGR newborns.

Serum LDL-cholesterol:

Serum LDL-c level was found to be lower in IUGR group than in AGA group, however the difference was not statistically significant (31.47± 30.12 vs. 42.52± 22.59, p=0.058). This finding was in agreement with Jadhao et al., [18] and Pecks U et al., [20] Jadhao et al., [18] reported LDL-c level of 53.09±1.34 in IUGR newborns as compared to 56.58±1.16 in AGA newborns (not significant). Liver is thought to be the main site of LDL cholesterol synthesis. Hence, the low concentration of LDL in IUGR newborns may be secondary to limited cholesterol pool of the fetus. Persistent reduction of LDL receptor activity is associated with failure of growth of fetal liver

which is also a possible explanation. Demographic characteristics like mode of delivery, sex distribution, socioeconomic status, gestational age, birth weight, use of antenatal corticosteroid, multiple gestation, maternal diabetes, maternal hypertension and maternal BMI were compared in both IUGR and AGA groups. No significant difference was seen among both the groups based on demography except for birth weight which was as expected lower in IUGR group ($p=0.016$).Mean levels of all lipid parameters were measured based on gestational age in IUGR group . No significant difference of lipid parameters was found between two groups of 28-<34 wk and ≥34 wk gestational age. Correlation of gestation age with lipid profile was seen in both IUGR and AGA groups by Pearson correlation. A negative correlation was found with the levels of total cholesterol, HDL-c , LDL-c level and gestational age in both the IUGR and AGA groups which was in agreement with Donega et al [25]. However significant inverse correlation was observed with serum LDL-c level in the IUGR group ($r= -0.334$). As liver is thought to be the main site for LDL cholesterol synthesis in late gestation, the persistent reduction of LDL receptor activity associated with failure of growth of fetal liver in IUGR newborns is a possible explanation for the significant negative correlation of LDL-c level with gestation age in IUGR newborns [26]. There was a positive correlation of gestational age with serum triglyceride level in both the IUGR and AGA groups, however a significant correlation was found among gestational age and serum TG level in AGA newborns ($r= 0.430$ vs. $r= 0.071$). This finding was similar with Donega et al [25]. This study included 22 male (51.2%) and 21 female (48.8%) among 43 newborns in IUGR group and 25 male (58.1%) and 18 female (41.9%) among 43 newborns in AGA group. The lipid profiles in male and female IUGR infants were not significantly different, however the mean levels of all the lipid parameters were higher in the female group than male group. This finding was similar with the finding of Seyyed et al., [27] Badiee et al., reported that all lipid levels in female newborns were significantly higher than male newborns. Comparison of lipid profile in IUGR newborns was also done on the basis of maternal post-delivery BMI. Study done by Anderson 1989 [29] in India showed that mean weight gain during pregnancy in Indian women was only about 6kg, it is felt that postpartum weight closely reflects pre-pregnancy weight in our population. Therefore, postpartum BMI closely reflects pre-pregnancy BMI. The total cholesterol, Triglyceride and HDL levels were found to be higher among those newborns with maternal BMI<25 kg/m² as compared to maternal BMI≥25 kg/m², however the difference was not statistically significant. This finding was in agreement

with Nayak et al [26]. In contrast Seyyed et al. [27] reported higher level of Total cholesterol level in BMI ≥25 kg/m² group. Nayak et al. [26] concluded that maternal BMI had no effect on neonate's lipid profile. Results from human observational studies have been a bit conflicting regarding association between Antenatal corticosteroid exposure and later risk factors for cardiometabolic disease. Some studies have shown no association, [30, 31] while some studies have showed a small increase in blood Pressure, [32] impaired β-cell function and evidence of increased aortic stiffness [33]. In this study it was found that total cholesterol level was slightly higher in those IUGR newborns who received complete dose of antenatal corticosteroid as compared to those who did not (77.34± 36.15 vs. 64.76± 27.67 , p= 0.079), however the difference was not statistically significant. This finding was similar to Norberg et al [34].

Conclusion

As compared to AGA newborns, IUGR infants had significantly higher levels of triglyceride and lower levels of HDL-c. Significant negative correlation was observed between gestation age and LDL-c in IUGR newborns. However factors such as gender, maternal BMI, use of antenatal corticosteroid had no significant influence on the lipid profile of IUGR newborns.

Limitation And Recommendation

- Small study population
- Maternal lipid profile was unknown

This study recommends long term prospective study with bigger sample size to see the effects of dyslipidemia in IUGR newborns in their future life.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

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