Original Research Article

Third trimester maternal blood and at birth cord blood lipid profile characteristics in pregnant woman with or without fetal growth restriction

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ABSTRACT

Background: To study the lipid profile of 3rd trimester pregnant women and their cord blood with and without intrauterine growth restriction Design: Observational study, Setting: Department of Obstetrics and Neonatology, in a teaching hospital in North India during February 2013 to August 2014.
Methods: Third trimester pregnant women and their neonates. Enrolled 250 women were divided in intrauterine growth restricted and control groups. Outcome Measures: Venous blood Lipid levels of 3rd trimester mothers and their neonate at birth.
Results: Women of IUGR group had significantly lowered total cholesterol (TC), triglycerides (TG), high density lipoproteins (HDL) and low density lipoproteins (LDL)210.2 (19.8), 221.6 (36.2),65.4(11.7)and 130.7 (20.8)compared to 251(55.3), 234.7(35.6), 70.8(19.9) and 181.3(16.8) mg/dl control group. The TC, TG and LDL levels in cord blood of IUGR group were 93.6(16.5), 50.4 (6.5) and 51.8(12.6) as compared 106.4(17.7), 30.7(4.4) and 55.9(12.1) mg/dl to control group (p value <0.05). HDL levels were significantly lower 15.8(4.6) in IUGR group as compared to 26.5(5.4) in control group. The LDL: HDL and TC: HDL ratio was significantly higher in IUGR group. Maternal weight, gestational age, urban residence, primi parity, birth weight and APGAR score were lower, while maternal age, parity, smoking, blood pressure, cesarean sections (%) and male sex (%) of baby was higher in IUGR group.
Conclusions: Lipid profile of mothers of IUGR fetuses had significantly lowered cholesterol levels and their cord blood had shown atherogenic phenotype.

Keywords: Intrauterine growth restriction, Lipid profile, Neonates, Pregnancy, 3rd trimester pregnancy

INTRODUCTION

Maternal nutrition plays a major role in fetal growth and birth outcome. However, the association between maternal nutrition and birth outcome is complex and is influenced by many biologic, socioeconomic, and demographic factors.[1] Maternal nutrition depends on intake of carbohydrates, proteins, lipids and micronutrients. Lipids are one of the macronutrients and transferred to the fetus in form of cholesterol from mother via placenta.[2] Altered lipid levels were found in mothers with intrauterine growth restricted (IUGR)fetus

and preeclampsia.[3] Pecks et al has shown decreased high density lipoproteins (HDL) concentration in cord blood of intrauterine growth restricted babies even without Preeclampsia.[4] Altered lipid levels during pregnancy in mother are linked with fetal growth. Although developing countries like India have higher incidence of IUGR births as compared to developed countries, yet there is limited data about maternal lipid levels and its effect on fetal growth.[5] Hence an observational study was planned with objective to detect the difference in lipid levels of third trimester pregnant women during their first visit and their cord blood with or without intrauterine growth restriction.

METHODS

It was an observational study and conducted at department of Obstetrics and Neonatology in a tertiary care hospital in north India during February 2013 to August 2014. The study was approved by Institutional Ethics Committee (IEC). Informed written consent was obtained from the pregnant women at her first visit during 3rd trimester of pregnancy before onset of active labor.

Pregnant women who came to antenatal clinic at her first visit during third trimester were included in the study on first come first basis (1:1).

The exclusion criteria was women who had multiple gestations, fetal anomalies, placental anomalies, diabetes mellitus/ gestational diabetes, obesity (BMI: $>25 \, kg/m^2$), under nutrition (BMI: $<18.5 \, kg/m^2$), short stature (<145cm), chronic illness, pregnancy induced hypertension, family history of IUGR birth and TORCH infections. Enrolled mothers were assigned in 2 groups to normal pregnancy (Control) group and IUGR (study) group. Gestational age was determined by last menstrual period (LMP) and by ultrasound of first trimester, if LMP was not available. IUGR pregnancy was diagnosed according to American College of Obstetrics and Gynaecology (ACOG) guideline: estimated fetal weight <10 percentile with any of the following: deceleration of growth velocity during last 4 weeks, elevated resistance index (RI) in umbilical artery >95 percentile, fetal asymmetry, oligohydramnios (Amniotic Fluid Index <5cm) and normal fetus was diagnosed as estimated fetal weight between 10-90 percentile.

Sample size was calculated on the basis of previous study by Pecks et al.[4] Expecting the difference in average LDL/HDL ratio of mothers of IUGR and normal neonates (2.26±0.79 v/s 1.84±0.64) the sample size required for detecting the differences at 95% confidence interval and 80% power was 222. Considering the 10% attrition rate on the follow-up, the sample size was upscaled to 125 women in each group. So, a total of 250 mothers was enrolled and analyzed 222 mothers (111 in each group) and their neonates.

Standardized protocol for collection of blood and transportation to lab was followed. Blood samples (ante-cubital vein) of all enrolled mothers were collected at first visit during third trimester. The mothers kept six hours of fasting just before sampling. Mothers who required LSCS also kept nil per orally for six hours before delivery and received maintain ace intravenous fluids. The cord blood was collected just after delivery of the baby from umbilical vein in test vials and sent laboratory immediately. The biochemist kept blinded to the study group. Cholesterol was measured by using oxidase peroxidase method, triglycerides by Glycerol 3 oxidase Peroxidase (GPO-POD) method, HDL by 3rdgeneration direct homogenous assay and LDL/VLDL by Fried Wald formula.[6]

Relevant maternal and newborn details like maternal age, body weight, weight gain during pregnancy, gestational age, urban/rural residence, parity, smoking, blood pressure, need of LSCS, birth weight, APGAR score and sex of baby were obtained by history, examination and medical records. Follow ups from initial ANC visit to delivery was ensured.

Quantitative data was summarized in form of Mean±SD. The difference in mean of both groups was analyzed by using 'Z' test. Categorical data were presented by frequencies and percentages. Qualitative data were summarized in form of proportions and chi square or fisher exact test were used as applicable. The level of significance was kept 95% for all statistical analysis. Correlations were analyzed by Pearson's correlation coefficient. Statistical analysis was done by using graph pad software freely available at net: www.graphpad.com.

RESULTS

Total 20,000 women attended Antenatal Clinic (ANC)during the study period. Out of them 1300 women were in 3rd trimester. All 1300 women were accessed for eligibility. We excluded 1050 women for different reasons (216 first visit with active labour, 195 refused for consent, 10 multiple gestations, 18 fetal and placental anomalies, 12 diabetes/ GDM, 198 under-nutrition, 23 obese, 27 PIH, 56 history of previous IUGR birth, 24 TORCH positive, 35 chronic illness, 36 short stature). Two hundred fifty (125 in each group) women who fulfilled the inclusion criteria were enrolled. Out of them 222 women completed the study and their blood samples were analyzed.

Baseline characteristics like maternal weight, weight gain during pregnancy, gestational age, urban residence, primi parity, birth weight and APGAR score of baby was lower in IUGR group as compared to control group, while maternal age, total parity, smoking, blood pressure, need of LSCS and male sex of baby was higher in IUGR group as compared to control group (Table 1).

Table 1: Comparison of baseline characteristics between IUGR and control groups.

Characteristics	IUGR Group (n=111)	Control Group (n=111)	95% CI	p value
Maternal Age	28.9 (6.3)	26.1 (6.7)	-4.36 to -0.92	<0.05
Maternal Weight (kg)	58.4 (5.8)	63.3 (5.7)	3.38 to 6.44	<0.05
Weight Gain (Kg)	7.8 (1.0)	10.0 (1.8)	0.63 to 1.39	<0.05
Gestational age (wks)	35.4 (3.1)	38.2 (2.4)	2.0 to 3.5	<0.05
Parity	2.9 (1.7)	2.4 (1.6)	0.87 to 0.00	>0.05
Primi Mothers (%)	48 (43.2%)	55 (49.5%)	-	>0.05
Maternal Smoking (%)	22 (19.8%)	18 (16.2%)	-	>0.05
Urban (%)	58 (52.3%)	66 (59.5%)	-	>0.05
MOD: LSCS (%)	70 (63.1%)	40 (36.0%)	-	<0.05
SBP	122.9(4.6)	118.1 (4.2)	-5.03 to -2.71	<0.05
DBP	81.9 (3.9)	78.3 (3.0)	-3.91 to -2.05	<0.05
Baby Weight (Kg)	1.9 .2 (0.5)	2.8 (0.5)	0.39 to 0.65	<0.05
APGAR Score 1 min	6.7 (1.1)	7.7 (1.1)	0.72 to 1.28	<0.05
APGAR Score 5min	8.2 (1.0)	9.4 (0.8)	-0.39 to 2.75	>0.05
Baby Sex (Male %)	72 (64.7%)	47 (42.3%)	-	<0.05

CI: Confidence Interval, MOD: Mode of delivery, LSCS: Lower Section Caesarian Section, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Mothers, of IUGR group had significantly lower TC and TG, 210.2 (19.8) and 221.6 (36.2) compared to 251 (55.3) and 234.7 (35.6) mg/dl in control group. The HDL and LDL levels were significantly lower 65.4(11.7) and 130.7 (20.8) in IUGR group as compared to 70.8(19.9) and 181.3(16.8) mg/dl control group. The TC: HDL and LDL: HDL ratio was significantly lower in IUGR group 3.3 (0.8) and 2.0(0.5) as compared to 3.6 (1.3) and 2.9 (0.8) control group (Table 2, Figure1). The TC level 93.6 (16.5) mg/dl in cord of IUGR group was significantly lower 106.4 (17.7) mg/dl as compared to control group. The TG levels in newborns of IUGR group were 50.4 (6.5) mg/dl significantly higher as compared 30.7 (4.4) mg/dl to control group. The HDL levels were significantly lower 15.8 (4.6) in cord blood of IUGR group as compared to 26.5 (5.4) mg/dl in control group. The LDL (SD) levels were significantly lower 51.8 (12.6) in IUGR group as compared to 55.9 (12.1) in control group. The LDL: HDL and TC: HDL ratio 3.5 (1.5) was significantly higher in cord blood of IUGR group as compared 2.2 (75) to control group. The TC: HDL was significantly higher in cord blood of IUGR group 6.3 (1.6) as compared to control groups 4.2 (1.2) (Table 2).

Table 2: Comparison of lipid profile between IUGR and control group.

Parameters	IUGR Group (n=111)	Control Group(n=111)	95 % CI	p value
TC (Maternal)	210.2 (19.8)	251 (55.3)	30.6 to 52.6	0.0001
TC (Cord blood)	93.6 (16.5)	106.4 (17.7)	8.4 to 17.4	0.0001
TG (Maternal)	221.6(36.2)	234.7 (35.6)	3.6 to 22.6	0.007
TG (Cord blood)	50.4 (6.5)	30.7 (4.4)	-21.2 to -18.2	0.0001
HDL (Maternal)	65.4(11.7)	70.8(19.9)	0.1 to 9.7	0.02
HDL (Cord blood)	15.8 (4.6)	26.5 (5.4)	9.4 to 12.0	0.0001
LDL (Maternal)	130.7 (20.8)	181.29 (16.8)	45.6 to 55.6	0.0001
LDL (Cord blood)	51.8 (12.6)	55.9 (12.1)	0.8 to 7.4	0.01
TC: HDL (Maternal)	3.30 (0.8)	3.62 (1.3)	0.04 to 0.6	0.03
TC: HDL (Cord blood)	6.3 (1.6)	4.2 (1.2)	-2.5 to -1.7	0.0001
LDL: HDL (Maternal)	1.99 (0.5)	2.93 (0.8)	0.77 to 1.1	0.0001
LDL: HDL (Cord blood)	3.5 (1.5)	2.2 (0.8)	-1.7 to -1.04	0.0001

IUGR: intrauterine Growth Restriction, CI: Confidence Interval, TC: Total Cholesterol, TG: Triglycerides, HDL: High Density Lipoproteins, LDL: Low Density Lipoproteins, Values (SD).

There were weak positive correlation between maternal and fetal TC, TG, HDL, LDL and LDL: HDL ratio in control group, while a weak negative correlation for TC: HDL between maternal and fetal levels. There was a

weak positive correlation between maternal and fetal HDL in IUGR group, while there was a weak negative

correlation for TC, TG, LDL, TC: HDL and LDL: HDL in IUGR group (Table 3).

Table 3: Correlation between maternal and cord lipid levels.

Parameters	Mother	Baby	Correlation Coefficient (r)	p value
TC (IUGR)	210.2 (19.8)	93.6 (16.5)	-0.01	0.92
TC (CN)	251 (55.3)	106.43 (17.7)	0.01	0.92
TG (IUGR)	221.6 (36.2)	50.43 (6.5)	-0.06	0.53
TG (CN)	234.7 (35.6)	30.72 (4.4)	0.04	0.66
HDL(IUGR)	65.44 (11.7)	15.80 (4.6)	0.002	0.98
HDL (CN)	70.84 (19.8)	26.50 (5.4)	0.07	0.45
LDL(IUGR)	130.67 (20.8)	51.82 (12.6)	-0.10	0.30
LDL (CN)	181.29 (16.8)	55.90 (12.1)	0.16	0.09
TC: HDL (IUGR)	3.30 (0.8)	6.29 (1.6)	-0.04	0.68
TC: HDL (CN)	3.62 (1.3)	4.22 (1.2)	-0.001	0.99
LDL: HDL(IUGR)	1.99 (0.5)	3.54 (1.5)	-0.03	0.75
LDL: HDL (CN)	2.93 (0.8)	2.19 (0.8)	0.10	0.28

IUGR: Intrauterine Growth Restriction, CN: Control, CI: Confidence Interval, TC: Total Cholesterol, TG: Triglycerides, HDL: High Density Lipoproteins, LDL: Low Density Lipoproteins, Values (SD).

DISCUSSION

In IUGR group the rate of rural background (47.75%) was higher than control group (40.64%). The possible reasons of higher IUGR birth with rural background are poverty; illiteracy and less accessibility to medical care. Mean systolic and diastolic blood pressure in mothers of IUGR group was significantly higher; however, no mother had pregnancy induced hypertension. The IUGR group had significantly higher male sex of baby 72 (64.86) as compared to control group 47 (42.34%) while Pecks et al, did not found any sex difference in the two groups.[4]

Women of IUGR groups were more likely to have higher maternal age, smoking habits, rural background, high blood pressure, high need for cesarean section, male sex, low Apgar score, lower maternal weight and weight gain during pregnancy, low gestational age as compared to mothers of control group. Pecks et al, had similar trends in all baseline characteristics other than maternal age, primi parity, rural population and sex of baby.[4] Pecks et al reported higher mean maternal age in both groups, possibly because of late marriages in their set up.[4]

The pregnant women of IUGR group had lower total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL), high density lipoproteins (HDL), TC: HDL and LDL: HDL ratio as compared to control group. The TC, LDL and HDL levels in cord blood of IUGR group were significantly lower. The TG, LDL: HDL and TC: HDL ratio was significantly higher in IUGR group. There was a weak positive correlation between maternal and fetal HDL in IUGR group, while a weak negative

correlation for TC, TG, LDL, TC: HDL and LDL: HDL in IUGR group. There were weak positive correlations between maternal and fetal TC, TG, HDL, LDL and LDL: HDL ratio, while a weak negative correlation for TC: HDL in control group.

Cord blood lipids levels in IUGR group in our study reflected an atherogenic phenotype. The decreased maternal lipid level in IUGR group limited the lipid availability for placental transfer to the fetus and explains the lower cholesterol levels in IUGR fetuses.[7] Decreased cholesterol efflux capacity in placental endothelium in IUGR group might played a role for lower lipid levels; however we had not documented it.[7] Reduced de novo synthesis in fetal liver could be another reason. Maternal hypertriglyceridemia is a characteristic feature during pregnancy.[8] Decreased lipid levels and subtract availability in IUGR pregnancy might lead a physiological response to this adverse in utero environment in form of alteration in lipid metabolism in fetus. The altered lipid levels in fetus might result in variance in vascular viscosity and lead to endothelial damage.[9] The damaged endothelium is more prone for atherosclerotic lesion.

The alteration in lipid level in mothers with pregnancy induced hypertension and intrauterine growth retardation of fetus has well documented. It is due to insufficient trophoblast invasion with failed remodeling of spiral arteries in the placental bed.[10,11] This inadequate placentation leads to alterations in blood flow within placental spiral arteries and result in ischemia reperfusion and formation of reactive oxygen species and disturbed placental protein synthesis and LDL-receptor function.[12-15] The mechanism in preeclampsia for altered lipid

metabolism is somewhat similar to this study. The altered lipid profile and vascular disturbances are responsible for higher blood pressures in Preeclemptic mothers.[16] A higher mean blood pressure was noticed in IUGR group which is attributed to endothelial damage; however, any mother with labeled PIH was not found. The pathophysiology of atherogenic lipid levels is related with reduced HDL. High density lipoproteins protect LDL from oxidation. Oxidization of LDL particles is the key mechanism for the pathogenesis of atherosclerosis.[17] Reduced HDL can lead to increased oxidation of LDL and formation of atherogenic ox LDL.

It is a known fact that an intrauterine environment and fetal programming can have long-term impact on chronic diseases in later life. Barker hypothesis explains how the intrauterine alterations in lipid metabolism can impact future outcomes.[18] According to it the intrauterine period has highest plasticity and more susceptible to environmental influences. It leads to permanent disruptive changes in vessel integrity in neonates. Atherosclerotic lesions may have their genesis in adverse intrauterine conditions.[19-21]

The correlations between maternal and cord blood lipid levels were weak. This weak correlation is suggestive of role of multiple factors on maternal and cord lipid levels, rather than maternal lipid levels alone. Pecks et al also reported similar lipid metabolic alteration in IUGR group as compared to our study.[4] VA Rodie et al, found that fetal lipids did not show significant correlation with maternal lipids in IUGR group.[22] Hezek Z et al, concluded that IUGR was associated with higher lipid levels (Apo lipoproteins).[23] In two other studies, minor changes (TC) were observed in SGA cord blood.[22,24] In contrary to this study and Pecks et al study, Diaz M et al, reported higher HDL cord blood levels in SGA neonates compared to normal neonates.[25] Spencer et al, and Pecks et al, showed a significant decrease of esterified cholesterol and TC concentrations in cord blood of IUGR as compared to a control group.[4,26]

The strength of present study was its good sample size, meticulous data collection, standardization blood test analysis and interpretation of the results. However, it had had some limitations. We did not observe direct effects of maternal nutrition, supplements, drugs during pregnancy, maternal short term illness, prematurity and maternal stress during pregnancy. Additionally, it was an observational study and only Indian women were included, therefore the generalizability is a limitation.

CONCLUSION

Mothers with IUGR fetus had lower cholesterol levels during 3rd trimester of pregnancy and their cord blood had lipid levels with atherogenic indices. IUGR pregnancy had relation to extremes of maternal age, higher parity, smoking, and poor weight gain during pregnancy.

Implication for Practice includes intrauterine growth restricted babies' needs to be evaluated for atherogenic lipid profile at birth and should be followed up.

PIH has altered lipid metabolism and associated with intrauterine growth retardation.

Indian mothers with intrauterine growth retardation had lower cholesterol levels and cord blood of them had atherogenic phenotype. IUGR pregnancy had relation to extremes of maternal age, higher parity, smoking, poor weight gain and higher blood pressure during pregnancy.

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