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A Cross-Sectional Study of Lipids and Lipoproteins in Pregnancies with Intrauterine Growth Retardation

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OBJECTIVE – To study the blood rheology of otherwise uncomplicated IUGR pregnancies and its comparison with that in normal pregnancies. **METHOD** – The present study is a cross-sectional study in which the lipoprotein profile of 25 women with IUGR pregnancies was compared with that in 25 women having normal pregnancies. Serum lipid profile estimations were performed by enzymatic method using infinite lipid kits from Accurex Biomedical Pvt. Ltd. Results were analyzed using standard statistical methods. **RESULTS** – Serum cholesterol, serum triglycerides, serum LDL cholesterol and VLDL cholesterol were observed to increase with increasing gestational age in normal pregnancies while all these decreased with increasing gestational age in pregnancies with intrauterine growth retardation. HDL cholesterol decreased with increasing gestational age (at sampling) in normal pregnancies as compared to an increase in pregnancies complicated with IUGR but there was no statistically significant correlation between increasing gestational age and HDL cholesterol values in both study and control group. Serum cholesterol and LDL cholesterol of women with IUGR were significantly lower as compared to those in normal women. **CONCLUSION** – Pregnancies having IUGR are associated with an abnormal lipid profile, particularly decreased levels of serum cholesterol, serum triglycerides, LDL cholesterol and HDL cholesterol. This may be responsible for abnormal substrate availability to and utilization by the fetus.

Key words : lipoproteins, pregnancy, intrauterine growth retardation.

Introduction

Pregnancy is associated with significant variation in blood rheology (lipid metabolism), consequent mainly to changes in lipoprotein profile[1-3]. Although these changes were first described in 1845 by Bacquerel and Rodier, the exact elucidation of these changes is yet to be defined[4]. An extensive review of the literature has revealed conflicting observations and implications of lipoprotein metabolism on normal and abnormal pregnancies[6]. Both genetic and non-genetic (hormonal) factors have been implicated for the changes in lipid metabolism during pregnancy. Many studies in the recent past have also incriminated abnormal lipid metabolism during pregnancy in the pathogenesis of atherogenesis and ischemic heart licence (IHD) due to changes in maternal microcirculation[1]. Similar, but yet unclear changes have also been ascribed to development of intrauterine growth retardation associated in pregnancies complicated with pre-eclampsia[5, 7-9]. The role of lipid metabolism in intrauterine growth retardation during otherwise normal pregnancy has been recently studied[2,10]. But these studies have not been able to clearly define the role of lipid metabolism in pathogenesis of intrauterine growth retardation during normal pregnancy and there is still a dearth of literature on this aspect. The precent study was undertaken to unravel the role of lipid metabolism and specifically some of the aspects of lipoprotein metabolism in intrauterine growth retardation during otherwise normal pregnancy.

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Material and Methods

The study was conducted from October 2000 to May 2001. The study group comprised of 25 women with pregnancy complicated by IUGR in third trimester detected by sonographic examination by an expert (Obstetrician / Radiologist). Twenty-five appropriately matched women with normal pregnancy in third trimester served as control (Table I). Pregnancies with pregnancy induced hypertension, pre-eclampsia, maternal diabetes, maternal alcohol consumption > 20 gm/day, fetal congenital anomalies or malformations, maternal hepatic/renal/thyroid diseases and any other confounding factor which may affect fetal nutrition and growth were excluded from the study. The purpose of interrogation and investigation was explained to every mother and her informed consent was obtained. The weight and height of all mothers were measured and body mass index was calculated. Blood for lipid profile and other investigations was obtained by vene-puncture

Table 1. Maternal Characteristics of Group A and Group B

	Group A (Study group) (n=25)	Group B (Control group) (n=25)	P Value
Age (years)	23.03 ± 3.1	23.3 ± 2.7	NS
Parity (nulli/multiparous)	13/12	15/10	NS
Rural/Urban	12/13	10/15	NS
BMI	22.1 ± 1.6	22.2 ± 1.9	NS
Gestational age at sampling (weeks)	34.1 ± 3.2	33.8 ± 3.0	NS
Gestational age at birth (weeks)	39.2 ± 0.8	39.5 ± 0.70	NS
Birth weight (gm) of neonate	2180 ± 156.7	2894±282.6	P<0.001
Ponderal index of neonate	2.03 ± 0.09	2.6 ± 0.19	P<0.001

Table II. Changes in Lipid and Lipoprotein Concentrations with Increasing Gestational Age at Sampling

	Group A			Group B		
	Gestational age in weeks			Gestational age in weeks		
	28-31 (n=6)	32-36 (n=13)	37-40 (n=6)	28-31 (n=7)	32-36 (n=11)	37-40 (=7)
Serum Cholesterol (mg/dL)	216.3 ± 29.2	202.5 ±26.0[a]	191.5 ± 34.5[b]	238 ± 17.0	250.7 ± 27.6[a]	260.3 ± 23.6[b]
Serum Triglycerides (mg/dL)	173.83 ± 78.18	168.23 ± 51.73	137.83 ± 18.25	148.25 ± 15.31	160.36 ± 24.43	171.14 ± 41.56
HDL Cholesterol (mg/dL)	42.0 ± 5.3	43.0 ± 4.4	46.4 ± 3.2	44.4 ± 4.5	43.0 ± 6.0	41.6 ± 8.2
LDL Cholesterol (mg/dL)	139.4 ± 23.9[e]	126.3 ± 21.8[c]	117.0 ± 31.8[d]	165.9 ± 26.5[e]	174.8 ± 26.5[c]	184.5 ± 23.4[d]
VLDL Cholesterol (mg/dL)	34.76 ± 15.63	33.64 ± 10.34	27.26 ± 3.81	29.77 ± 3.06	32.05 ± 4.91	34.22 ± 8.31

[a] – p<0.001 [b] – p<0.001 [c]- p <0.01 [d]– p < 0.001 [e] – p <0.05

Table III. Lipid and lipoprotein concentrations in women with IUGR (group A) and in normal pregnancy (Group B)

Lipoprotein concentration (mg/dL)	Group A (n-25)	Group B (n=25)	*P* value
Serum cholesterol	203.2 ± 28.9	249.8 ± 24.6	P<0.001
Serum triglyceride	162.3 ± 53.7	160.1 ± 28.5	NS
HDL cholesterol	43.6 ± 4.6	43.0 ± 6.2	NS
LDL cholesterol	127.2 ± 25.1	175.0 ± 24.4	P < 0.001

in sitting posture after an overnight fasting. After delivery, a detailed examination of newborns including anthropometry was performed. IUGR in this study was defined as birth weight < 10th percentile for gestational age as determined by Lubchenco's charts.

Serum lipid profile estimations were performed by enzymatic method using infinite lipid kits from Accurex Biomedical Pvt Ltd. Results were analyzed using standard statistical methods.

Results and Analysis

The mean age of mothers in the study group was 23+3.08 years as compared to 23.36±2.67 years in the control group. However, the difference between the groups was not statistically significant. There was also no statistically significant difference between the mean weight, body mass index and gestational age at sampling between the study and the control groups. The mean gestational age of the babies in the study group at birth was 39.36 ± 0.81 weeks as compared to 39.56 ±0.76 weeks in the control group, but the difference was not statistically significant. The ponderal index of babies delivered in the study group was 2.03 ± 0.09, while it was statistically significantly higher at 2.6 ± 0.19 (p<0.001) in the control group. Women with IUGR pregnancies also gave birth to babies with significantly lower birth weight (2180 ± 156.70 gms) as compared to women in the control group (2894±282.59 gms) (p<0.001, Table I). In the present study a detailed analysis of effects of parity on lipoprotein metabolism revealed no statistically significant difference between lipid profile of multiparous women as compared to that of nulliparous women in both the groups. Similarly, no statistically significant effect of age, residence and weight of mothers was observed on lipid profile in the two groups.

Interstingly, serum cholesterol, serum triglycerides (TGL), serum LDL cholesterol and VLDL cholesterol were observed to increase with increasing gestational age (at sampling) in normal pregnancies while all these decreased with increasing gestational age (at sampling) in pregnancies with intrauterine growth retardation. HDL cholesterol decreased with increasing gestational age (at sampling) in normal pregnancies while it increased in pregnancies complicated with IUGR (Table II). But there was no statistically significant correlation between increasing gestational age and HDL cholesterol values in both the groups. Serum cholesterol and LDL cholesterol of the study group (203.2 ± 28.95; 127.25 ± 25.11) were significantly lower (p<0.001) as compared to those of the control group (249.94 ± 24.58; 175.04 ±24.46). However, there was no statistically significant difference between the serum triglycerides (TGL), HDL and VLDL cholesterol values of the two groups (Table III). It was also observed that the serum total cholesterol levels of the study group were also significantly lower as compared to those of the control group at sampling gestational ages of 32-36 weeks (202.5±26.0 and 250.2 ±27.6; p<0.001) and 37-40 weeks (191.5 ±34.5 and 260 ± 23.6; p<0.001) (Table II). The difference between the serum total cholesterol at 28-31 weeks between the study and control group was not statistically significant. Similar observations were also made with LDL cholesterol of study and control group at various gestational age (at sampling). At 32-36 weeks LDL cholesterol was 126.3 ± 21.8 mg/dL in the study group and 174.8± 26.5 mg/dL in the control group (p<0.01) while at 37- 40 week, LDL cholesterol values were 117 ± 31.8 mg/dL and 184.5 ± 23.4 mg/dL in the study and control group respectively (p<0.001). Also, no significant difference was observed between total serum TGL, HDL cholesterol and VLDL cholesterol values in the two groups at various gestational ages (at sampling).

Discussion

In the recent past, many studies have focused on the relationship between blood rheology during preeclampsia and its effect on fetal growth [2,11-13]. It is now well established that the rise in lipid and lipoprotein levels is substantially higher during preeclampsia leading to an assumption that these changes may have a role in producing endothelial

damage characteristic of pre-eclampsia which may be responsible for IUGR. Interestingly, a review of recent literature reveals that there may also be some relationship between blood lipid and lipoprotein profiles during otherwise normal pregnancy associated with IUGR[10,14]. However, these changes are yet poorly understood because of a lack of specific research elucidating the mechanism of this phenomenon. In the present study, it was observed that the concentration of serum cholesterol, serum TGL, LDL cholesterol and VLDL cholesterol in pregnancies associated with normal birth weight increased with increasing gestational age at sampling, while HDL cholesterol levels did not change significantly. Similar observations have also been reported in studies conducted by Potter and Nestel[13], van Stiphout et al[15], Fahraeus et al[16], Knopp et al[17] and Jimenez et al[18].

We also observed that in both the groups there was no statistically significant difference between the lipid concentrations when analyzed separately for maternal age, weight, parity and place of residence. This indicates that there was no significant influence of these factors on lipid profile in both the groups. In the present study, it was revealed that serum cholesterol, serum TGL, LDL cholesterol and VLDL cholesterol in pregnancies associated with IUGR decreased with increasing gestational age. The HDL cholesterol levels increased slightly from early 3rd trimester until late 3rd trimester. It was also observed that the levels of total cholesterol and LDL cholesterol were significantly lower in pregnancies associated with intrauterine growth retardation as compared to those in the control group. However, the levels of serum TGL and HDL cholesterol were comparable in both the groups during third trimester. Our findings certainly indicate that pregnancies having intrauterine growth retardation are associated with an abnormal lipid profile, particularly decreased levels of serum cholesterol, serum TGL, LDL cholesterol and HDL cholesterol. Munoz et al[14] in their study observed that plasma TGL, LDL cholesterol and total cholesterol increase progressively throughout pregnancy with significantly higher values after 25th week of gestation. They concluded that apolipoprotein A and TGL concentration were significantly lower in the IUGR group than in the normal group. The HDL / Apo A ratio in their study was higher in the IUGR group than in the control group, as was the Apo B / Apo A ratio. They concluded that hemorheological modifications in the IUGR group are partly secondary to changes in HDL metabolism and the competitive inhibition of fibrinolysis by Apo B which is increased in pregnancies with IUGR. They indicated that Apo A / Apo B ratio could be good markers for the early detection of IUGR.

For technical reasons we could not analyze the levels of Apo B and Apo A, but like Munoz et al[14] we also observed a significant decrease in plasma TGL in pregnancies associated with IUGR. However, for unexplained reasons there was also a lower concentration of LDL and VLDL cholesterol in pregnancies associated with IUGR in our study.

In a review article, Herrara[10] stressed that during early pregnancy there is increased body fat accumulation associated with both hyperphagia and increased lipogenesis. During late pregnancy there is an accelerated breakdown of fat depots, which plays an important role in fetal development. Besides using placentally transferred fatty acids, the fetus is also benefited from glycerol and ketone bodies. Although glycerol crosses the placenta in small proportion, it is a preferential substrate for maternal gluconeogenesis and maternal glucose is quantitatively the main substrate crossing the placenta. Enhanced ketogenesis under fasting conditions and early transfer of ketones to the fetus allow maternal ketone bodies to reach the fetus to be used as fuel for oxidative metabolism as well as lipogenic substrate. Although maternal cholesterol is an important source of cholesterol for the fetus during early gestation, it is of less importance during late pregnancy owing to the high capacity of fetal tissues to synthesize cholesterol. Maternal hyper-triglyceridemia is a characteristic feature during normal pregnancy and corresponds to an accumulation of triglycerides not only in VLDL but also in LDL and HDL. Although TGL do not cross the placenta, the presence of lipoprotein receptors in the placenta, along with lipoprotein lipase, phospholipase and intracellular lipase activities allow the release of polyunsaturated fatty acids to the fetus, transported as TGL in maternal plasma lipoprotein. It is well known that normal fetal development needs the availability of both essential fatty acids and long chain polyunsaturated fatty acids, thus making a persuasive case indicating a relationship between nutritional status of mother during gestation reflecting her lipid profile and fetal growth.

In our study also, it is possible that the decreased concentration of serum cholesterol, serum TGL, VLDL and LDL cholesterol may have decreased the availability of glycerol, long chain polyunsaturated fatty acids and essential fatty acids to the fetuses of mothers with otherwise normal pregnancy ultimately leading to intrauterine growth retardation. Since, in the present study, we did not perform a detailed dietary analysis of our patients, we are unable to comment on the reasons for decreased LDL, VLDL and serum total cholesterol in our study. We are also unable to comment on the status of apolipoprotein B and its exact contribution to intrauterine growth retardation in our study. Besides,

like Munoz et al[14], we are also not clear regarding the exact reason for such low lipid levels in IUGR pregnancies observed in our study.

Sattar et al[19] proposed that women destined to develop IUGR had lower starting cholesterol levels during early pregnancy. They also observed that apart from decrease in LDL cholesterol, there was also a decrease in levels of $VLDL_2$ and intermediate density lipoproteins (IDL) in IUGR pregnancies, which are precursors of LDL. It may, therefore, be possible that in our study decreased cholesterol levels (reflected mainly as decreased LDL cholesterol) may be due to decreased synthesis of LDL cholesterol in women with IUGR. It has already been pointed that in IUGR pregnancies, TGL synthesis in liver (as $VLDL_1$) is maintained at the cost of $VLDL_2$ (precursor of LDL) leading to a decreased synthesis of LDL cholesterol in liver. However, even with the aforementioned studies it is very difficult to say whether substrate deficiency caused decreased fetal growth or decreased fetal growth was in itself responsible for decreased LDL cholesterol levels which may have been diverted for maintaining fetal nutrition during periods of growth in the third trimester.

Our study definitely generates considerable interest in certain aspects of fetal growth and its relationship to blood lipid levels during pregnancy. It is however, still not certain which came first, hen or egg. Certain components of our body lipids such as serum triglycerides definitely reduce in IUGR pregnancies but the reason for this decrease is not very obvious. It can be hypothesized that this decrease in serum TGL (and probably LDL cholesterol and $VLDL_2$ cholesterol) compromises the supply of substrate for energy production to the growing fetus resulting in IUGR. The effects of this change in lipid profile and its translation in changes in blood viscosity needs more extensive research including a detailed analysis of Apo lipoprotein B and A levels in these patients. We, therefore, recommend more similar studies aimed at analyzing the otherwise normal pregnancies associated with IUGR and the individual effect of this component on fetal growth.

References

1. Brizzi P, Tonolo G, Esposito F et al. Lipoprotein metabolism during normal pregnancy. *Am J Obstet Gynecol 1999;181:430-4.*
2. Sattar N, Gaw A, Packard CJ, et al. Potential pathogenic roles of aberrant lipoprotein and fatty acid metabolism in pre-eclampsia. *Br J Obstet Gynecol 1996;103:614-20.*
3. Kuzawa CW, Adair LS. Lipid profiles in adolescent Filipinos: relation to birth weight and maternal energy status during pregnancy. *Am J Clin Nutr 2003; 77:960-6.*
4. Tonolo G, Ciccarese M, Brizzi P et al. Cyclical variation of plasma lipids, apolipoproteins and lipoprotein A during menstrual cycle in normal women. *Am J Physiol 1995;269:E 1101-5.*
5. Winkler K, Wetzka B, Hoffmann MM et al. Triglyceride-rich lipoproteins are associated with hypertension in preeclampsia. *J Clin Endocrinol Metab 2003;88:1162-6.*
6. Sitadevi C, Patrudu MB, Kumar YM et al. Longitudinal study of serum lipids and lipoproteins in normal pregnancy and puerperium. *Trop Geogr Med 1981;33:319-23.*
7. Cong KJ, Wang TT, Liu GR. Lipid metabolism and pregnancy induced hypertension. *Zhonghua Fu Chan Ke Za Zhi 1994;29:651-3 and 697-8.*
8. Franz H, Wendler D. A controlled study of maternal serum concentration of lipoproteins in pregnancy induced hypertension. *Arch Gynecol Obstet 1992;252:1-6.*
9. Ogura K, Miyatake T, Fukui O et al. Low-density lipoprotein particle diameter in normal pregnancy and preeclampsia. *J Atheroscler Thromb 2002;9:42-7.*
10. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. *Endocrine 2002;19:43-55.*
11. Franz, Wendler D. A controlled study of maternal serum concentration of lipoproteins in pregnancy induced hypertension. *Arch Gynecol Obstet 1992;252:81-6.*
12. Kontineen A, Pyorala T, Carpen E. Serum Lipid pattern in normal pregnancy and pre-eclampsia. *Br J Obstet Gynecol 1964;71:453-7.*
13. Potter JM, Nestel PJ. The hyperlipidemia of pregnancy in normal and complicated pregnancies. *Am J Obstet Gynecol 1979;133:165-70.*
14. Munoz A, Uberos J, Molina A et al. Relationship of blood rheology to lipoprotein profile during normal pregnancieis and those with intrauterine growth retardation. *Clinical Pathol 1995;48:571-4.*
15. van Stiphout WA, Hofman A, De Bruijin AM. Serum lipids in young women before during and after pregnancy. *Am J Epidemiol 1997;126:922-8.*
16. Fahraeus L, Larsson-Cohn U, Wallentin L. Plasma lipoproteins including high density lipoprotein

subfractions during normal pregnancy. *Obstet Gynecol 1995;66:468-72.*

17. Knopp RH, Warth MR, Charles D et al. Lipoprotein metabolism in pregnancy, fat transport to the fetus and the effect of diabetes. *Biol Neonate 1996;50:297-317.*

18. Jimenez DM, Pocovi M, Ramon CJ et al. Longitudional study of plasma lipids and lipoprotein cholesterol in normal pregnancy and puerperium. *Gynecol Obstet Invest 1988;25:158-64.*

19. Sattar N, Greer IA, Galloway PJ et al. Lipid and Lipoprotien concentration in pregnancies complicated by intrauterine growth retardation. *J Clin Endocrinol Metab 1999;84:128-30.*