IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 8 Ver. 9 (August. 2018), PP 24-28
www.iosrjournals.org

Lipid Profile in Normotensive and Hypertensive Pregnant Women-A Randomized prospective study

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Abstract: *Hypertension (HTN) during pregnancy is one of the leading causes of maternal and perinatal morbidity and mortality. The aim of our study was to evaluate the alteration of serum lipid profile during normotensive and hypertensive pregnancy.*
A cross-sectional comparative study was performed at tertiary care teaching hospital. Blood samples were collected from normal pregnant women(Group 1, n=50) & women with already diagnosed preeclampsia(Group 2, n=50) in third trimesters of pregnancy& concentration of serum triglyceride, VLDL, LDL, totalcholesterol & HDL was compared.
Results: *Group2 was associated with a significant rise in triglyceride (208.80±7.30 mg%vs. 109.20±1.29 mg %) compared to group1. There wasfall in mean HDL cholesterolconcentration in group2 (37.52 ± 0.74 mg % as against 38.9 mg ± 0.37mg % in group1) (P<0.05). The mean values of total cholesterol in normotensives was 169.74 ± 3.98 mg/dl and in hypertensive 235.40±6.02 mg %) (P<0.0001). Also LDL-cholesterol was significantly increased in group2 (mean 153.88±6.21mg %) and 129.94 ± 3.73 mg % in group1 (P < 0.0001). Very LDL-C was significantly increased in hypertensive pregnancies with mean 45.36 ± 1.99) mg% while in normotensives it was 22.24± 0.71 mg%.*
We conclude that human gestation is associated with an 'atherogenic' lipid profile that is further enhanced in preeclampsia and this profile may be a potential contributor to endothelial cell dysfunction.
We recommend that pregnant female with serum lipid concentrations higher than normal pregnancy should be suspected to development of preeclampsia.
Keywords: *Normal pregnancy, Dyslipidemia, Lipid Profile, Atherosclerosis, Preeclampsia, High Density Lipoproteins, Triglycerides, Low Density Lipoprotein, Very Low Density Lipoprotein, Total Cholesterol, Endothelial dysfunction.*

Date of Submission: 08-08-2018 Date Of Acceptance: 22-08-2018

I. Introduction

Hypertension during pregnancy (Pregnancy induced hypertension-PIH) is a major health problem. It is one of the leading causes of maternal and perinatal morbidity and mortality [1, 2]. It complicates 10-15% of all pregnancies [3]. The etiology and pathogenesis of pre-eclampsia remains to be elucidated. Until date, endothelial dysfunction in the placental vasculature is considered as a widely accepted theory for the etiology and pathogenesis of the disease. Several other factors including genetic, immune, vascular and oxidative stress are also implicated in the pathogenesis of pre-eclampsia [1].

Human pregnancy is associated with pronounced physiological hyperlipidaemia[4]. In normal pregnancy this feature is not atherogenic and is believed to be under hormonal control [5]. Studies have shown that in preeclampsia, plasma lipids climb substantially above levels seen in normal pregnancies [3, 4]. Such lipid changes may play a role in the endothelial damage characteristic of preeclampsia. It has also been shown that altered levels of serum lipids in early pregnancy increase the risk of PIH [3, 4].

This association may be significant in understanding the process of pre-eclampsia and may help in developing strategies for its prevention and early diagnosis.

The high levels of lipid indexes raise a question: whether hypercholesterolemia and hypertriglyceridemia of pregnancy must be cured or not. Therefore, the present study was designed with an aim to investigate the alteration in serum lipid profile including triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL)-cholesterol in pre-eclamptic and normal pregnant women.

II. Material And Methods

Study Design: This is a prospective randomized double blind hospital-based comparative study. Subjects were recruited from antenatal cases attending Obstetrics &Gynaecology Department, DrShankarraoChavan Govt. Medical College & hospital, Vishnupuri, Nanded (Maharashtra), a tertiary care teaching hospital.

Study Duration: The study was conducted within a period of 60 days from 1st May to 30th June 2017.
This was a prospective hospital-based comparative study. It was approved by the Institutional Ethical Committee of DrShankarraoChavan Govt. Medical College, Nanded. The study population comprised of 100 pregnant females, selected from those attending the Obstetrics and Gynecology department at tertiary care teaching hospital.

Inclusion criteria: Enrolment of the patients and controls for the study was done by twice daily visits to the antenatal clinics.The control group (Group-I: 50 Normotensive pregnant women) comprised consecutive samples of pregnant women of age 18-40 years, followed-up at our setting and undergoing third-trimester blood analysis and with none of the exclusion criteria.The study group (Group-II: 50 pre-eclamptic or eclamptic subjects) comprised preeclamptic patients diagnosed by the presence of persistent hypertension (more than 140/90 mm of Hg), gross proteinuria (tested by heat test of urine), and pathological oedema. The eclamptic patients were diagnosed by the additional feature of convulsion or coma.All the study subjects belonged to third trimester.

Exclusion criteria: Pregnant patients with diabetes mellitus, heart disease, obesity, known renal disease, pre-existing hypertension and those with family history of hyperlipidemia were excluded from the study. Patients on treatment with drugs that may influence lipid profile, all maternal and/or fetal abnormalities expect PIH were excluded from this study in both control and test groups. The study procedure was explained to those pregnant females & those willing to participate in the study were enrolled. Written informed consent was obtained from all participants in the study.

Measurement of Body Mass Index-We measured body weight in kilogram & height in meters. Body Mass Index (BMI) was calculated using the formula; weight in kilogram divided by height in meter squared.

Measurement of blood pressure: Following a rest period of about 30 minutes in the hospital, the systolic and diastolic pressures were measured in each subject on the brachial artery using auscultatory method using mercury sphygmomanometer. Diastolic pressure was determined as the disappearance of the Korotkoff's sound.

Blood Sampling:A blood sample of 3 ml was collected from the subjects after an overnight fast from the cephalic vein, using sterile syringes into plain bottles and then the blood was allowed to clot at room temperature, serum then separated in sterile containers without anticoagulant and stored at 4 ^{0}C pending assay for lipid profile.

Chemical analysis: The blood was processed in biochemistry laboratory of DrShankarraoChavan Govt. Medical College & hospital, Vishnupuri, Nanded. Total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) & high density lipoprotein (HDL) cholesterol was estimated using commercially available enzymatic colorimetric test following the protocol & instructions of the manufacturer.The values obtained were compared between the hypertensive and normotensive groups.The normal values of lipid profile according to recent National Cholesterol Education Programme Guidelines were taken as follows:
TC: <200 mg/dl, LDL-C: <100 mg/dl, HDL-C: > 40 mg/dl
TGs: 35-<150 mg/dl, very LDL-C (VLDL-C):<30 mg/dl.

Sample size: By convenience sampling 100 pregnant women 50 normotensive & 50 with PIH were recruited.

Statistical analysis:Data was gathered in Excel sheets & presented as mean ± standard error mean (SEM). The descriptive data was analyzed using Student t- test, ; value of $p < 0.05$ considered statistically significant.
All statistical analyses were performed with openEpi software Version 3.01 (www.OpenEpi.com updated on 2013/04/06).

III. Result

Hundred subjects participated in the study with fifty subjects in study group and fifty in control group. The mean age for the subjects were 23.5 ±0.34 years for study group & 24.5 ±0.44 years for control group (Table 1). There were statistical difference ($p < 0.05$) between the body mass indices (BMI) for control and

study groups. Body mass index was significantly increased in all the study participants (Table 1).
In preeclampsia subjects, the mean systolic pressure was significantly higher than that of controls, whereas no significant differences were found in diastolic BP (Table 1).

The mean plasma lipid profile values for the control and the test subjects are shown in table 2. The results revealed that the levels of TG, total cholesterol, LDL cholesterol and VLDL cholesterol in women of study group were found significantly higher ($p < 0.05$) than the normal pregnant women at third trimester. Also, the study revealed significant decrease ($p < 0.05$) in HDL cholesterol when compared to the normal pregnant women at third trimester.

Table no 1: Distribution of patients according to their age, BMI, systolic and diastolic blood pressure in normal pregnancy and Pregnancy induced hypertension.

PatientParameter	Group 1 (n=50)	Group 2 (n=50)	*P* value
Maternal Age (Years)	23.5±0.34	24.5±0.44	0.074
BMI (kg/m^2)	23.38±0.44	25.35±0.32	0.027
Systolic BP (mmHg)	117.00±1.00	144.20±1.83	0.000042
Diastolic BP (mmHg)	76.60±1.29	96.80±1.047	0.14

Group 1- Normal pregnancy, Group 2- Pregnancy induced hypertension.
Values are Mean± SE
*-p value statistically significant
BMI- Body mass index.

Table no 2: Lipid Profile in normal pregnancy and preeclampsia Pregnancy induced hypertension.

Patient Parameter	Group 1 (n=50)	Group 2 (n=50)	*P* value
Triglyceride (mg%)	109.20±1.29	208.80±7.30	<0.0000001
Total Cholesterol (mg%)	169.74±3.98	235.40±6.02	0.0043
LDL- Cholesterol (mg%)	129.94±3.73	153.88±6.21	0.00050
VLDL- Cholesterol (mg%)	22.24±0.71	45.36±1.99	<0.0000001
HDL- Cholesterol (mg%)	38.90±0.37	37.52±0.74	0.0000032

Group 1- Normal pregnancy, Group 2- Pregnancy induced hypertension.
Values are Mean± SE
*-p value statistically significant

IV. Discussion

Preeclampsia is a triad of oedema, hypertension, and proteinuria occurring primarily in nulliparous after the 20th gestational week and most frequently near term [3]. Therefore we have selected subjects in third trimester of pregnancy rather than first or second trimester.

During pregnancy, all lipid fractions increase in parallel to the increase in pregnancy age [3]. This increase is secondary to the increase in estrogen and progesterone levels during pregnancy which induce biosynthesis of TG (Salameh and Mastrogiannis., 1994; Potter and Nestel., 1979) [5, 13, 21]. Moreover, previous studies demonstrated that, serum total cholesterol, triglyceride, and LDL cholesterol concentrations were increased in women with preeclampsia and this may contribute to endothelial cell dysfunction in preeclampsia [1].

The findings in our study suggest that the women with pre-eclampsia and eclampsia had disturbed lipid profile due to abnormal lipid metabolism. This association may be significant in understanding the pathological process of preeclampsia and may help in developing strategies for prevention and early diagnosis of pre-eclampsia and eclampsia.

Increased TG, found in pregnancy induced hypertension, is likely to be deposited in predisposed vessels, such as the uterine spiral arteries and contributes to the endothelial dysfunction, both directly and indirectly through generation of small, dense LDL [1, 11, 13]. Moreover, this hypertriglyceridemia may be associated with hypercoagulability [5, 11, 12, 15] In our study, in contrast to normal pregnant women, the rise in serum TG was statistically significant ($P<0.05$)

Women with a history of pre-eclampsia have significant differences in lipid parameters and an increased susceptibility to lipoprotein oxidation when compared with women who had normal pregnancy. In view of the above findings it is postulated that alteration of lipid metabolism may play a key role in the

development of symptoms of Pre-eclampsia and Eclampsia.

There was a positive correlation between preeclampsia and lipid parameters. Serum triglyceride concentration rise more significantly in pre-eclampsia in our study which corroborated with the findings of many research workers [11]. The pattern of triglyceride increase in this study is almost double the controls. In preeclampsia, the vascularization of the fetoplacental unit may be impaired, resulting in yet-undefined compensatory mechanisms that may further increase synthesis of maternal Triglyceride (TG) levels. In addition, the decreased catabolism of TG-rich lipoproteins by reduced placental uptake and the putative concomitant decrease of lipoprotein lipolysis results in the accumulation of TG-rich remnant lipoproteins in the maternal circulation.Remnant lipoproteins may induce platelet activation and endothelial dysfunction, thus leading to the major clinical symptoms of preeclampsia [14].

The principle modulator of this hypertriglyceridemia is oestrogen as pregnancy is associated with hyperoestrogenaemia. Oestrogen induces hepatic biosynthesis of endogenous triglycerides, which is carried by VLDL. This process may be modulated by hyperinsulinism found in pregnancy. Serum triglyceride concentration also rose much more significantly in toxaemia of pregnancy in our study which corroborated with the findings of many workers. The above mentioned interactions alongwith increased endothelial triglyceride accumulation may result in endothelial cell dysfunction.

Furthermore, the increase in cholesterol may be an adaptation by the body to serve its function as a precursor for the formation of the steroid hormones of pregnancy. The daily production of progesterone increases thirtyfold, while that of oestrogen increases tenfold during pregnancy. Progesterone increases plasma levels of LDL cholesterol and total cholesterol while lowering HDL-cholesterol but oestrogen has an opposite effect [5, 13, 21].

The VLDLC level, as reported by some researchers, might raiseupto 2.5 folds at term over the pre-pregnancy level. VLDL level further increase in PIH as evidenced in the present study in corroboration with those of other workers, perhaps due to increased VLDL lipoproteins which accumulate over the maternal vascular endothelium, particularly those of uterine and renal vessels. Further VLDL may cause injury to the endothelium.

Evidence of increased oxidative stress due to endothelial dysfunction in pre-eclampsia has been well-established. Increase in the oxidative stress is associated with abnormal lipid profile.We agree that in preeclampsia a combination of certain risk factors (increased small dense LDL and TG concentrations and reduced HDLc and apo A-I levels) may lead to the atherosclerotic process in decidual vessels.

Lipid peroxides are normally present in lipoproteins and seem to contribute to vascular tone regulation through stimulation of the arachidonic acid enzymatic pathways. Disorders of lipoprotein metabolism are reported to be a major cause of hypertension and proteinuria in Pre HDL is good cholesterol for our health as it regulates the BP towards normal levels. The decreased levels of HDL in the third trimester of hypertensive pregnant women in our study are in agreement with already published reports.

Inpreeclamptic patients oestrogen is responsible for induction of TG and HDL and suppression of serum LDL and oestrogen level falls in preeclampsia. The Low level of HDL in pre-eclampsia is however not only because of hypooestrogenaemia but also due to insulin resistance.

The limitation of this study could be the small sample size, antepartum dietary history was not taken in to account & the serum progesterone and estrogen concentrations of the subjects were not assessed.
It would be more appropriate to perform serial measurements of lipid levels to study patterns of their changes.

V. Conclusion

Our data suggest that an abnormal lipid metabolism and particularly high triglycerides, LDL-C, VLDL-C, total cholesterol and low HDL-C concentrations may have potential role in pathogenesis of preeclampsia. We conclude that the atherogenic profile, well tolerated by the mother during normal pregnancy, might disrupt the normal processes in the preeclamptic mother. Moreover, abnormal lipid profile may contribute to promotion of oxidative stress and vascular dysfunction seen in preeclampsia.

VI. Recommendation

Simple measurement of serum lipid parameters may be of good predictive value in toxaemia of pregnancy Further studies are needed to investigate the role of serial measurement of lipid profileas a screening test to predict development of PIH.Thus the assessment of blood lipids may behelpful in prevention of complications in PIH.

Lifestyle programs in women of reproductive age with a focus on lowering triglyceride levels (*i.e.* diet, weight reduction, and physical activity) may help to prevent hypertensive complications during pregnancy and adverse birth outcomes.

Acknowledgments

The authors wish to thank Department of Biochemistry for the biochemical evaluation. We are grateful to Head of Department of Obstetrics and Gynecology for their cooperation during conduct of study. Thanks to the participants those given consent for the research work.

Conflict of Interest: There is no conflict of interest for the study.

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Khadke ChaitaliVenkatesh "Lipid Profile in Normotensive and Hypertensive Pregnant Women-A Randomized prospective study."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 8, 2018, pp24-28.