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Biochemistry Section

Association of Lipid Profile and Uric Acid with Pre-Eclampsia of Third Trimester in Nullipara Women

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ABSTRACT

Background: Pre-eclampsia affects approximately 3% of all pregnancies worldwide, with onset of symptoms in the late second or third trimester, commonly after 32nd week. It is common in nulliparous women. To avoid complications it is necessary to diagnose it in advance, but the available tools are unable to clinch the diagnosis of preeclampsia effectively in majority.

Aim: To find out an association of lipid profile and uric acid with pre-eclampsia in nullipara pregnant women in third trimester.

Materials and Methods: One hundred nulliparous pregnant women in their third trimester of 18-35 years were divided into; 50 pre-eclamptics of study group and 50 non pre-eclamptic in control group; further subdivided according to age, 18-26 and 27-35 yrs. Diagnosis was confirmed as per the standard criteria. Lipid profile and uric acid levels were estimated by Vitros 250 dry chemistry analyser. Data was analysed statistically by student t-test at $p<0.01$ level of significance.

Results: TC, LDL-c and VLDL-c levels in the study group as a whole and in the patients between 18-26 years were significant; HDL-c levels in the patients between 27-35 years were significant while TG and uric acid levels in all the three study groups were significant.

Conclusion: Total cholesterol, LDL-c, VLDL-c, triglycerides and uric acid levels were raised in preeclampsia and statistically significant; while HDL-c levels were raised in these patients but statistically non-significant, it can be concluded that there exists an association in lipid profile and uric acid with pre-eclampsia therefore dyslipidemia and raised uric acid levels are the features of pre-eclampsia in nullipara pregnant women in their third trimester.

Keywords: Lipid profile, Preeclampsia, Uric acid

INTRODUCTION

Pre-eclampsia affects approximately 3% of all pregnancies worldwide [1], with onset of symptoms in the late second or third trimester, most commonly after the 32nd week. Pre-eclampsia is a multi-system disorder of pregnancy, which is characterised by new onset hypertension and proteinuria that develop after 20 weeks of gestation in previously normotensive women [2,3].

The disorder has a higher incidence among nulliparous women, in women who conceive with assisted reproduction techniques, and in women affected by autoimmune disorders, reflecting the probable influence of an "inexperienced" or dysregulated maternal immune system in its emergence [4,5]. On the other hand, women with pre-existing metabolic, vascular or renal disease are especially at increased risk for superimposed pre-eclampsia [6].

The mechanism of causation of preeclampsia is not well understood. The available tools for its diagnosis are effective only when the disease sets in, and in many cases at this stage; it becomes difficult to avoid complications. It is necessary to diagnose this condition in advance so that the future complications of mother as well as fetus may be prevented.

Early pregnancy dyslipidemia is associated with an increased risk of Pre-eclampsia. In pregnancy, lipolysis of TG-rich lipoproteins is reduced because of decreased lipolytic activities of the mother. In Pre-eclampsia, 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 PE [7].

There are several potential origins for uric acid in preeclampsia; abnormal renal function, increased tissue breakdown, acidosis and increased activity of the enzyme xanthine oxidase/dehydrogenase [8].

We have done an extensive review of the literature relating lipid profile and uric acid with pre-eclampsia. Several studies we found were conducted outside India, very few studies conducted on Indian population are available; so we decided, "To find out any possible correlation between lipid profile and uric acid level with pre-eclampsia in nullipara pregnant women in their third trimester".

OBJECTIVE

To find out an association of lipid profile and uric acid with pre-eclampsia in nullipara pregnant women in third trimester.

MATERIALS AND METHODS

Nulliparous pregnant women in their third trimester (25-36 weeks of gestation), attending Obstetrics and Gynecology Department, Chhatrapati Shivaji Subharti Hospital were enrolled and divided into study group (Pre-eclamptic) and control group (Normotensive with no proteinuria). Each group had 50 subjects. Clearance was obtained from the Institutional Ethical Committee and informed consent was obtained from every subject.

Patients with Diabetes Mellitus, Gestational Diabetes, Chronic hypertension (hypertension arising before 20 weeks gestation), Coronary artery disease, Hepatitis B infections, Human immunodeficiency virus (HIV) infection, Chronic obstructive

Distribution of Cases	Groups	Mean ± SD (mg/dl)	Probability of Unpaired t-Test	p-Value/ Significance
18-26 Yrs.	Study (n=43)	201.86±25.73	.0000	p<0.01 (significant)
	Control (n=46)	165.13±19.30		
27-35 Yrs.	Study (n=7)	192.42±38.12	.2390	p>0.01 (N.S.)
	Control (n=4)	170±20.84		
TOTAL	Study (n=50)	200.54±27.50	.0000	p<0.01 (significant)
	Control (n=50)	165.52±19.24		

[Table/Fig-1]: Total cholesterol level and its statistical significance in different groups

Distribution of Cases	Groups	Mean ± SD (mg/dl)	Probability of Unpaired t-Test	p-Value/ Significance
18-26 Yrs.	Study (n=43)	37.18±10.95	.2897	p>0.01 (N.S.)
	Control (n=46)	35.13±6.49		
27-35 Yrs.	Study (n=7)	42.85±12.41	.0001	p<0.01 (significant)
	Control (n=4)	32±7.11		
TOTAL	Study (n=50)	37.98±11.21	.0951	p>0.01 (N.S.)
	Control (n=50)	34.88±6.527		

[Table/Fig-2]:HDL cholesterol level and its statistical significance in different groups

Distribution of Cases	Groups	Mean ± SD (mg/dl)	Probability of Unpaired t-Test	p-Value/ Significance
18-26 Yrs.	Study (n=43)	117±25.75	.0046	p<0.01 (significant)
	Control (n=46)	103.17±19.30		
27-35 Yrs.	Study (n=7)	106.85±16.72	.0985	p>0.01 (N.S.)
	Control (n=4)	110.50±14.88		
TOTAL	Study (n=50)	116±24.82	.0074	p<0.01 (significant)
	Control (n=50)	104±19		

[Table/Fig-3]: LDL cholesterol level and its statistical significance in different groups

Distribution of Cases	Groups	Mean ± SD (mg/dl)	Probability of Unpaired t-Test	p-Value/ Significance
18-26 Yrs.	Study (n=43)	47.25±7.79	.0000	p<0.01 (significant)
	Control (n=46)	26.71±2.23		
27-35 Yrs.	Study (n=7)	51.57±8.05	.7201	p>0.01 (N.S.)
	Control (n=4)	27.50±1.73		
TOTAL	Study (n=50)	47.86±7.89	.0000	p<0.01 (significant)
	Control (n=50)	26.78±2.19		

[Table/Fig-4]: VLDL cholesterol level and its statistical significance in different groups

Distribution of Cases	Groups	Mean ± SD (mg/gl)	Probability of Unpaired t-Test	p-Value/ Significance
18-26 Yrs.	Study (n=43)	236.48±39.06	.0000	p<0.01 (significant)
	Control (n=46)	133.60±11.72		
27-35 Yrs.	Study (n=7)	257.85±40.29	.0001	p<0.01 (significant)
	Control (n=4)	138±9.89		
TOTAL	Study (n=50)	239.50±39.54	.0000	p<0.01 (significant)
	Control (n=50)	134±11.56		

[Table/Fig-5]: Triglyceride level and its statistical ignificance in different groups

Distribution of Cases	Groups	Mean ± SD (mg/dl)	Probability of Unpaired t-Test	p-Value/ Significance
18-26 Yrs.	Study (n=43)	8.195±1.170	.0000	p<0.01 (significant)
	Control (n=46)	4.658±0.839		
27-35 Yrs.	Study (n=7)	8.385±0.944	.0011	p<0.01 (significant)
	Control (n=4)	4.425±1.084		
TOTAL	Study (n=50)	8.222±1.1346	.0000	p<0.01 (significant)
	Control (n=50)	4.64±0.8506		

[Table/Fig-6]: Uric acid level and its statistical significance in different groups

pulmonary disease (COPD), Complicated and/or multiple pregnancies, women consuming antihypertensive medication, aspirin and / or corticosteroids, Undiagnosed patients and patients positive for urinary protein with urinary tract infection were not included in the study.

General information(s), detailed history, complete general and systemic examination and routine investigations were done in all subjects.

Sample was collected from the antecubital vein, aseptically through venipuncture. Hemolysed samples were discarded. Either the blood sample was immediately processed or stored in a fridge at 2-8°C. In some events the serum was separated, labeled and stored at -70°C. These samples were thawed prior to analysis.

Pre-eclampsia was diagnosed as a blood pressure level ≥ 140/90 mm of Hg; confirmed by at least two blood pressure measurements six hours apart and proteinuria ≥2+ by dipstick in "clean-catch-midstream" random sample of urine, collected at the time of enrollment.

Lipid profile including TC, TG, HDL-c, LDL-c, VLDL-c and Serum uric acid levels were investigated in all the subjects.

The serum was processed in Vitros-250 auto analyser using readymade dry chemistry kits procured from Ortho-Clinical Diagnostics, Johnson & Johnson, USA. Internal and external quality controls were followed as per NABL accreditation program. Levi-Jenning Plot was fed in Vitros 250 auto analyser and strictly followed. Samples giving readings above or below two SD were reprocessed / discarded.

All the data recorded was compiled and statistically analysed by using Mean, Standard deviation and Students t-test.

RESULTS

The present study was conducted on 100 nulliparous pregnant women in their third trimester between the ages 18 to 35 years; fifty were patients of pre-eclampsia in study group and 50 normotensive non-pre-eclamptic women in control group. Pre-eclampsia was diagnosed on the basis of history, clinical examination, blood pressure findings and presence of proteinuria. Subjects were distributed as; between 18-26 and 27-35 years.

In the study group 43 (86%) were in the age group 18-26 years and 7 (14%) were between 27-35 years of age while in the control group distribution of subject was 46 (92%) and 4 (8%) respectively.

Results and observations are given in [Table/Fig-1-6].

DISCUSSION

Definition of pre-eclampsia has changed with time. The initial international classification and definition of the hypertensive disorders of pregnancy compiled by Davey et al., in 1988 defined it to be having a diastolic blood pressure of 90 mm Hg on two occasions, or 110 mm Hg on a single occasion [9].

In pre-eclampsia the glomerular barrier is certainly altered and there is an increased excretion of protein including albumin. When total protein excreted (TPE) exceeds 1 g/24 hours or 1+ by dipstick, tubular protein reabsorption will be saturated and individual proteins excretion rates will be related to their molecular weights (Davison) [10].

We selected nullipara women for the present study as nulliparity is not only have high risk of pre-eclampsia but is the most common maternal risk factor which can easily be assessed just by the history. Duckitt et al., concluded in their study that nulliparity is not only the most common maternal risk factor but it has been shown to almost triple the risk of PE [11].

It was found that TC, LDL-c and VLDL-c levels in the study group as a whole and in the patients between 18-26 years were statistically significant at $p<0.01$ level of significance; while HDL-c levels were found raised in all the three subgroups in patients of pre-eclampsia compared to normotensive pregnant women and were found to be statistically significant only in patients between 27-35 years.

It was also observed that TG and uric acid levels were found raised in all the three subgroups in patients of pre-eclampsia as compared to normotensive pregnant women and that these levels in all the three study groups were statistically significant.

Wladimiroff et al., [12] and Cleusen et al., [13] obtained similar findings for lipid profile in Pre-eclamtic and Normotensive pregnancies.

Increased levels of triglycerides with reduced HDL-C have been observed in our study. Enquobahrie et al., [14] and Gractacose et al., [15]; in their respective studies concluded that hypertriglyceridemia is probably a consequence of competition between chylomicrons and very low-density lipoprotein (VLDL) cholesterol for the lipoprotein lipase.

The principle modulator of this hypertriglyceridemia is oestrogen as pregnancy is associated with hyperoestrogenaemia. Oestrogen induces hepatic biosynthesis of endogenous triglyceride which is carried by VLDL [16]. This process may be modulated by hyper insulinism found in pregnancy [17]. Serum triglyceride concentration increases much more significantly in pre-eclamtic pregnancy. Our study also corroborated with the findings of Equobohrie et al., [14] and Cekmen et al., [18].

The above mentioned interactions along with increased endothelial triglyceride accumulation may result in endothelial cell dysfunction [19]. Increased TG found in pregnancy induced hypertension including pre-eclampsia, 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 [20].

In the present study, serum VLDL-c level was also significantly higher ($p < 0.01$) in the third trimester of pre-eclamptic pregnancy which is probably due to hypertriglyceridemia leading to enhanced entry of VLDL that carries endogenous triglyceride into circulation. VLDL levels were also found increased in pre-eclampsia in the studies conducted by Kokio et al., and Teichmann et al., this is probably due to increased VLDL lipoproteins which accumulate over the maternal vascular endothelium, particularly those of uterine and renal vessels. The VLDL–c level as reported by some researchers might increases upto 2.5 folds at term over the pre-pregnancy level [21,22].

A significant higher level of LDL-c level, as was found in the present study, was also reported by Grratacos et al. and wakatsuki et al., in third trimester of pre-eclamptic pregnancy, may be attributed to hyperestrogenacmia [23].

Lipid metabolism is altered during pregnancy and is characterised by normal or even low cholesterol during early pregnancy and hypertriglyceridaemia in late pregnancy. The anabolic phase of early pregnancy produces metabolic changes that encourage lipogenesis and fat storage in preparation for the catabolic phase of late pregnancy in which there is rapid fetal growth. The insulin resistance of pregnancy increases lipolyis in adipose tissue, leading to an enhanced flux of fatty acids to the liver. This promotes the synthesis of very low density lipoproteins (VLDL) and as a result, increased triglyceride concentrations. In addition, insulin resistance reduces the activity of lipoprotein lipase an insulin dependent enzyme that is responsible for VLDL clearance from plasma. Therefore, VLDL remains in the plasma for longer and ultimately leads to accumulation of low density lipoprotein (LDL) [24].

In the past, uric acid was only considered as being the cause of gout; however, it is now increasingly thought of as a factor that can alter endothelial cell function. Hence, interest has been renewed in uric acid as a possible initiator of the maternal response in pre-eclampsia, rather than it being just a 'bystander' marker of the disorder. Over the past 10–20 years, a number of biochemical markers have been proposed to predict which women will develop preeclampsia. These markers include human chorionic gonadotropin, α-fetoprotein, urinary calcium, antiphospholipid antibodies, urinary kallikrein and homocysteine. In the past 5–10 years, additional factors, such as soluble endoglin, P1GF and cellular fibronectin have also been proposed as biomarkers for pre-eclampsia [25].These markers were identified based on the pathophysiological abnormalities associated with pre-eclampsia, including placental dysfunction, endothelial and coagulation activation and systemic inflammation. However, data regarding the reliability of these markers as predictors of the development of pre-eclampsia have been inconsistent, as most markers lack the specificity and sensitivity needed for routine clinical use [26].

It was observed from the present study that uric acid levels were not only found raised in all the three subgroups in patients of pre-eclampsia as compared to normotensive pregnant women but they were highly significant also. Lilliana Susanana et al., have made similar observations of higher levels of uric acid in serum of patients of pre-eclampsia which were statistically significant in their study which compared these levels in essential hypertensives, normal and pre-eclamptic women during pregnancy in their third trimester [27].

Serum uric acid is one of the parameters used in early diagnosis of preeclampsia. An elevated level of uric acid reflects the degree of placental cell destruction as well as severity of preeclampsia [28]. This may lead to decrease in the renal tubular excretion. Altered renal handling of urate clearance may be due to renal dysfunction and increased xanthine oxidase activity. Thus hyperuricemia in pre-eclampsia is primarily due to decreased renal clearance and increased tubular reabsorption of uric acid, because of the reduction in glomerular filtration rate [29,30].

AC Martin et al., concluded that increased uric acid concentrations may be part of the pathogenesis of the clinical syndrome rather than a marker of pre-eclampsia. Alternatively, production of uric acid might increase in pre-eclamptic women as part of an appropriate response to inflammation. The known role of uric acid as a scavenger of oxygen free radicals supports this theory [31].

Uric acid has important role in vascular damage and oxidative stress. Hyperuricemia may also reflect impaired endothelial integrity and contribute to the pathogenesis of pre-eclampsia. Hence, early estimation of serum uric acid might reduce systemic complications

and maternal deaths due to pre-eclampsia [28].

LIMITATIONS

1. Single sample was tested for lipid profile and uric acid levels.

2. Results were not compared with non pregnant women.

RECOMMENDATIONS

1. Sample should be drawn serially at definite intervals in third trimester and tested for lipid profile and uric acid levels.

2. A group including normal healthy non-pregnant women in same age should also be included in the study and their levels of lipid profile and uric acid be compared with the existing two groups.

CONCLUSION

Total cholesterol, LDL-c, VLDL-c, triglycerides and uric acid levels were raised in pre-eclampsia and statistically significant; while HDL-c levels were raised in these patients but statistically non-significant, it can be concluded that there exists an association in lipid profile and uric acid with pre-eclampsia therefore dyslipidemia and raised uric acid levels are the features of pre-eclampsia in nullipara pregnant women in their third trimester.

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