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Lipid profile parameters in normal and preeclampsia complicating pregnancies - A prospective observational study

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Abstract

This was an open labeled clinical study to compare the lipid profile in normotensive and hypertensive pregnant women. The study included two groups-50 normotensive and 50 preeclamptic pregnant women in whom fasting blood samples were sent for estimation of serum lipid profile during their third trimester. There was a significant increase ($p<0.5$) in total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides in preeclamptic group compared to normotensive group. There was a significant decrease in HDL cholesterol in preeclamptic group compared to normotensive group. This study in correlation with various other studies concluded that dyslipidemia plays an important role in the pathogenesis of preeclampsia.

Keywords: Lipid profile, preeclampsia, gestational hypertension

INTRODUCTION

Hypertension is the most common medical problem encountered in pregnancy and remains an important cause of maternal, and fetal, morbidity and mortality. The hypertensive disorders of pregnancy cover a spectrum of conditions, of which pre-eclampsia poses the greatest potential risk and remains one of the most common causes of maternal death Table-1 [1]. Preeclampsia is known to be a multi-system disorder of pregnancy [2]. The cardinal clinical features of the condition are hypertension and proteinuria occurring after 20 weeks gestation in women who were not previously known to be hypertensive. Other signs and symptoms include edema and headache, and in severe cases, the condition is associated with seizures (eclampsia), liver, and kidney dysfunction as well as clotting abnormalities, Adult Respiratory Distress Syndrome and fetal growth restriction (FGR) [3]. The incidence of preeclampsia varies widely from 5-15%. In India the incidence of preeclampsia is reported to be 8-10% of the pregnancies [4].

The association of alteration in serum cholesterol, triglycerides and HDL-C in essential hypertension is well documented. Various studies claim that abnormal lipid synthesis leading to increase of thromboxane level and the decrease of prostaglandin levels as well as the imbalance of lipid peroxidase and antioxidants is responsible for preeclampsia Table-2 [5-7]. The characteristic preeclampsia uteroplacental lesion is similar to atherosclerotic lesions; both display vessel wall necrosis and accumulation of lipid laden foam cells, a hallmark of oxidized low-density lipoproteins (LDL) [8].

Metabolic Factor

Recent studies have indicated a relationship between elements of the metabolic syndrome such as elevated serum triglycerides and free fatty acids, insulin resistance and glucose intolerance and the occurrence of preeclampsia. Fatty acids may contribute to endothelial dysfunction by serving as substrates to generate lipid peroxides that are significantly increased in plasma from women with preeclampsia. Therefore, the generation of free radicals, lipid peroxides, and reactive oxygen species may be an important mechanism

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Table 1. Classification of Hypertension in Pregnancy

Classification	GA	Definition
Chronic hypertension	≤20 wk	SBP≥140 mm Hg, or DBP>90 mm Hg at ≤20 wk GA, and/or hypertension diagnosed at any time during pregnancy, with persistence after 12 wk postpartum
Preeclampsia	≥20 wk, with documentation of normal BPs before 20 wk	**Mild preeclampsia** • SBP≥140 or DBP≥90 on 2 occasions≥6 hr apart • Proteinuria≥300 mg over 24 hours or≥1+protein on dipstick if 24-hr urine unavailable **Severe preeclampsia** • SBP>160 or DBP≥110 on 2 occasions ≥6 hours apart, and/or • Proteinuria>5 grams protein over 24 hr or ≥3+ protein on 2 random urine samples that are collected ≥4 hours apart, or • End-organ signs or symptoms
Preeclampsia superimposed on chronic hypertension	≥20 wk	**Patients without prior proteinuria** • Development of new-onset proteinuria after 20 wk GA **Patients with prior proteinuria** • Sudden increase in proteinuria • Sudden increase in BP that was previously well controlled • Thrombocytopenia (≤100,000 platelets/mm^3) • Elevated liver function tests
Gestational hypertension	≥20 wk	• SBP≥140 or DBP ≥ 90 • Absence of proteinuria
Transient hypertension of pregnancy	12 wk postpartum	Diagnosis of gestational hypertension during pregnancy with normalization of BP by 12 wk postpartum

Abbreviations: BP=Blood pressure; DBP= diastolic blood pressure; GA=Gestational age; SBP=systolic blood pressure.
Data from National High Blood Pressure Education Program Working Group[2]; ACOG committee on Practice Bulletins-Obstetrics[3] ;ACOG Committee on Practice Bulletins[4]

contributing to endothelial dysfunction in preeclampsia .Although plasma levels of lipids are increased during normal pregnancy, plasma concentrations of both triglyceride-rich lipoproteins and nonesterified fatty acids are significantly increased in women that develop preeclampsia relative to normal pregnant women. This significantly increased plasma triglycerides in women with preeclampsia correlates with an increased plasma concentrations of low-density lipoprotein. The nature of this correlative data has provided difficulty in determining a causal effect for abnormal lipid metabolism in the pathogenesis of preeclampsia [9-10].

Lipid Metabolism In Pregnancy

Maternal accumulation of fat depots and hyperlipidemia are the two principal changes in lipid metabolism that occur during pregnancy [10]. Moreover, essential fatty acids (EFAs) and long-chain polyunsaturated fatty acids (LCPUFAs) are needed for fetal growth and development, and must be obtained from maternal circulation.

Maternal fat accumulation:

The accumulation of fat in maternal depots occurs during the first two-thirds of gestation. Maternal hyperphagia increases the availability of substrates, which together with higher insulin levels and even enhanced insulin sensitivity during early pregnancy, results in enhanced lipogenesis [11]. A second factor that appears to contribute to the accumulation of fat depots during early pregnancy is the increased activity of adipose tissue lipoprotein lipase (LPL) [12]. This enzyme, anchored in its active form in the capillary endothelium of extra hepatic tissues, hydrolyzes TAG circulating in plasma in the form of TAG-rich lipoproteins (i.e., chylomicrons and VLDL), and the hydrolytic products, fatty acids and glycerol, are mostly taken up by the subjacent tissue .In this way, LPL activity being a prerequisite for the uptake of fatty acids from circulating TAG by adipose tissue, its increase during early pregnancy would also contribute to the accumulation of lipids in maternal depots.

The increase in fat depot accumulation stops or even declines during the last third of gestation, as a consequence of both enhanced adipose tissue lipolytic activity and decreased adipose tissue LPL activity. Thus, the anabolic condition present in adipose tissue during early pregnancy switches to a net breakdown of maternal lipids, which is coincident with the highest rate of fetal growth. [13].

Table 2. Risk factors –NICE and PRECOG Guidelines

NICE guideline 2008	Pre-eclampsia community guideline (PRECOG)
Previous pre-eclampsia	Previous pre-eclampsia
Multiple pregnancy	Multiple pregnancy
	Underlying medical conditions
Pre existing vascular disease such as hypertension or pre existing renal disease	Pre existing hypertension or booking diastolic pressure ≥90mmHg
	Pre existing renal disease ≥+ on more than one occasion or ≥ 300mg per 24hrs
	Pre existing diabetes
	Presence of anti phospholipid antibodies
	OR
	Any two of the following:
Nulliparity	Nulliparity
Pregnancy interval of more than 10 years	Pregnancy interval of more than 10 years
Age≥ 40 years	Age≥ 40 years
Body Mass Index ≥30	Body Mass Index ≥35
Family history of pre eclampsia	Family history of pre eclampsia (mother/sister)
	Booking diastolic pressure ≥80 and ≤90mmHg

Table 3 : ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL). Optimal/Near-Optimal, Borderline, and High-Risk Serum Lipid Concentrations

Lipid	Optimal/near-optimal serum concentration	Borderline serum concentration	High-risk/very high-risk serum concentration
TC, mg/dL	<200	200-239	≥240
HDL-C, mg/dL	≥60 (negative risk factor)	40-59 (men) 50-59 (women)	<40 men <50 women[b]
LDL-C, mg/dL	<100 optimal (100-129 near-optimal)	130-159	160-189 high ≥190 very high
TG[a], mg/dL	<150	150-199	200-499 high ≥500 very high

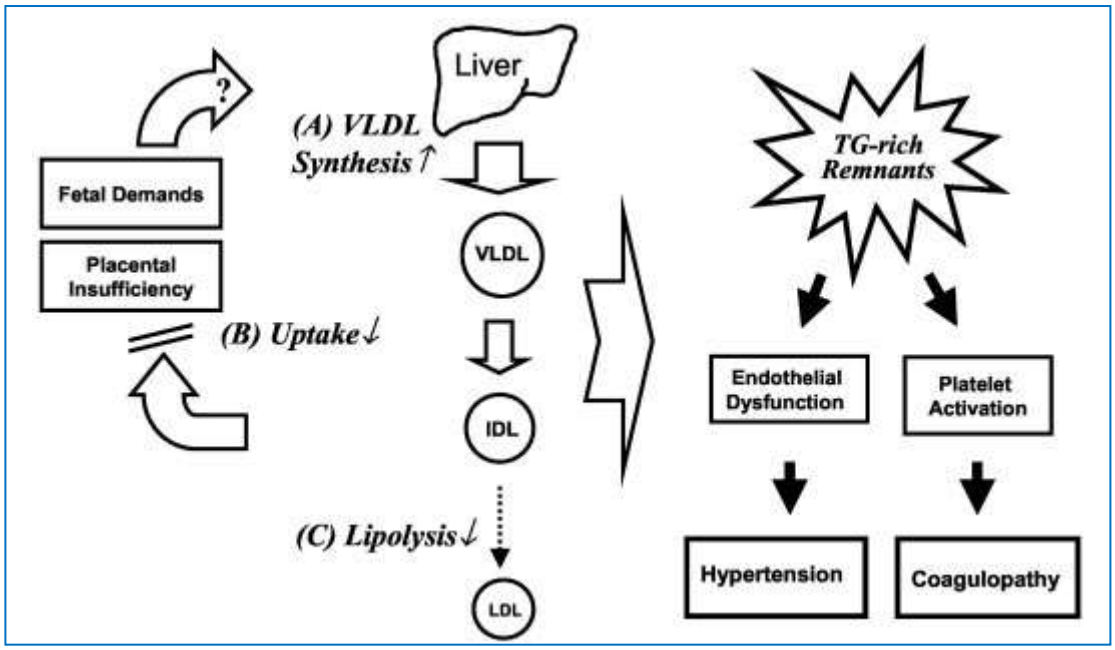
Lipid Metabolism In Preeclampsia (Figure-1)

In pregnancy, lipolysis of TG-rich lipoproteins is reduced because of decreased lipolytic activities of the mother, whereas placental VLDL receptors are up-regulated. This results in a rerouting of TG-rich lipoproteins to the fetoplacental unit (Table-3). However, in PE, the vascularization of the fetoplacentalunit may be impaired, resulting in yet-undefined compensatory mechanisms that may further increase synthesis of maternal TG levels (A). In addition, the decreased catabolism of TG-rich lipoproteins by reduced placental uptake (B) and the putative concomitant decrease of lipoprotein lipolysis (C) 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.

The hormonal imbalance is a prime factor for the aetiopathogenesis of preeclampsia. Preeclampsia is a state of hypoestrogenemia [14]. Decreased uteroplacental blood flow which is the main pathophysiological event in preeclampsia leads to impairment in the formation of Dehydroepiandrosterone sulphate (DHEAS) by fetal adrenal glands. DHEAS is the important source of estrogen in pregnancy, (i.e.) 90% of estrogen in maternal circulation is from fetal DHEAS which is converted to estriol in placenta. Hypoestrogenemia also leads to decreased expression of VLDL/apo E receptors resulting in reduced transport of VLDL to fetal compartment and so there is maternal hypertriglyceridemia [15,19]. Further LDL taken up by the fetus for the synthesis of DHEA is decreased due to reduced fetoplacental perfusion leading to increased LDL. Triglyceride represents an important biomarker of CVD risk because of its association with atherogenic remnant particles and Apo CIII.

The elevated triglycerides result in increased atherogenic small dense LDL and reduced HDL levels in Gestational hypertension [16]. This may be the result of increased exchange of TGL into LDL and HDL. At least three hypothesized mechanisms for the dyslipidemia and pre-eclampsia association have been described in the literature. First, investigators have noted that elevated plasma lipid and lipoprotein may induce endothelial dysfunction secondary to oxidative stress. They also noted that dyslipidemia may impair trophoblast invasion thus contributing to a cascade of pathophysiologic events that lead to the development of pre-eclampsia [4,17]. The second mechanism is the

Figure 1. Lipid metabolism in Preeclampsia (PE)



pathologic process of pre-eclampsia via dysregulation of lipoprotein lipase resulting in a dyslipidemic lipid profile. Sera from preeclamptic women had both a higher ratio of free fatty acids to albumin and increased uptake of free fatty acids, which are further esterified to triglycerides [13,18]. A third possible mechanism may be via the metabolic syndrome. Metabolic characteristics of "insulin resistance syndrome" namely, hyperinsulinemia and hyperuricaemia are also present in preeclampsia. [19,20].

MATERIALS AND METHODS

Study design:

This is an open labeled clinical study to compare the lipid profiles of normotensive and hypertensive pregnant women in third trimester. The present study was conducted in the Department of Obstetrics and Gynecology, King George Hospital, Visakhapatnam between November, 2012 and September, 2013. Informed consent was taken from women inducted into the study. The study comprised of 50 normotensive pregnant women and 50 hypertensive pregnant women. History was taken and physical examination was conducted as per the pre-designed case record form.
Inclusion criteria for controls:

Women aged between 18 to 30 years in the third trimester of pregnancy with normal blood pressure without any endocrine or systemic disorder.

Inclusion criteria for cases:

Women aged between 18 to 30 years in the third trimester of pregnancy with hypertension according to criteria established by The National High Blood Pressure Education Program Working Group without any endocrine or systemic disorder.
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Exclusion criteria for cases and controls:

Present pregnancy and past history] Eclampsia, Diabetes mellitus, Chronic hypertension, Kidney disease, Thyroid disorders, Collagen vascular disorder, Obesity (BMI >30 kg/m^2), Anemia. Group I consisting of 50 normotensive pregnant women who served as controls. Group II consisting of 50 cases of hypertensive pregnant women.

Parameters studied:

Fasting blood sample (5ml) was collected by venipuncture and the following parameters (Table-4) estimated in both cases and controls.

Table-4. Lipid profile parameters and measuring methods

Lipid	Method
Total cholesterol	Enzymatic method in auto analyzer
Triglycerides	GPO-PAP method
HDL cholesterol	Phosphotungstic acid method
VLDL	TG/5
LDL	Friedewald equation LDL = TC- (HDL+ TG/5)

Statistical Analysis:

Data was entered and graphs prepared in Microsoft Excel. Data was analyzed using Graph Pad Prism version 6.00. Unpaired t test was used for comparison of continuous variables between the two groups. P value less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

In this study, preeclamptic women showed higher serum concentrations of total cholesterol, LDL, VLDL and TG when compared to the normotensive women which was statistically significant (Table-5). In this study, a statistically significant decrease in HDLC was observed in preeclamptic women. Estrogen is responsible for induction of TG and HDL. Estrogen level falls in preeclampsia. The low level of HDL is however not only because of hypoestrogenemia but also due to insulin resistance [5]. The present study also showed a significant rise in TG in preeclamptic patients in comparison to normotensive pregnant women. During pregnancy, there is an increase in the hepatic lipase activity and decrease in lipoprotein lipase activity. Hepatic lipase is responsible for the increased synthesis of the triglycerides at the hepatic level, and the decreased activity of lipoprotein lipase is responsible for the decreased catabolism at the adipose tissue level, whereas placental VLDL receptors are up regulated. This results in re-routing of TG rich lipoproteins to the feto-placental unit. However in preeclampsia the vascularization of the fetoplacental unit may be impaired, resulting in yet-undefined compensatory mechanisms that may further increase synthesis of maternal TG levels. 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 [5, 19, 21] Another hypothesis is that hypertriglyceridemia is probably a consequence of competition between chylomicrons and very low-density lipoprotein cholesterol for the lipoprotein lipase. Classically, chylomicron clearance occurs in two sequential steps: (1) triglyceride hydrolysis by lipoprotein lipase, (2) uptake of the remnant by the liver. Delay in the second step leads to accumulation of remnants in plasma and is generally thought to represent the atherogenic risk of hyper-triglyceridemia [22,23].

In a review of 22 studies, Ray et al reported that women with elevated triglycerides had twice the risk of preeclampsia, studies that adjusted for confounders (age, BMI and parity) indicated that the risk was four times higher, compared with women with normal triglycerides [8.10]. In this study, there is a significant increase in serum VLDL in the preeclamptic women which may be due to hypertriglyceridemia leading to increased entry of VLDL that carries endogenous triglycerides into the circulation [24,25,26].

Table-6. Showing % increase in values of lipid subfractions in preecclamptic women in various studies

	TC	LDL	VLDL	TG
Amandeep *et al*	5.45	35	39	38.6
Gabil *et al*	5	30	35	40
Prasad *et al*	10	25	30	40
Present study	5	23	26	39

The present study is comparable to other studies (Table-6) in confirming that the lipid subtractions in preecclamptic women especially in TG, LDL AND VLDL show significant and substantial rise.

CONCLUSION

Normal human pregnancy results in pronounced physiologic hyperlipidemia involving gestational rise in blood triglycerides and cholesterol. Women with preeclampsia display additional alteration in lipids reflecting a disordered lipid and lipoprotein metabolism. Other studies have shown that predominantly low HDL and high triglyceride concentration may promote vascular dysfunction and oxidative stress seen in hypertensive disorders of pregnancy. Thus, considering the results in this study correlating with the various other studies, it can be concluded that dyslipidemia is significantly evident in preeclampsia which may play an important pathological role. Future studies are required to evaluate causative factors for altered lipid profile in preeclampsia and its prevention

Ethics statement

Ethics approval was not sought for this article.

Competing interests

The authors have declared that no competing interests exist.

Table-5. Comparison of mean values of lipid sub fractions in both groups

Lipid Subfractions	Controls (Values in Mg/Dl) Mean ±SD	CASES (Values in mg/dl)	*t* value	*P* value
TC	199±34	227±31	3.89	0.0002
HDL	58±5	51±5	6.06	<0.0001
LDL	101±32	132±34	4.56	<0.0001
VLDL	39±8	43±10	2.37	0.0196
TG	196±41	219±58	2.26	0.0258

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