"EVALUATION OF SERUM LIPID PROFILE IN PREGNANCY INDUCED HYPERTENSION "

By

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In partial fulfillment
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MSc.MLT
In
BIOCHEMISTRY

Under the guidance of
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DECLARATION

I, ANIL DAVIS, hereby declare that this dissertation entitled, **'EVALUATION OF SERUM LIPID PROFILE IN PREGNANCY INDUCED HYPERTENSION '** has been prepared by me under the guidance and direct supervision of Dr. RADHIKA KRISHNASWAMY, MD.DNB, Associate Professor, Dept of Biochemistry, St. John's Medical College. This dissertation is submitted in partial fulfillment of the regulations of Rajiv Gandhi University of Health Sciences and has not formed the basis of a degree or diploma to me by any other university before.

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ABSTRACT

BACKGROUND

Hypertensive disorders are common medical complication of pregnancy with a reported incidence of about 10% of first pregnancies and 20-25% of women with a chronic hypertension. The abnormal lipid metabolism seems important in the pathogenesis of pregnancy induced hypertension

AIMS AND OBJECTIVES

To estimate the serum lipid profile in pregnant women having hypertension at the third trimester(pre-eclampsia) and to correlate the lipid profile with pregnancy induced hypertension by analyzing the data using student's 't' test.

MATERIALS AND METHODS

The study was conducted at St.John's Medical College, Bangalore in collaboration with department of obstetrics and gynecology during the period of 2009 January to 2009 December. The serum lipid profile was analyzed in normotensive pregnant women and pre-eclamptic patients. The study was conducted on 40 women ranging in age from 18-30years who were divided into two groups. Group A includes 20 normal normotensive pregnant women at third trimester and group B includes 20 pre-eclamptic patients at third trimester who were diagnosed by the presence of persistent hypertension (140/90mm of Hg), gross proteinuria and edema.

RESULTS

In the present study the serum triglycerides and total cholesterol was found to be significantly high and HDL-C was significantly low in pre-eclamptic patients when compared to normotensive pregnant women..

CONCLUSION

The significant rise in Triglycerides, total cholesterol and decrease in HDL-C which are possible causative factors of pathogenesis of PIH. Hence early detection of these parameters is going to aid in better management of preeclampsia. Which is important to improve the maternal and fetal outcome of preeclampsia.

KEY WORDS

Pre-eclampsia, Normal pregnancy, serum lipid profile

1. INTRODUCTION

Pre-eclampsia develops in about 2% of pregnancies and is still responsible for a significant proportion of perinatal and maternal morbidity and mortality[1]. Current concepts of the pathophysiology of pre-eclampsia suggest endothelial cell injury and altered endothelial cell function play a pivotal role[2]. It has been proposed that the poorly perfused placenta is the origin of a humoral factor that affects maternal systemic function, directly or indirectly, by activating endothelial cells, with resultant vascular injury[3]. The characteristic pathologic lesion seen in the uteroplacental bed of patients with pre-eclampsia is a necrotizing arteriopathy consisting of fibrinoid necrosis, accumulation of foam cells or lipid-laden macrophages in the decidua, fibroblast proliferation , and a perivascular infiltrate. This lesion has been termed “acute atherosis.”[4]

Work in the field of cardiovascular research has shown that serum lipids have a direct effect on endothelial function and that abnormal serum lipid profiles are associated with endothelial dysfunction[4-5]. As such the potential role of abnormal lipid metabolism in the genesis or expression of pre-eclampsia is a subject of increasing interest. Lipid and lipoprotein levels undergo dramatic changes in pregnancy, presumably to supply lipid

nutrients to the growing fetus. Plasma concentrations of triglyceride and cholesterol increase approximately 30%and 50%, respectively[7].

Although the presence of hyperlipidemia has been documented in normal pregnancies, the magnitude and significance of the lipid changes in pregnancies complicated by PIH has not been well defined. Increases in plasma cholesterol, triglycerides , and very low density lipoprotein have been noted. The histopathological finding noted in the uterine spiral arteries in patients with PIH may theoretically be associated with changes in serum lipid fraction[1]. In women with pre-eclampsia, plasma free fatty acids and triglyceride concentrations climb substantially above those observed in normal pregnancy, and do so well before the appearance of clinical manifestations of the disorder[6].

This study was undertaken in order to evaluate the serum lipids changes in pregnancies complicated by hypertensive disorders.

2. AIMS AND OBJECTIVES

1. Estimation of serum lipid profile in pregnant women having hypertension at the third trimester (pre-eclampsia).

2. To correlate the lipid profile with pregnancy induced hypertension by analyzing the data using student's 't' test.

3. REVIEW OF LITERATURE

Hypertension, especially when complicated by pre-eclampsia is a major cause of both maternal and fetal morbidity and mortality. The association of alteration of serum lipid profile in essential hypertension is well documented. The abnormal lipid metabolism seems important in the pathogenesis of pregnancy induced hypertension.

Hypertensive disorders in pregnancy is classified as

1. Gestational hypertension
2. pre- eclampsia
3. Eclampsia
4. Pre- eclampsia superimposed on chronic hypertension
5. Chronic hypertension [7]

3.1 PRE-ECLAMPSIA - ECLAMPSIA

Pre-eclampsia complicates 5-7% of all pregnancies[11]. Pre-eclampsia is the development of hypertension with proteinuria, edema, or both, after the 20th week of gestation. It may develop earlier in case of hydatidiform mole. If pre-eclampsia progresses without proper treatment, patient may eventually develop eclamptic convulsions.[8]

Throughout the world population, preeclampsia-eclampsia is primarily a disease of the indigent primigravida who has received little or no prenatal care. In spite of a vigorous search for a deficiency of a single food substance, vitamin, or trace element , a specific absence or in adequacy of food material has never been demonstrated . It is

interesting to note that eclamptic patients in their succeeding pregnancies indicating that there are other factors operating besides dietary ones.[8]

Severe preeclampsia (criteria)

1. Hypertension : ≤ 160/110 mmHg
2. Proteinuria : > 5gm/24hour urine collection
3. Oliguria : < 400ml in 24 hour
4. Epigastric or right hypochondriac pain
5. Cerebral or visual symptoms
6. Thrombocytopenia < 1,00,000/mm^3
7. Increased liver function tests
8. Pulmonary edema
9. Hyperuricemia
10. ↑↑ serum creatinine >1.2mg/dl
11. Eclampsia
12. Fetal growth restriction

Hypertension and proteinuria are two important criteria diagnostic of the severe disease, any of all of the remaining criteria may be absent in particular case[10]

3.1.1 ETIOLOGY

Exact etiology is not known till now. It is called ''disease of theories''. Some of the predisposing or high risk factors are

1. Nulliparous patient
2. Extremes of age
3. Family history of preeclampsia – first degree relative
4. Medical diseases: Diabetes, chronic hypertension, chronic renal disease, sickle cell disease.
5. Obstetrics problem : multiple pregnancy, hydatidiform mole, hydropsfetalis

Placenta has a controlling role in preeclampsia. Since its delivery reverses the sign and symptoms of disease. Women with increased placental tissues e.g. hydatidiform mole and twin pregnancy have increased incidence of pre-eclampsia[10].

Current theories under focus are :-

1. Immunological – Increased incidence observed in patients using barrier contraceptives, nulliparous patients or multiparous women conceiving with a new partner suggests immunological role (less exposed to paternal antigens)

2. Genetic – strong family history suggests genetic role. Probably it is transmitted by single recessive gene.HLADR4 is under research.

   Fetal trisomy (13), triploidy (partial mole) have high incidence of preeclampsia, which also suggest genetic role.

3. Increased sensitivity to vasoconstrictors (angiotensin II) or increase in number of active circulatory mediators are responsible. Increased TXA_2/PGI_2 ratio, endothelin, / EDRF (No) ratio and ↑↑ free radicals generators due to ↓↓ in number of serum antioxidants are considered important.

4. Dietary – protein deficiency, calcium deficiency, not enough fresh fruits and vegetables (antioxidants) are suggested.

5. Hyperdynamic model – This theory postulates that increased cardiac output and hyper perfusion leads to compensatory vasodilation, after which the capillaries and damaged by exposure to elevated pressure and flow. The endothelial cells thus injured trigger the process. Ultimately incases of PIH there is vasoconstriction and volume contraction[10].

3.1.2 PATHOPHYSIOLOGY

Generalized vasospasm is characteristics of pre-eclampsia and can be readily observed in the retinal arterioles. The resulting increase in peripheral resistance then produces hypertension. There is an associated increase in vascular sensitivity to pressor substances such as angiotensin II, norepinephrine and vasopressin.[12] There may be increased sensitivity to infusion of angiotensin prior to the clinical manifestation of preeclampsia in certain cases, but the results may not be so well defined in other patients[17]. Sodium retention has been noted in preeclampsia, and in severe preeclampsia or eclampsia there is, in addition, a marked reduction in size of the vascular compartment with extravasations of fluid in to the extra cellular spaces. In such patients central venous pressure readings are extremely low[10].

As a result of systemic vasospasm there is decreased circulation to vital organs namely the brain, liver, kidney, and placenta. Although the actual cerebral blood flow is not altered, the cerebral resistance is measurably increased[13]. The decreased oxygenation of the brain resulting from vasospasm and cerebral edema produces cerebral irritability and may eventuate in seizures. Further more, the systemic vasospasm causes metabolic dysfunction in the kidney, liver, and placenta. The decreased perfusion of the placental cotyledons may produce small infarcted placentas and place the fetus in jeopardy of circulatory and nutritional deficits[10].

Renal function studies, including renal plasma flow, glomerular filtration rate, and uric acid clearance, are all decreased with preeclampsia. One must remember that in normal pregnancy renal clearances are all increased; all renal function studies must therefore be evaluated in terms of normal pregnancy changes. Unfortunately, in such evaluations there is relatively poor correlation between the degree of renal depression and the clinical severity of preeclampsia because of wide fluctuations of values in both normal and abnormal pregnancies[10].

Histological changes in the kidney have shown enlarged glomeruli with swollen endothelial cells. With electron microscopy, investigators in recent years have described specific renal lesions such as glomerular capillary endotheliosis with sub endothelial deposits[18]. A high correlation was reported between the degree of renal pathology and its clinical severity. Our own studies on renal biopsies from 57 cases, reviewed by two experienced renal pathologists who did not know the clinical status of the patients, did not show a similar degree of correlation[14]. In addition no diagnosis of primary renal disease was made in spite of five cases so diagnosed clinically. These results suggest that the kidney changes are not pathognomonic but in all probability are secondary changes, albeit very important ones. The findings also attest to the protean nature of the disease[10].

Placental perfusion is thought to be decreased in preeclampsia although it is exceedingly difficult to accurately measure uterine blood flow in pregnant women. The problem is further compounded by the lack of reliable animal models on which to perform such measurements. Since the conversion of administered labeled dehydroepiandrosterone sulfate (DHS) to 17 beta-estradiol largely by the placenta appears to correlate with placental perfusion, Gant and coworkers have reported decreased placental perfusion in patients with preeclampsia by demonstrating decreased conversion of DHS to estradiol.

The involvement of the renin-angiotensin system has been an intriguing problem in preeclampsia. The infusion of angiotensin into nonpregnant women or into preeclamptic patients elicits a hypertensive response, whereas similar infusion into normal pregnant women produces a blunted response. Studies have shown that the renin substrate, renin activating system, and angiotensin are all augmented to the highest degree in the normal pregnant women and to a lesser degree in preeclamptic patients, with the nonpregnant women demonstrating the lowest values[15]. The hypertensive response in the preeclamptic patient is a result of attenuated peripheral vasomotor response, its cause so far undetermined.

3.1.3 LABORATORY STUDIES

Besides the usual admission laboratory tests, additional studies should include:

1. Urine protein over 24 hours. This is the single most reliable laboratory test to ascertain the severity of preeclampsia and should be run frequently. Values over 0.5 g per 24 hours are considered abnormal. During the 24 hour collection period, qualitative check periodically by dip test is extremely helpful.

2. Urinalysis and urine culture. Occasionally, the clinical status of a preeclamptic patient is complicated by an occult pyelonephritis. The proper treatment of such an infection will improve the patient's preeclamptic status.

3. Blood urea nitrogen (BUN). Normally decreases markedly during pregnancy due to expanded blood volume, enhanced renal clearance, and anabolic state of protein metabolism. Values such as 15 to 18 mg per 100 mL in the last trimester of pregnancy signify definite renal decompensation. BUN may occasionally be elevated due to dietary changes[9].

4. Serum creatinine. Represents an adjunctive test to BUN to evaluate renal function. Normal values should be less than 1 mg per 100 ml.

5. Blood uric acid. Normally during the third trimester, the blood uric acid is less than 4 mg per 100 Ml because of augmented blood volume, increased renal clearance, and decreased catabolism of purines. Hyperuricemia is the most

characteristic blood change in preeclampsia, resulting from decreased renal clearance, lactic acidemia, and increased placental catabolism[9].

6. Altered hematological parameters

   Hemoglobin / haematocrit is increased

   Thrombocytopenia[16], a decreased platelet count (<100,000/mm^3 is also part of HELLP syndrome (hemolysis elevated liver enzymes and low platelet count)[21]

   Serum fibrinogen: increased unless there is a superimposed disseminated intravascular coagulation (DIC)

   Hemolysis, prothrombin time and activated partial thromboplastin time are prolonged in cases with DIC [20]

7. Liver enzyme studies including SGOT (serum glutamic oxaloacetic transaminase), LDH(lactate dehydrogenase) and CPK (creatine phosphokinase) are all elevated in serious cases of preeclampsia. Periportal necrosis and liver capsular hemorrhage have been observed and indicate hepatic involvement in this disease alkaline phosphatase is markedly elevated in normal pregnancy due to the presence of phosphatase in placenta.

Other studies such as serum electrolytes, protein and A/G (albumin/globulin) ratio, and cholesterol, are less helpful in following the progress of preeclampsia. In spite of enthusiastic advocate, we do not find urinary estriol, alkaline phosphatase, and HPL mandatory in the practical management of hypertensive disorders of pregnancy.[10]

In the management and treatment of preeclampsia-eclampsia , there are several broad concepts to keep in mind:

1. The only finite treatment is the delivery of the fetus and the placenta
2. The mother is young; once delivered alive, she still will have many reproductive years remaining.
3. Bed rest in the hospital must be an integral part of the conservative management of the preeclamptic patient. The best treatment for a preeclamptic patient is bed rest lying on her side: it promotes active diuresis.
4. In the total treatment, the severity of the preeclampsia is balanced against the prematurity and viability of the infant. The final judgment is based on the synthesis of all the clinical findings and laboratory tests [10]

3.2. Plasma lipids

Total plasma lipid is 400-600mg/dl

Plasma lipid profile (normal values)	
analyte	*normal value*
Total plasma lipid	400-600 mg/dl
Total cholesterol	140-200 mg/dl
HDL cholesterol, male	30-60 mg/dl
HDL cholesterol, female	35-75 mg dl
LDL cholesterol, 30-39 years	80-130 mg/dl
Triglycerides, male	50-150 mg/dl
Triglycerides, female	40-150mg/dl
phospholipids	150-200 mg/dl
Free fatty acids(FFA)	10-20 mg/dl

Table.1 plasma lipid profile(normal values)

One third of plasma lipid is cholesterol, one third is triglyceride and one third is phospholipid. Since lipids are insoluble in water, they need the help of carriers in plasma.Therefore they are complexed with proteins to form lipoproteins . The protein part of lipoprotein is called apolipoprotein. The lipoproteins are usually abbreviated as Lp.[22]

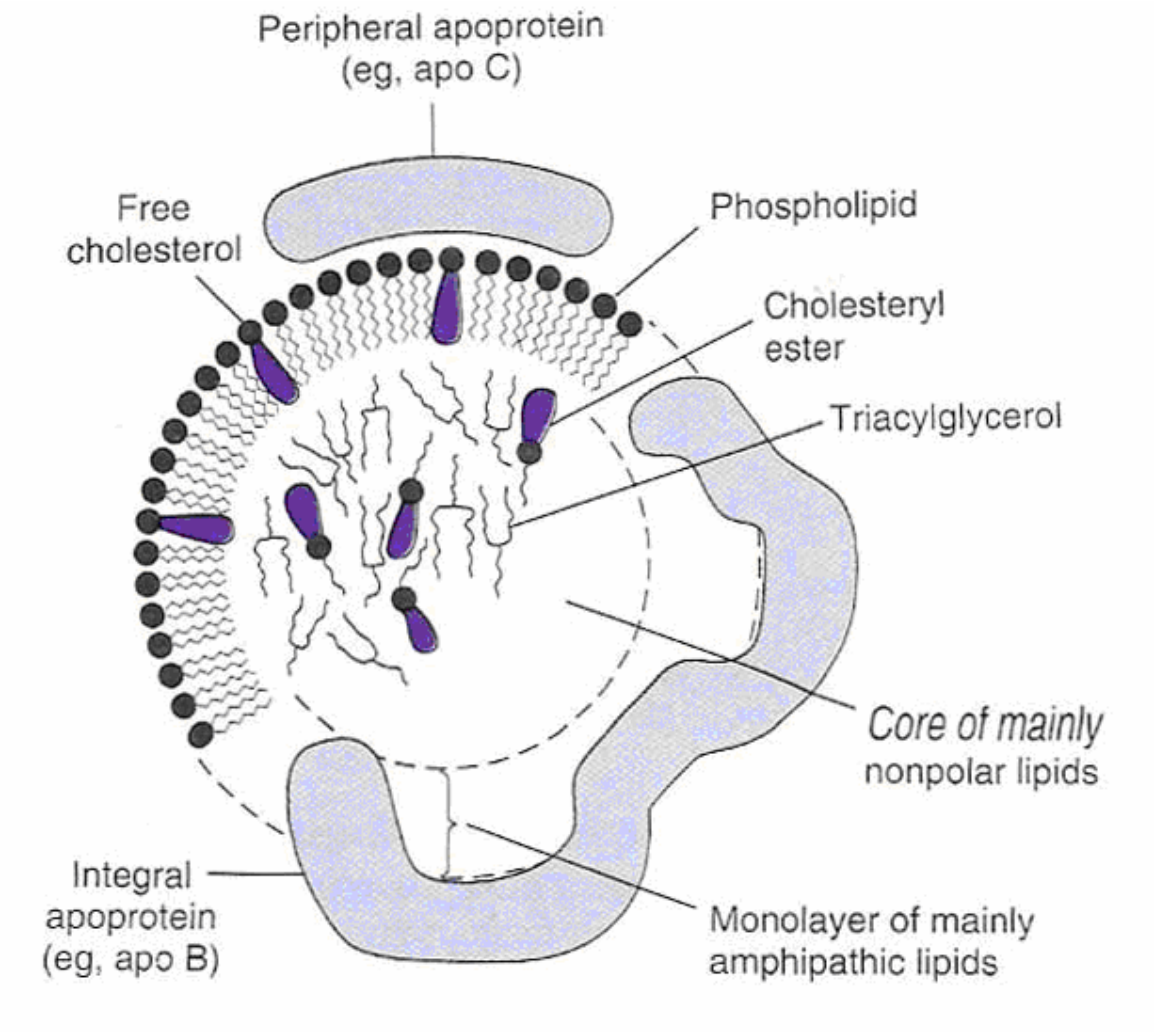


Fig.1 Generalized structure of a plasma lipoprotein[23]

3.2.1 Classification of lipoproteins: Five major classes of lipoproteins are identified in human plasma, based on their separation by electrophoresis.

1. Chylomicrons: They are synthesized in the intestine and transport exogenous triacylglycerol to various tissues. They consist of highest (99%) quantity of lipid and lowest (1%) concentration of protein. The chylomicrons are the least in density and the largest in size, among the lipoproteins.

2. Very low density lipoproteins (VLDL): They are produced in liver and intestine and are responsible for the transport of endogenously synthesized triacylglycerols.

3. Low density lipoproteins (LDL): They are formed from VLDL in the blood circulation. They transport cholesterol from liver to other tissues.

4. High density lipoproteins (HDL): They are mostly synthesized in liver. These contain the highest protein concentration[26]. Three different fractions of HDL (1, 2 and 3) can be identified by ultracentrifugation. HDL particles transport cholesterol from peripheral tissues to liver (reverse cholesterol transport).

5. Free fatty acids-albumin: Free fatty acids in the circulation are in a bound form to albumin. Each molecule of albumin can hold about 20-30 molecules of free fatty acids. This lipoprotein cannot be separated by electrophoresis[25].

TABLE:II CHARACTERISTICS OF DIFFERENT CLASSES OF LIPOPROTIENS[22]

	chylomicron	VLDL	IDL	LDL	HDL	FFA
Density	<0.95	0.95-1.006	1.006-1.019	1.019-1.063	1.063-1.121	1.28-1.3
Diameter(nm)	500	70	30	25	15	-
Electrophoretic mobility	origin	Pre-beta	Broad beta	beta	alpha	albumin
%composition						
protein	2	10	16	22	30-60	99
TAG	83	50	30	10	8	0
Phospholipids	7	18	22	22	20-30	0
cholesterol	8	22	32	46	10-30	0
FFA	0	0	0	0	0	1
Apoproteins	A,B-48,C-11,E	B-100,C-11,E	B-100,E	B-100	A-1,C,E	Albumin
Transport function	TAG from gut to muscle and adipose tissue	TAG from liver to muscle		Cholesterol from liver to peripheral tissues	Cholesterol from peripheral tissues to liver	FFA from adipose to muscle and liver

3.2.2 APOLIPOPROTEINS

The protein part of lipoprotein is called apolipoproteins (apo-Lp) or apoprotein. All apoproteins are mainly synthesized in liver, but small quantities are produced from almost all organs. Intestinal cells produce small quantities of apo-A. Apart from solubilising the lipid part, the protein components have specific functions[24].

They are important in :

- Maintaining the structural integrity of the lipoprotein
- Regulating certain enzymes which act on lipoproteins
- Receptor recognition[28]

TABLE III. CHARACTERISTICS OF APOPROTEINS AND THEIR FUNCTIONS[22]

Apoprotein	Molecular weight	Blood level Mg/dl	Site of production	Component of	Functions
apo A-I	28,000	150	Intestine;liver	HDL-2	Activation of LCAT;ligand for HDL receptor,anti-atherogenic
apo A-II	17,000	30	do	HDL-3	Inhibitor of LCAT; stimulates hepatic lipase
apo B-100	500,000	100	liver	LDL;VLDL	Binds LDL receptor
apo B-48	250,000		Intestine	chylomicrons	48% size of B-100, hence the name
apo C-I	7,000	10	liver	chylo;VLDL	Activation of LCAT
apo C-II	8,900	5	liver	do	Activates extra hepatic lipoprotein lipase in vessel walls; clearance of TAG from chylomicrons and VLDL
apo c-III	8,700	10	liver	do	Inhibits lipoprotein lipase;anti atherogenic
apo D	20,000			HDL-3	Lipid transfer protein
apo E	30,000	2	liver	LDL;VLDL;chylo	Arginine rich; ligand for hepatic uptake
apo Lp(a)		<30	liver	Lp(a)	Attached to B-100; impairs fibrinolysis; highly atherogenic

3.3 METABOLISM OF LIPOPROTEINS

Lipoprotein metabolism can be thought of as two cycles, one exogenous and one endogenous: both centered on the liver. These cycles are interconnected. Two key enzyme systems involved in lipoprotein metabolism are[24]

3.3.1 ENZYMES INVOLVED IN LIPID TRANSPORT

Lecithin cholesterol Acyl trasferase (LCAT)

LCAT catalyses the transfer of an acyl group (fatty acid residue) from lecithin to cholesterol, forming a cholesterol ester. LCAT activity is associated exclusively in HDL and stimulated by apo A-I.

Lipoprotein Lipase

Lipoprotein lipase is attached to tissue capillary endothelium and hydrolyses triacylglycerol present in chylomicrons and VLDL to glycerol and fatty acids during circulation.

Lipoprotein lipase activity increases after a meal due to activation by apo C-II present on the surface of tryacylglycerol bearing lipoproteins (Chylomicron and VLDL).

Hepatic lipase

Action of hepatic lipase is similar to that of lipoprotein lipase.

Mobilizing lipase

Mobilizing lipase is present in adipose tissue cells and regulates the release of fatty acids from adipose tissue into plasma. It is activated by catecholamine, growth hormones and glucocorticoids (e.g. cortisol) and inhibited by glucose and insulin[24]

3.3.2 THE EXOGENOUS LIPOPROTEIN METABOLIC CYCLE

METABOLISM OF CHYLOMICRONS

Dietary lipid is absorbed in the small intestine and incorporated into *chylomicrons* which are secreted into the lymphatics and reach the blood stream via the thoracic duct.

In the circulation they transfer apo A to HDL and acquire apo C and apo E from HDL. The apo C-11 then activates lipoprotein lipase in the tissues and tryacylglycerol is gradually removed from chylomicrons by the action of lipoprotein lipase. This enzyme is present on the walls of the blood capillaries of a number of tissues, predominantly adipose tissue and skeletal muscles.

As it loses triacylglycerol, (approximately 90% of the tryacylglycerol of chylomicrons), the resulting chylomicron becomes smaller and relatively enriched in cholesterol and cholesterol ester called chylomicron remnants because of the loss of triacylglycerol,

These remnants are removed by the liver where they are catabolised.

In the liver cholesterol may be utilized to form cell membrane components or bile salts or may be excreted in the bile.

The liver provides the only route by which cholesterol leaves the body in significant amount[24].

3.3.3 THE ENDOGENOUS LIPOPROTEIN METABOLIC CYCLE

Metabolism of VLDL

The liver plays a very important role in the synthesis of triacylglycerols and phospholipids from both endogenous and dietary fatty acids carried by blood to the liver, where they are converted to triacylglycerol, phospholipids and cholesterol esters. These lipids form complexes with apo B_{100} and lesser amounts of apo E. Apo c-11 is then acquired, mainly from HDL and secreted into the plasma as lipoprotein VLDL for transport from the liver.

The liver synthesizes VLDL-particles which are catabolised similar to that of chylomicrons by the action of lipoprotein lipase(LPL).

This results in the formation of VLDL remnant an intermediate density lipoprotein (IDL), which becomes low density lipoprotein (LDL), when further catabolised, or removed from the circulation by the liver[24].

Metabolism of LDL

LDL particles contain much less triacyl glycerol than their VLDL predecessors, and have a high concentration of cholesterol and cholesteryl esters[27]. All LDL arises from VLDL metabolism. The LDL are rich in cholesterol esters, probably derived from HDL. The apolipoprotein present in LDL is only apo $B_{100.}$

LDL is removed from the circulation by two processes,

1. One is regulated and
2. The other is unregulated

3.4. REGULATED MECHANISM FOR REMOVAL OF LDL FROM BLOOD

It involves the binding of LDL to specific apo B_{100} receptors present on the 'surface pits' of hepatocytes and other peripheral tissue cells

The entire LDL particle is incorporated into the cell by invagination of the cell membrane.

Inside the cell the particle fuses with lysosomes, apo B is then broken down and the cholesterol esters are hydrolyzed, thereby making unesterited cholesterol available to the cell.

Approximately 30% of LDL is degraded in extra hepatic tissues and 70% in the liver[24].

3.5 THE UNREGULATED MECHANISM FOR REMOVAL OF LDL FROM BLOOD

It involves receptor independent mechanisms of cholesterol uptake by cells. These are present particularly in macrophages.

These mechanisms are active when plasma cholesterol concentration is increased[24].

3.6 METABOLISM OF HDL AND ROLE OF LCAT

HDL particles are synthesized and secreted from both liver and intestine.

Nascent (newly secreted) HDL consists of,

-Discoid phospholipid bilayer containing free cholesterol,

Lecithin-cholesterolacyl transferase, LCAT and LCAT activator apoA-1 bind to disc.

The nascent HDL then undergo exchanges of lipid and protein with other plasma lipoproteins.

HDL acts as cholesterol ester shuttles, removing the cholesterol from the peripheral tissues and returning it to the liver.

The HDL takes up free cholesterol released from extrahepatic tissues. The cholesterol that is taken up is converted to cholesterol ester by LCAT and transferred to LDL, which in turn, is mainly taken up by the liver. Thus HDL forms the principal route whereby cholesterol can return from peripheral tissues to the liver.

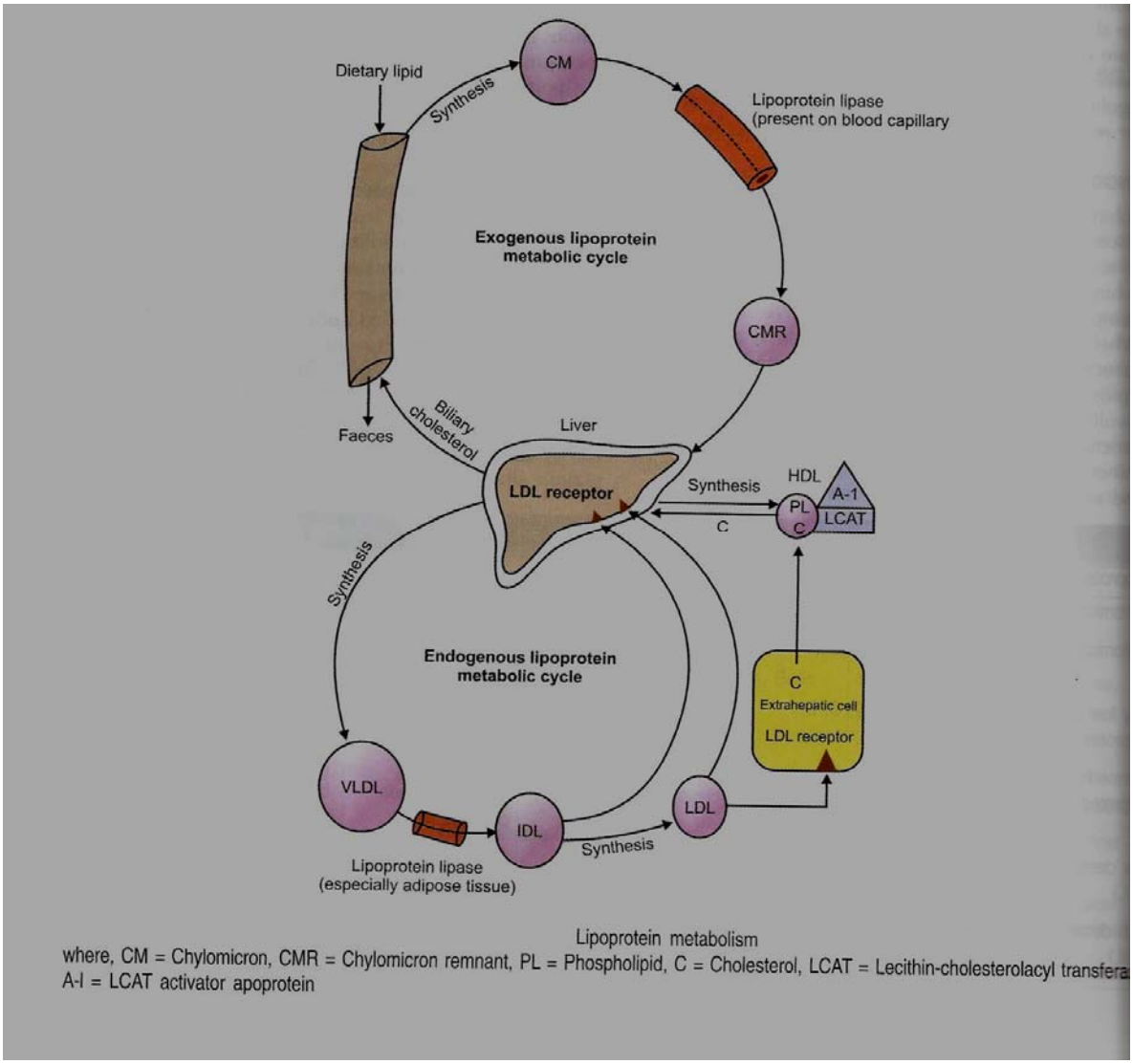
In this reaction, a fatty acid contained in the 2-position of phosphatidylcholine (of surface phospholipid), is transferred directly to cholesterol without passing acylCoA.

As cholesterol in HDL becomes esterified by LCAT activity, it creates a concentration gradient and draws in free cholesterol from tissues and from other lipoproteins, which deliver it to the liver. *Thus esterification by LCAT serves to trap cholesterol within the lipoprotein, preventing it from deposition in the tissues*[24].

The HDL is taken up either directly by the liver or indirectly by being transferred to other circulating lipoproteins, which then return it to the liver

HDL cycle transports cholesterol from tissues to the liver, a process known as reverse *cholesterol transport.* This process is thought to be anti atherogenic, and an elevated HDL cholesterol (good cholesterol) level has been shown to confer a decreased risk of coronary heart disease on an individual[24].

FIG.2 lipoprotein metabolism



Lipoprotein metabolism

where, CM = Chylomicron, CMR = Chylomicron remnant, PL = Phospholipid, C = Cholesterol, LCAT = Lecithin-cholesterolacyl transfera
A-I = LCAT activator apoprotein

3.7 DIAGNOSTIC IMPORTANCE OF LIPOPROTEINS

The blood levels of certain lipoproteins have diagnostic importance.

The ratio of HDL cholesterol to that in the LDL can be used to evaluate susceptibility to the development of heart disease.

For healthy person LDL/HDL ratio is 3:5.

Raised plasma LDL-cholesterol concentration is associated with an increased risk of ischaemic heart disease.

Where as raised plasma concentration of HDL cholesterol is associated with a decreased risk of ischaemic heart disease and seems to have protective effect

The exact nature of the protective effect of HDL levels is not known.

LDL cholesterol is called bad cholesterol because excess cholesterol is present in the form of LDL and HDL cholesterol is called good cholesterol[24]

3.8 DISORDERS OF LIPOPROTEIN METABOLISM

Hyperlipoproteinemia and

Hypolipoproteinemia

3.8.1 HYPERLIPOPROTEINEMIA

The causes of hyperlipoproteinemia are complex, and different disease mechanisms can give rise to similar lipid patterns.

In practice lipoprotein disorders are classified as follows:

The primary hyperlipoproteinemia -when the disorder is not due to some other disorders.

Secondary hyperlipoproteinemia-when the disorder is manifested due to some other disease.

Primary hyperlipoproteinemia

The Fredrickson or World Health Organization classification of the primary hyperlipoproteinemia is the most accepted one

TABLE IV. Fredrickson (WHO) classification of hyperlipoproteinemia

Types	normal	Type I	Type IIa	Type IIb	Type III	Type IV	Type V
lipoprotein	N	↑ chylomicrons	↑ LDL	↑ LDL ↑ VLDL	↑ LDL	↑ VLDL	↑ chylomicrons ↑ VLDL
Total cholesterol	N	N or ↑	↑	↑	↑	N or ↑	N or ↑
Tryacyl-glycerol	N	↑↑	N	↑	↑	↑	↑↑
LDL-cholesterol	N	N or ↓	↑	↑	N or ↓	N	N
HDL-cholesterol	N	N or ↓	N or ↓	N or ↓	N or ↓	N or ↓	N or ↑

This classification relies on the findings of plasma analysis, rather than genetics. As a result, patients with the same genetic defect may fall into different groups or may change grouping as the disease progressive or is treated.

This classification gives some guidance for treatment and is widely accepted.

Type I and V are rare, while types II a, II b and and IV are common. Type III hyperlipoproteinemia, also known as familial dybetalipoproteinemia[24].

TABLE V. Some genetic causes of primary hyperlipoproteinemia

Disorder	Fredrickson type	Genetic defect	Risk
Familial hyper-cholesterolemia	II a or II b	Reduced numbers of functional LDL receptors	Coronary heart disease
Familial hyper-triglyceridemia	IV or V	Possible single gene defect	Coronary heart disease
Familial combined hyperlipidemia	II a, II b, IV or V	Possible single gene defect	Coronary heart disease
Lipoprotein lipase deficiency	I	Reduced level of lipoprotein lipase	Pancreatitis
ApoC-II deficiency	I	Inability to synthesize apo C-II	pancreatitis

Secondary hyperlipoproteinemia

Secondary hyperlipoproteinemia is seen in the following diseases.

- Renal failure
- Nephritic syndrome
- Cirrhosis of the liver
- Hypothyroidism
- Diabetes mellitus
- Alcohol abuse
- Women taking estrogen containing oral contraceptives.

TABLE VI. Some common causes of secondary hyperlipoproteinemia

Causes	Affected lipid
Nephrotic syndrome	Hypercholesterolemia
Hypothyroidism	Hypercholesterolemia
Chronic renal failure Alcohol abuse(excess)	Hypertriglyceridemia Hypertriglyceridemia
Diabetes mellitus	Hypertriglyceridemia
Use of contraceptive containing estrogen	Hypertriglyceridemia

3.8.2 HYPOLIPOPROTEINEMIA

Hypolipoproteinemia is also classified as,

Primary hypolipoproteinemia is due to reduced synthesis of protein, e.g.

- Abetalipoproteinemia and
- Tangier disease

Secondary hypolipoproteinemia, e.g.

- Kwashiorkor in children
- Severe malabsorption
- Some forms of chronic liver disease[24]

4. MATERIALS AND METHODS

4.1 MATERIALS

4.1.1 SOURCE OF DATA

The study was performed in the Department of Biochemistry in St John's Medical college and hospital, Bangalore in collaboration with department of obstetrics and gynaecology during the period of 2009 January to 2009 December.

4.1.2 INCLUSION CRITERIA

The study were conducted on 40 women ranging in age from 18-30 years they were divided into two groups.

Group A includes 20 normal normotensive pregnant women at third trimester

Group B includes 20 preeclamptic patients at third trimester they were diagnosed by the presence of persistent hypertension (140/90mm of Hg), gross proteinuria, oedema

4.1.3 EXCLUSION CRITERIA

People with past history of cardiac, renal, hepatic dysfunction or dislipidemia were excluded from the studies.

4.2 METHOD OF COLLECTION OF DATA

Samples were drawn after an overnight fasting from the ante cubital vein from inpatients. 4ml whole blood was collected in red capped vacutainer tube containing clot activator and left at room temperature to clot for half an hour. Serum was separated by centrifugation at 1200rpm and analysed using siemens dimension RxL MaX

The following parameters were analysed

TABLE VII. METHODOLOGY OF LIPID PARAMETERS

parameters	Methodology
Total cholesterol	CE/CO/HPO
HDL cholesterol	Accelerator selective detergent
LDL cholesterol	Detergent/CE/CO/POD
Triglycerides	LPL/GK/GPO/POD

4.2.1 ESTIMATION OF TOTAL CHOLESTEROL

PRINCIPLE

Cholesterol esterase catalyzes the hydrolysis of cholesterol esters to produce free cholesterol which, along with preexisting free cholesterol is oxidized in reaction catalyzed by cholesterol oxidase (co) to form cholest-4-ene-3-one and hydrogen peroxide. In the presence of horseradish peroxidase (HPO), the hydrogen peroxide thus formed is used to oxidize N,N diethyl aniline-Hcl/4-aminoantipyrine (DEA-HCl/AAP) is directly proportional to the total cholesterol concentration and and is measured using a poly chromatic (453, 540, 700 nm) end point technique.

$$\text{Cholesterol esters} \xrightarrow{\text{CE}} \text{cholesterol + fatty acids}$$

$$\text{Cholesterol + } o_2 \xrightarrow{\text{CO}} \text{cholesst-4-ene-3-one + } H_2O_2$$

$$2\ H_2O_2 + \text{DEA.HCl/AAP} \xrightarrow{\text{HPO}} 4\ H_2O + \text{oxidized DEA.HCl/AAP}$$

Precaution : Used cuvettes contains human body fluids; handle with appropriate care to avoid skin contact and ingestion.

Reagent preparation : hydrating diluting and mixing are automatically performed by the instrument.

Procedure

Test steps : sampling, reagent delivery, mixing, processing, and printing of results are automatically performed by the dimension® system.

The sample container must contain sufficient quantity to accommodate the sample volume plus dead volume. Precise container filling is not required.

Test conditions

Sample size	3 µl
Reagent 1 volume	88 µL
Reagent 2 volume	26 µL
Diluent volume	241 µL
Temperature	37^0C
Wavelength	452, 540, and 700nm
Type of measurement	polychromatic end point

Interfering substances

Potassium oxalate/sodium fluoride can decrease cholesterol results an average of 12%

Li Heparin can depress cholesterol results by an average of 4mg/dL at a level of 200mg/dL

Bilirubin (conjugated) of 8.1mg/dL and bilirubin (unconjugated) of 9.4mg/dL decrease the CHOL result by 15mg/dL at CHOL concentration of 150mg/dL

Bilirubin (conjugated) of 12.8mg/dL and bilirubin (unconjugated) of 14.7mg/dL decrease the CHOL result by 25mg/dL at CHOL concentration of 250mg/Dl

Bilirubin of 20mg/dL decreases a CHOL result of 178mg/dL by 15%.

Hemoglobin of 1000mg/dL decreases a CHOL result of 177mg/dL by 15%

Lipemia at 1000mg/dL tripped a test report message; therefore the magnitude of the interference could not be determined.

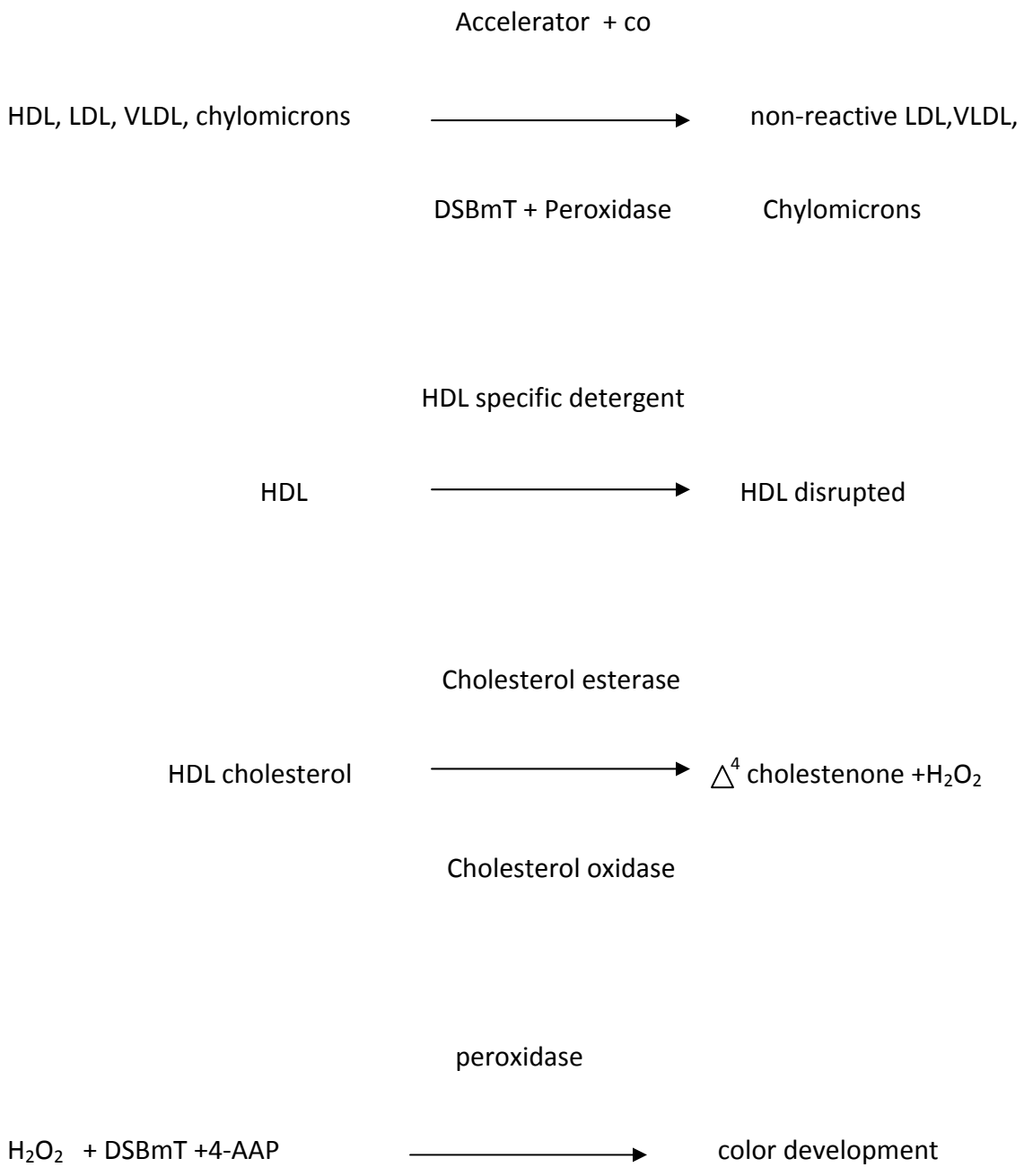
4.2.2 ESTIMATION OF HDL CHOLESTEROL

PRINCIPLE

The HDL cholesterol assay is a homogenous method for directly measuring HDL-C levels without the need for off- line pretreatment or centrifugation steps.

The method is in a two reagent format and depends on the properties of a unique detergent, as illustrated. This method is based on accelerating the reaction of cholesterol oxidase (co) with non-HDL unesterified cholesterol and dissolving HDL selectively using a specific detergent. In the first reagent, non-HDL unesterified cholesterol is subject to an enzyme reaction and the peroxide generated is consumed by a peroxidase reaction with DSBmT yielding a colorless product. The second reagent consists of a detergent capable of solubilizing HDL- specifically, cholesterol esterase and chromagenic coupler to develop color for the quantitative determination of HDL-C. this may be referred to as the accelerator selective detergent methodology.

Accelerator selective deter gent methodology



Precaution: used cuvettes contain human body fluids; handle with appropriate care to avoid skin contact or ingestion.

Reagent preparation : All reagents are liquid and ready to use.

procedure

Test steps: sampling, reagent delivery, mixing, separation, processing and printing of results are automatically performed by the Dimension system.

	Test conditions
Sample volume	3µL
Reagent 1 volume	300µL(cholesterol oxidase,peroxidase in MES buffer)
Reagent 2 volume	100µL(cholesterol esterase,4 aminoantipyrine in MES buffer)
Temperature	37^0C
Wavelength	600 and 700 nm
Type of measurement	Bichromatic endpoint

HDL Interference

The HDL method was evaluated for interference from hemolysis, icterus and lipemia according to CLSI/NCCLS/EP7-P. Bias is the difference in the results between the control sample and the test sample expressed in percent. Bias exceeding 10% is considered interference.

4.2.3 ESTIMATION OF LDL CHOLESTEROL

PRINCIPLE

The LDL cholesterol assay is a homogenous method for directly measuring LDL-C levels in human serum or plasma, without the need for any off-line pretreatment or centrifugation steps.

The method is in a two reagent format and depends on the properties of detergent 1 which solubilizes only non- LDL particles. Cholesterol released is consumed by cholesterol esterase cholesterol oxidase in a non color forming reaction. Detergent 2 solubilizes the remaining LDL particles. The soluble LDL-C is then oxidized by the action of cholesterol esterase and cholesterol oxidase forming cholestenone and hydrogen peroxide . The enzymatic action of peroxidase on H_2O_2 produces color in the presence of N,N-bis(4-sulfobutyl)-m-toluidine, disodium salt and 4-aminoantipyrine that is measured using a bichromatic (540, 700 nm) end point technique. The color produced is directly proportional to the amount of LDL-C present in the sample.

DETERGENT 1

Nonsoluble LDL-C, VLDL-C, HDL-C, Chylomicrons —(DSBmT + peroxidase)→ Soluble Non-LDL-C (VLDL-C, HDL-C, Chylomicrons)

Cholesterol esterase

Soluble Non-LDL-C —→ Non color forming

Cholesterol oxidase

Detergent 2

Non soluble LDL-C —→ soluble LDL-C

Cholesterol esterase

Soluble LDL-C + O_2 —→ cholestenone + H_2O_2

Cholesterol oxidase

Peroxidase

H_2O_2 + DSBmT + 4-AA —→ color development

Precaution: used cuvettes contain human body fluids; handle with appropriate care to avoid skin contact and ingestion.

Reagent preparation: All reagents are liquid and ready to use

Procedure

Test steps: sampling, reagent delivery, mixing, processing, and printing of results are automatically performed by the dimension system.

Test conditions

Sample size	3µL
Reagent 1 volume	300µL
Reagent 2 volume	100µL
Temperature	37^0C
Wavelength	540 and 700 nm
Type of measurement	Bichromatic endpoint

Interfering substances

Bilirubin (unconjugated) of 80 mg/dL will decrease an LDL result of 124 mg/dL by 10%

Lipemia of 3000 mg/dL will decrease an LDL result of 122 mg/dL by 19%

4.2.4 ESTIMATION OF TRIGLYCERIDES

PRINCIPLE

The triglycerides method is based on an enzymatic procedure in which combinations of enzymes are employed for the measurement of serum or plasma triglicerides. The sample is incubated with lipoprotein lipase (LPL) enzyme reagent that converts triglycerides into free glycerol and fatty acids. Glycerol kinase catalyzes the phosphorylation of glycerol by adenosine-5-triphosphate to glycerol-3-phosphate. Glycerol-3 phosphate–oxidase oxidizes glycerol-3-phosphate to dihydroxyacetone phosphate and hydrogen peroxidase. The catalytic action of peroxidase forms quinoneimine from H_2O_2, aminoantipyrine and 4-chlorophenol. The change in absorbance due to the formation of quinoneimine is directly proportional to the total amount of glycerol and its precursors in the sample and is measured using a bichromatic end point technique.

LPL

triglycerides ⟶ glycerol + fatty acids

GK

Glycerol + ATP ⟶ Glycerol-3-phosphate + ADP

GPO

Glycerol-3 phosphate + O_2 ⟶ dihydroxiacetone phosphate + HO

POD

2 H_2O_2 +Aminoantipyrine + ⟶ quinoneimine + HCL + 4 H_2O

4-chlorophenol

Precaution: contains sodium azide (< 0.1%) as a preservative sodium azide can react with copper or lead pipes in drain lines to form explosive compounds. Dispose of properly in accordance with local regulations

Used cuvette contains human body fluids; handle with appropriate care to avoid skin contact and ingestion.

Store at 2-8^0 C

Procedure

Test steps: sampling, reagent delivery, mixing, processing, and printing of results are automatically performed by the dimension system.

	Test conditions
Sample size4	4µL
Reagent 1 volume	133µL
Temperature	37^{0}C
Wavelengths	510 and 700 nm
Type of measurement	bichromatic endpoint

INTERFERING SUBSTANCES

Small amounts of free glycerol may be found in blood samples from healthy individuals due to natural lipolysis. The concentration of free glycerol may be increased by stress, disease states or administration of intravenous infusates, free glycerol or other polyols may cause a positive interference

Glycerol based quality control products should not be used with this method.

Hemoglobin of 500 mg/dL will increase a triglycerides result of 155 mg/dL by

12%

Bilirubin (unconjugated) of 20 mg/dL will increase a triglycerides results of 156mg/dL by 11%.

5. RESULTS

A total of 40 samples were included in this study, 20 were normal normotensive pregnant women at third trimester and 20 were pre-eclamptic patients at third trimester. Lipid profile was performed on both normal and the pre-eclamptic group.

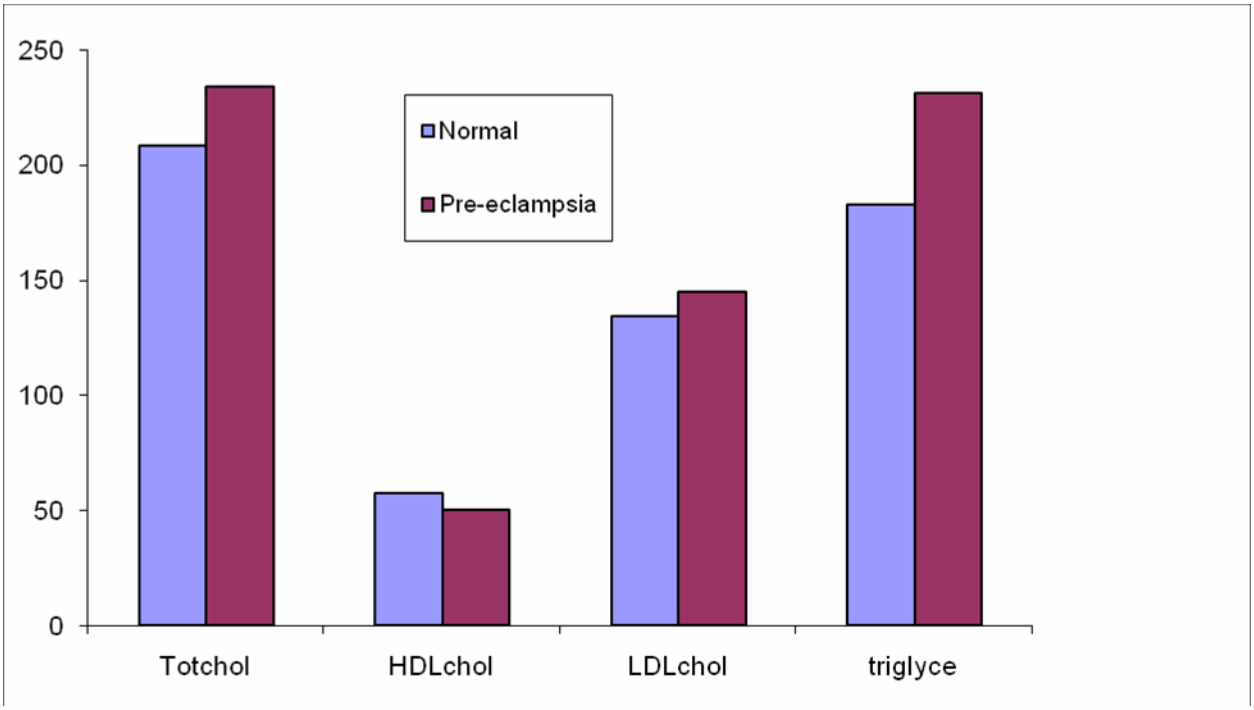


Fig.3. LIPID PROFILE IN NORMAL AND PRE-ECLAMPTIC GROUP

T-Test

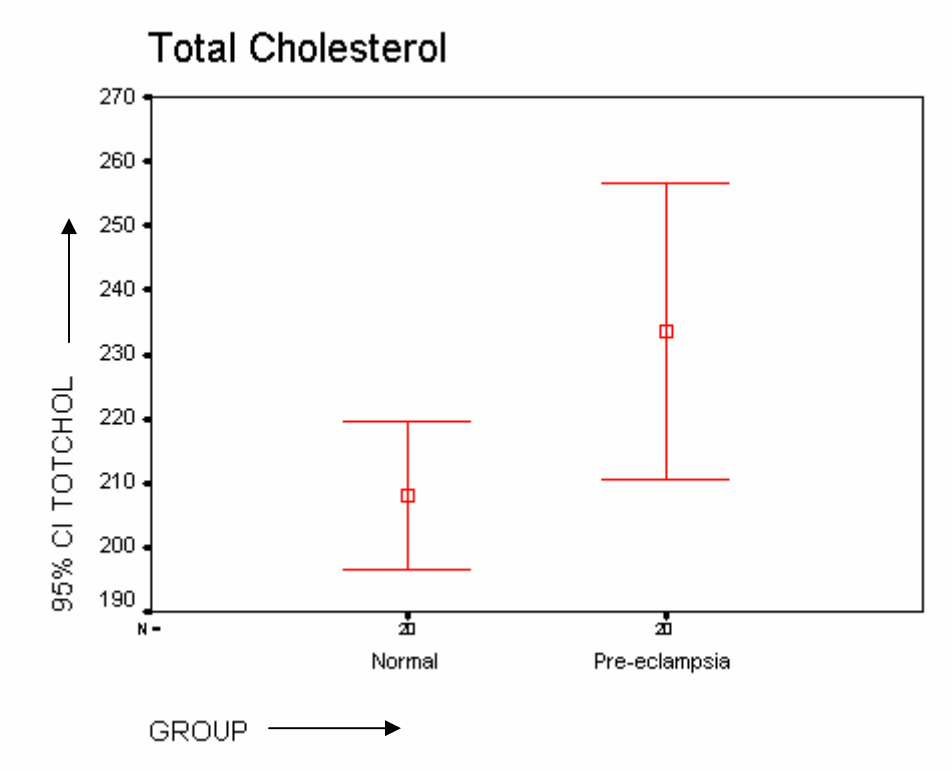
Group Statistics					
	GROUP	N	Mean	Std. Deviation	Std. Error Mean
TOTCHOL	Normal	20	208.10	24.683	5.519
	Pre-eclampsia	20	233.65	49.065	10.971
HDLCHOL	Normal	20	57.20	6.849	1.531
	Pre-eclampsia	20	49.90	6.851	1.532
LDLCHOL	Normal	20	134.10	25.074	5.607
	Pre-eclampsia	20	144.55	35.280	7.889
TRIGLYCE	Normal	20	182.50	37.128	8.302
	Pre-eclampsia	20	231.20	46.487	10.395

TABLE VIII. GROUP STATISTICS

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
TOTCHOL	Equal variances assumed	10.515	.002	-2.080	38	.044	-25.55	12.281	-50.412	-.688
	Equal variances not assumed			-2.080	28.038	.047	-25.55	12.281	-50.706	-.394
HDLCHOL	Equal variances assumed	.034	.854	3.370	38	.002	7.30	2.166	2.915	11.685
	Equal variances not assumed			3.370	38.000	.002	7.30	2.166	2.915	11.685
LDLCHOL	Equal variances assumed	2.271	.140	-1.080	38	.287	-10.45	9.678	-30.043	9.143
	Equal variances not assumed			-1.080	34.293	.288	-10.45	9.678	-30.113	9.213
TRIGLYCE	Equal variances assumed	.235	.631	-3.661	38	.001	-48.70	13.303	-75.631	-21.769
	Equal variances not assumed			-3.661	36.229	.001	-48.70	13.303	-75.674	-21.726

TABLE IX. INDEPENDENT SAMPLES TEST

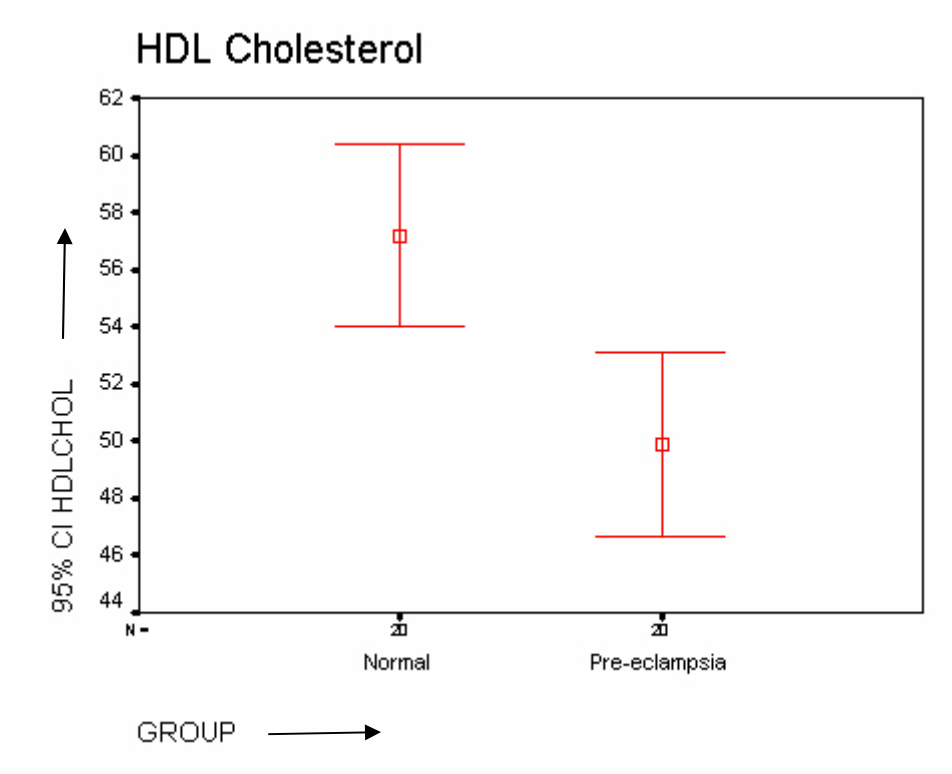
FIG.4. PERCENTAGE OF TOTAL CHOLESTEROL IN NORMAL AND PREECLAMPTIC PATIENTS



Increase in the Total cholesterol was seen in preeclamptic patients than the normotensive pregnant women. A statistical analysis was done and found to be as follows.

The mean was found to be 208.10 in normotensive women and 233.65 in pre-eclamptic patients. It was found that the total cholesterol was very significantly increased in pre-eclamptic patients compared to the normotensive pregnant women.

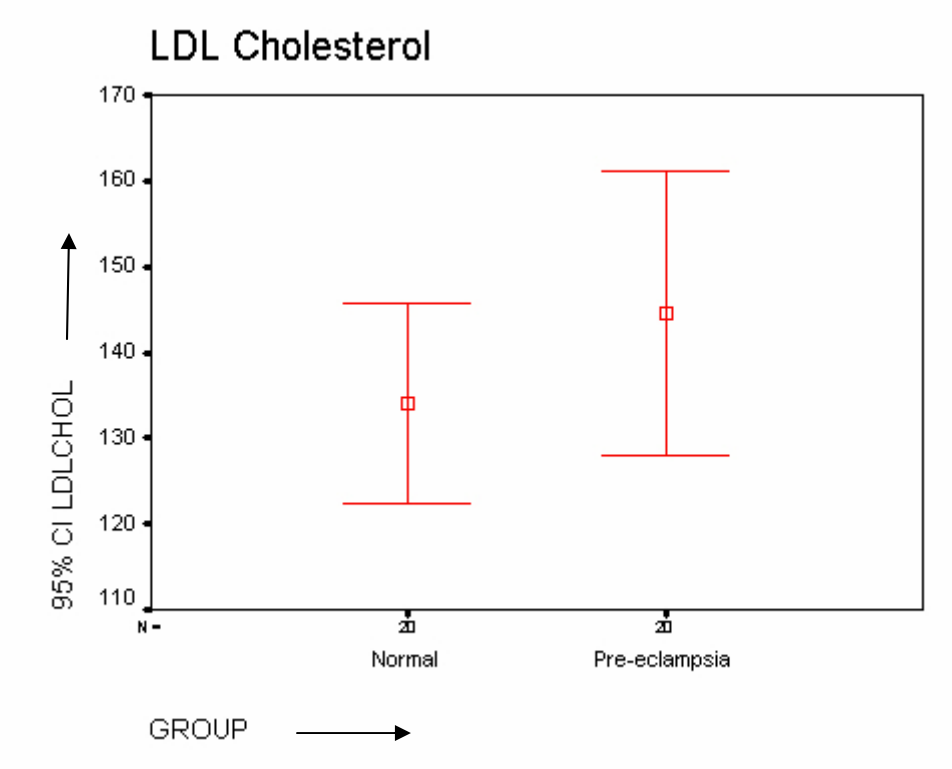
FIG.5. PERCENTAGE OF HDL-C IN NORMAL AND PREECLAMPTIC PATIENTS



Decrease in the HDL cholesterol was seen in pre-eclamptic than the normotensive women. A statistical analysis was done and found to be as follows.

The mean was found to be 57.20 in normotensive pregnant women and 49.90 in pre-eclamptic patients. HDL cholesterol was significantly decreased in pre-eclamptic patients compared to the normotensive pregnant women.

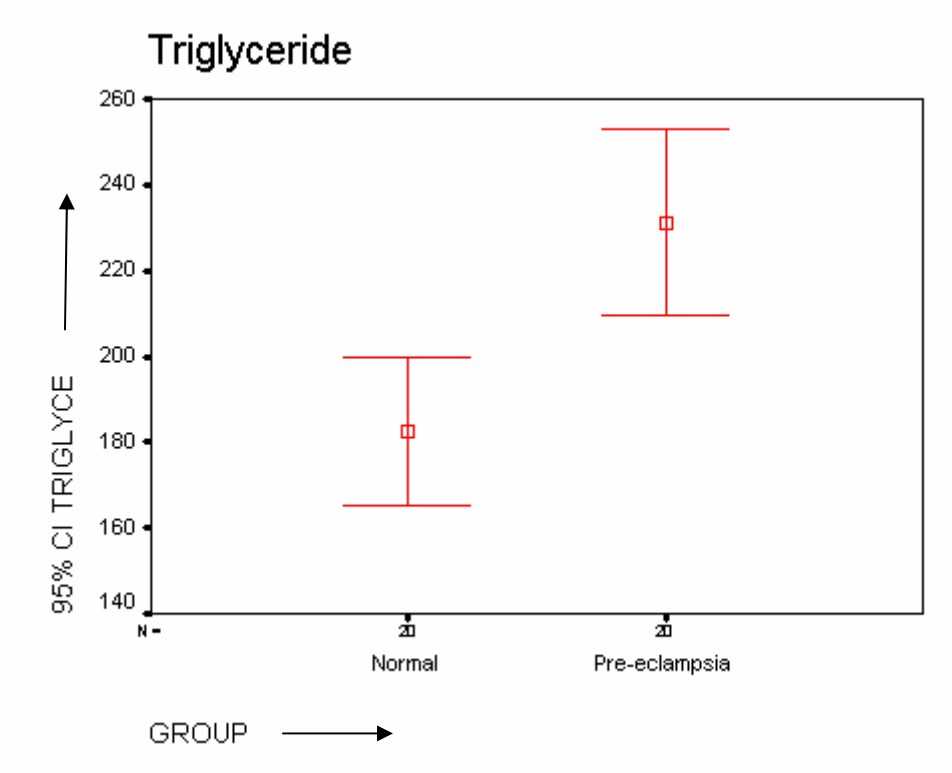
FIG.6 . PERCENTAGE OF LDL-C IN NORMAL AND PRE-ECLAMPTIC PATIENTS



Increase in the LDL cholesterol was seen in pre-eclamptic than the normotensive women. A statistical analysis was done and found to be as follows.

The mean was found to be 134.10 in normotensive pregnant women and 144.55 in pre-eclamptic patients. No significant increase in LDL cholesterol was found in pre-eclamptic patients compared to normotensive pregnant women.

FIG.7. PERCENTAGE OF TG IN NORMAL AND PRE-ECLAMPTIC PATIENTS



Increase in the Triglyceride level was seen in pre-eclamptic than the normotensive women. A statistical analysis was done and found to be as follows.

The mean was found to be 182.50 in normotensive pregnant women and 231.20 in pre-eclamptic patients. So there was a significant increase in triglyceride level in pre-eclamptic patients compared to normotensive pregnant women.

6 DISCUSSION

Preeclampsia is the development of hypertension with proteinuria, edema or both, after 20th week of gestation. If pre-eclampsia progresses without proper treatment patient may eventually develop eclamptic convulsions. Pre-eclampsia develops in about 2% of pregnancies and is still responsible for a significant proportion of perinatal and maternal morbidity and mortality[1]. A number of studies were done on the lipid profile in pregnancy induced hypertension.

In our study 20 pre-eclamptic pregnant women were studied and the results were compared with 20 normotensive women. A significant fall in HDL-C and increase of triglycerides and total cholesterol was found in pre-eclamptic cases in our study. . The results were similar to the study conducted by Jayanta De et al on serum lipid profile in pregnancy induced hypertension ,who found significant rise in the serum triglyceride level in pre-eclamptic patients. The principle modulator of this hypertriglyceridemia is hyperoestrogenemia in pregnancy that induces hepatic biosynthesis of endogenous triglycerides, which is carried by VLDL. Increased TG levels results in endothelial dysfunction and in pre-eclampsia gets deposited in predisposed vessels, causes generation of small dense LDL and hypercoagulability[31].In our study there was a significant fall in HDL-C in pre-eclamptic cases. Estrogen is responsible for induction of TG and HDL-C but in PIH there was a fall in estrogen levels as compared to normal pregnancy. The low level of HDL in pre-eclampsia is however not only because of hypooestrogenemia but also may be due to insulin resistance.[32.]

Also increase in total cholesterol in our study correlates well with study conducted by Suchanda Sahu et al who studied lipid profile, lipid peroxidation and vitamin E in pregnancy

induced hypertension and found a significant rise in total cholesterol levels in pre-eclampsia as compared to normal pregnancy which was similar to other reports. LDL-Cholesterol levels in our study are not are increased significantly in PIH than normotensive pregnant women. This is in contrast to many other studies which showed a significant elevation of these two parameters. But in some other studies they were fond that there was no significant alteration in this cholesterol level[33].

The present study indicates that significant rise in Triglycerides, Total cholesterol and decrease in HDL-C which are possible causative factors of pathogenesis of PIH. Hence estimation of these parameters will aid in early detection and better management of preeclmpsia which is important to improve the maternal and fetal outcome of preeclampsia.

7. SUMMARY

AIM : To evaluate the serum lipid profile in pregnant women having hypertension at the third trimester

OBJECTIVE: To correlate the lipid profile with pregnancy induced hypertension by analyzing the data using student's 't' test.

MATERIALS AND METHODS

The study was conducted at Department of Biochemistry, St.John's Medical College Hospital, Bangalore in collaboration with Department of obstetrics and gynecology during the period of 2009 January to 2009 December.

Fasting blood samples collected from 20 normotensive pregnant women at third trimester and 20 pre-eclamptic patients at third trimester aged between 18-30years.

The serum lipid profile was analyzed using autoanalyzer Siemens dimension RxL MaX

RESULTS : Significant elevation of serum triglycerides, total cholesterol, decrease in HDL cholesterol and no significant change in LDL cholesterol as compared to normotensive pregnant women.

CONCLUSION : The significant rise in Triglycerides, total cholesterol and decrease in HDL-C are possible causative factors of pathogenesis of PIH. Hence estimation of these parameters will aid in early detection and better management of preeclmpsia which is important to improve the maternal and fetal outcome of preeclampsia.

8. CONCLUSION

The estimation of serum lipid profile can be used to prevent the progressiveness of pregnancy induced hypertension in susceptible pregnant ladies. The significant rise in Triglycerides, Total cholesterol and decrease in HDL-C which are possible causative factors of pathogenesis of PIH. Hence estimation of these parameters will aid in early detection and better management of preeclmpsia which is important to improve the maternal and fetal outcome of preeclampsia.

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