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International Journal of Current Research
Vol. 7, Issue, 05, pp.16260-16264, May, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

STUDY OF EVALUATE THE ALTERATION IN SERM LIPID PROFILE IN PREGNANCY INDUCED HYPERTENSIVE PATIENTS

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ARTICLE INFO

Article History:
Received 20th February, 2015
Received in revised form
23rd March, 2015
Accepted 24th April, 2015
Published online 31st May, 2015

Key words:
Multiorganic
Multiparas
Eclampsia
Proteinuria.

ABSTRACT

Pre-eclampsia is one of the greatest medical enigmas of obstetrics machine all over the world. This peculiar multiorganic syndrome and its major catastrophe – Eclampsia still takes a large toll of maternal and fetal lives in underdeveloped and developing countries. Eclampsia was described several centuries before the time of Christ. The word eclampsia was used by
Hippocrates to mean "fever of sudden onset." Originally, the term Eclampsia is derived from a Greek word meaning "like a flash of lightening." Egyptian, Chinese, Indian and Greek literatures mention about this word. Both
Adharvana veda (1000-800 BC) and
Shushrutha, (1st century AD) have mentioned the grave prognosis of eclampsia.
Mauriceau (1694) observed that primiparas are more likely to develop convulsions than multiparas.
Hamilton (1775) noticed that twin gestation predisposed to eclampsia.
Lever and simpson (1848) observed proteinuria in pre-eclamptic pregnant women.
Sheeham (1950) concluded that edema is principally due to vasomotor disturbances.
The onset of pre-eclampsia occurs after 30th week of gestation in 90% of cases and between 30-36th week in 50-70% of cases. (Dickman, 1952). The combination of proteinuria and hypertension during pregnancy markedly increases the risk of prenatal mortality and morbidity.

Citation *Moulali, D. and Dr. Sarma, D.V.H.S. S*, 2015. "Study of evaluate the alteration in serm lipid profile in pregnancy induced hypertensive patients", *International Journal of Current Research*, 7, (5), 16260-16264.

INTRODUCTION

Pregnancy-induced hypertension is a rise in blood pressure (>140/90 mmHg), with or without proteinuria, during the second half of pregnancy. Pre-eclampsia is a multisystem disorder, which occurs only in pregnant women during the second and third trimesters of pregnancy and is associated with raised blood pressure and proteinuria. It rarely presents before 20 weeks of gestation (Dutta, 1998). Eclampsia is a syndrome with one or more episodes of convulsions in association with pre- eclampsia. In India, the national incidence of PIH is 15.2%, with the incidence in nulliparous women being four times greater than in multipara (Shruti Mohanty *et al*., 2006). The risk of developing pre-eclampsia appears to be greater in women who have family history of essential hypertension, and there may also be a relationship between pre-eclampsia and the metabolic syndrome. Pre-eclampsia is associated with substantial risks. For the fetus, these include intrauterine growth retardation, death and prematurity with attendant complications where as the mother is at risk of seizures (eclampsia), renal failure, pulmonary edema, stroke, and death (Rubina Aziz and Tabassum Mahboob, 2007). Pre-eclampsia is a syndrome, which affects virtually all maternal organ systems. The most important feature in toxaemia of pregnancy is hypertension which is supposed to be due to vasospastic phenomenon in kidney, uterus, placenta and brain. An abnormal lipid profile is known to be strongly associated with atherosclerotic cardiovascular diseases and has a direct effect on endothelial dysfunction. Altered lipid synthesis leading to decrease in PGI2: TXA2 ratio is also supposed to be an important way of pathogenesis in pregnancy induced hypertension. Thus abnormal lipid metabolism seems important in the pathogenesis of pregnancy induced hypertension (Jayanta De, 2006). 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. Elevated uric acid is another component of the preeclampsia syndrome. Although hyperuricemia does correlate with maternal morbidity, there is an even stronger association of uric acid with the risk for small birth weight infants and with overall foetal mortality (Adiga Usha and Adiga Sachidananda).

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The hyperuricemia of preeclampsia has been variably suggested to be associated with lactic acidosis, altered renal function or oxidative stress. Uric acid is excreted from the body by kidneys. In cases such as renal failure, acute infections, gut and Hemolytic anemia's uric acid levels increases (Geoffrey Chamberain). Proteinuria is required for the diagnosis of preeclampsia, and it is also a criterion for identifying the disease severity. The present study is based on evaluation of Serum Total Lipids viz, Cholesterol, Triglycerides, HDL Cholesterol, LDL Cholesterol and VLDL Cholesterol levels, Serum uric acid, Spot urinary protein in women with PIH and to compare the levels with those of normal normotensive pregnant women.

REVIEW OF LITERATURE

Historical Background (Lenon and Chesley, 1984)

The pre-Hippocratic *Coan* prognosis alluded to eclampsia; "in pregnancy drowsiness and headache accompanied by heaviness and convulsions is generally bad" (xxx1, 507). Ancient Egyptian, Chinese and Indian writings have been known to have mentioned eclampsia, but perusal of sources cited is unconvincing. Ancient Greeks also recognized pre-eclampsia: "in pregnancy onset of drowsy, headache with heaviness is bad; such cases are perhaps liable to some sort of fits at the same time" (xxx1, 523). *Vrandaeus* coined the term eclampsia in a treatise on gynaecology in 1619, (*G. Joshin Forth*). Eclampsia was not differentiated from epilepsy until 1739 when de *Sauvages* wrote that epilepsy was chronic with recurrence of convulsions through the years, all convulsions of acute causation, he called "eclampsia". 20 years later he defined several species of genes of eclampsia, in relation to various acute causes that Hippocrates had described, such as marked haemorrhages, severe pain, vermicular infestation and the like.

Demanet, in 1797 wrote that all six of his eclamptic patients had anasarca and suggested that edema be added to the three recognized causes of convulsions: depletion, repletion and the pains of labour. In 1840, *Rayer* observed Proteinuria in three edematous pregnant women. In 1843, the discovery of Proteinuria in eclampsia was made independently by *Lever* and *Simpson*. In 1851, *French* published an influential book on nephritis in which he wrote that eclampsia is a form of uremia, an opinion that held sway for half a century thereafter. *Vinay* in 1894, used a primitive sphygmomanometer and found BP ranging from 180-200 mmHg in pregnant and proteinuric women; pressure of up to 160 mmHg was normal as estimated by his instrument. Primary or essential hypertension was not recognized until 1896, when *Albutt* observed that middle aged and older persons, especially women often develop hypertension with no other evidence of renal disease. He called the disorder "Senile plethora", an appellation that had an unfortunate and lingering effect because obstetricians thought their patients were not old enough to have it. The discovery of eclamptic hypertension in generally credited to *Vasquez* and *Nobecourt* in 1897, but he remarked that they had confirmed Vinay's observation. *Vinay* had thought that his patients had nephritis but the equation that pre-eclampsia and eclampsia with nephritis was common in those days; actually the term "nephritic toxemia" persisted until about 1940. In 1952, American Committee on Maternal Welfare permitted the diagnosis of pre-eclampsia on the basis of the appearance of any one sign of either hypertension or Proteinuria, edema or weight gain more than 5 pounds within a week after the 20 weeks of gestation. In 1960, *Chesley Cosgrove* and *Arnitto* presented an analysis of pregnancies in 147 sister and the first 110 daughters of eclamptic women of whom, 1/3rd and 1/4th of them developed convulsions.

Pregnancy induced hyper tension (PIH)

Hypertensive disorders of pregnancy have been variously classified. The term pregnancy induced hypertension (PIH) is used to describe any new pregnancy onset related hypertension. It includes the development of hypertension without proteinuria and is a potential precursor to pre-eclampsia or eclampsia in the latter circumstance.

The classification of hypertensive disorders complicating pregnancy by working Group of the NHBPEP (2000). There are five types of hypertensive disorders of pregnancy.

- Gestational hypertension (previous pregnancy induced hypertension or transient hypertension).
- Pre-eclampsia.
- Eclampsia.
- Pre-eclampsia superimposed on chronic hypertension.
- Chronic hypertension.
- [Modified from National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000)[14]].

DIAGNOSIS OF HYPERTENSIVE DISORDERS COMPLICATING PREGNANCY[14]

Gestational hypertension (hypertension without proteinuria)[14]

- BP ≥ 140/90 mmHg for first time during pregnancy.
- BP return to normal within 12 weeks postpartum.
- May have other signs of pre-eclampsia like epigastric discomfort or thrombocytopenia.

Pre-eclampsia

Minimum criteria[14]

- BP > 140/90 mmHg after 20 weeks gestation.
- Proteinuria > 300mg/24hours or > 1+ dipstick Increased certainty of pre-eclampsia.
- BP >160/110mmHg.
- Proteinuria 2.0gm/24hours or > 2+dipstick.
- Serum creatinine >1.2mg/dl.
- Platelets <100,000/mm^3.
- Microangiopathic hemolysis(increased LDH).
- Increased ALT or AST.
- Persistent headache or other cerebral or visual disturbance persistent epigastric pain.

Eclampsia

- Seizures that cannot be attributed to other causes in a women with pre- eclampsia[14].

Superimposed pre-eclampsia (on chronic hypertension)[14]

- New onset proteinuria (> 300mg/24 hours) in hypertensive women but no proteinuria before 20 weeks of gestation.
- A Sudden increase in blood pressure or proteinuria.

Chronic hypertension[14]

- Hypertension (BP>140/90 mmHg) before pregnancy or diagnosed before 20 weeks of gestation (except in gestational trophoblastic disease).
- Hypertension persisting after 12 weeks postpartum.
- Severity of PIH Severity of PIH is assessed by the frequency and intensity of the abnormalities listed below. Importantly, the differentiation between mild and severe preeclampsia cannot be rigidly pursued because apparently mild disease may progress rapidly to severe disease.

ETIOLOGY

Hypertension

The underlying basic factor related with the pathologic state of the syndrome is intense vasospasm affecting almost all the vessels particularly those of the uterus and the kidney. The responsible agent for vasospasm still has not been isolated precisely, but it seems certain to be humoral in origin.

NORMAL PREGNANCY

Constant production of angiotensin-II is destroyed by angiotensinase which is liberated from the placenta. Thus the blood pressure is stabilized. The vascular system becomes refractory, selectively to pressor agent angiotensin-II. This is probably brought out by vascular synthesis of prostaglandin I_2 which has got vasodilator effect. The interaction between the two systems stabilises the blood pressure in normal pregnancy[15].

PRE-ECLAPMSIA

There is an imbalance of different components of prostaglandins- relative or absolute deficiency of vasodilator prostaglandin (PGI_2), synthesized in vascular endothelium and increased synthesis of thromboxane (TXA2), a potent vasoconstrictor in platelets. There is increased vascular sensitivity to the pressor agent angiotensin II. The sensitizing substances are yet to be explored. The role of steroid sex hormones oestrogen, progesterone or other metabolites still remains speculative. Increased vasoconstrictor effect on the sensitized blood vessels is due to elevated concentration of sodium in the extracellular Mucopolysaccharides on the arterial wall.

MATERIALS AND METHODS

This study was carried out in the department of Biochemistry, S.V.S Medical College, and Mahabubnagar.

The relevant data is gathered from the Department of Obstetrics and Gynaecology in, S.V.S medical college and Hospital during the year 12- The study was conducted on 60 subjects among them 30 were women with pregnancy induced hypertension and 30 were age matched normal pregnant women.

Inclusion criteria

- Pregnant women with PIH (with BP > 140/90 mmHg after 20 weeks of gestation).
- Pregnant women with previous history of PIH.

Exclusion criteria

- Pregnant women with other systemic disorders like gestational diabetes.
- Pregnant women with < 20 weeks of gestational age.

COLLECTION OF BLOOD SAMPLE FOR ANALYSIS

A random venous blood sample (5ml) was drawn from the patients and controls into a sterile disposable syringe which was transferred into centrifuge tubes and was allowed to clot for 30 minutes. The sample was centrifuged at 3000 rotations per minute for 10 minutes and the serum was separated and collected from the centrifuge tubes and stored at -20°C until analysed.

COLLECTION OF URINE SAMPLE

A random urine sample was collected from the patients and controls.

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS software version 11.0. The descriptive results were expressed as mean and standard deviation. Significance of difference between the patient and control groups observed was assessed by using the student 't'- test. The p- values were expressed along with mean values and standard deviation. The p values < 0.05 were considered statistically significant. Correlation co-efficient (Pearson's correlation) was calculated to measure the relationship among the variables.

The following parameters were estimated in all patients and controls.

- Serum Total Cholesterol and HDL Cholesterol
- Serum LDL
- Serum VLDL
- Serum Triglycerides
- Serum uric acid

RESULTS

The present study was undertaken in the Department of Biochemistry,, S.V.S Medical College, and Mahabubnagar. 30 pregnant women with PIH, whose gestational age is > 20 weeks, were selected as cases and 30 healthy ages matched pregnant women were selected as controls.

Serum lipid profile, uric acid and urinary protein were estimated in both the groups.

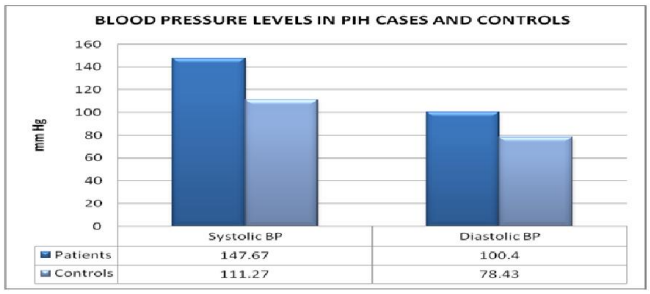
Table 1. Age Distribution Among Pih Patients and Controls

	PATIENTS (N=30)	CONTROLS (N=30)
RANGE (years)	18 – 29	18- 29
MEAN ± SD (years)	22.30 ± 3.10	23.0 ± 3.45

The age range was 18 to 29 years in both the patient and control group. The mean and SD was (22.30 ± 3.10) in cases and (23.0 ± 3.45) in the controls.

Table 2. Blood Pressure Levels in Pih Cases and Controls

Parameter	Patient Group Mean± SD (N= 30)	Control Group Mean± SD (N= 30)
Systolic BP (mm Hg)	147.67± 7.20	111.27± 8.56
Diastolic BP (mm Hg)	100.40± 11.49	78.43± 4.60



The mean and SD of systolic and diastolic BP in patient group is (147.67± 7.20) / (100.40± 11.49) and in controls it is (111.27± 8.56) / (78.43± 4.60). There is a significant increase in systolic and diastolic BP in patient group when compared to controls.

Table 3. Comparison of Lipid Profile Between Patient and Control Group

Parameters	Patient Group	Control Group	p-Value
Total cholesterol	207.8 ± 19.28	201.60± 16.81	NS
HDL	41.83 ± 7.62	58.80 ± 6.80	<0.0001
TGL	295.3 ± 101.94	203.07 ± 15.90	<0.0001
LDL	107.0 ± 26.27	102.27 ± 15.88	NS
VLDL	59.05 ± 20.38	40.46 ± 3.30	<0.0001

Mean and SD of serum Triglycerides,VLDL showed statistically significant increase and Serum HDL showed statistically significant decrease in women with PIH as compared to healthy pregnant women (p<0.0001) whereas serum total cholesterol and LDL were not significant. (p>0.05).

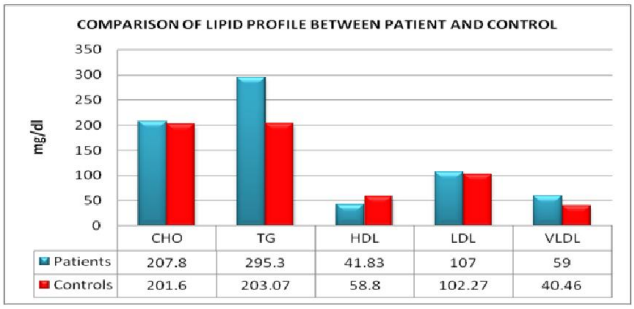


Table 4. Comparison of Different Lipid Ratio Between Patient and Control Group

Parameters	Patient Group (N=30)	Control Group (N=30)	p-Value
LDLC:HDLC	2.64±0.7	1.76±0.3	<0.0001
TCHO:HDLC	5.13±1.0	3.46±0.4	<0.0001
TGL:HDLC	7.48±3.4	3.50±0.5	<0.0001
HDLC:VLDC	0.7±0.3	1.46±0.2	<0.0001

Mean and SD of different lipid ratios are showed statistically significant in women with PIH as compared to healthy pregnant women (p<0.0001).

DISCUSSION

Preeclampsia has been traditionally defined as a triad of hypertension, oedema and proteinuria. It is now recognized that oedema is so consistent part of normal pregnancy that it has little or no value as a diagnostic sign of preeclampsia. Preeclampsia is a late and inconstant feature of the disorder. So, the only useful early sign is a change in the blood pressure. Because blood pressure measurement contains many errors, this only early diagnostic sign of preeclampsia is unsatisfactory. A rising serum uric acid is now recognized as an early feature of preeclampsia and its measurement greatly increases the accuracy of diagnosis[46]. Lipid metabolism plays a key role in the pathophysiology of pre-eclampsia. Increased triglycerides levels along with decreased HDL-cholesterol levels and delayed triglyceride clearance and high blood pressure are associated with development of preeclampsia (Rubina Aziz and Tabassum Mahboob, 2007).

These changes in the lipid levels could be related to the decrease in hepatic lipase activity during gestation. Activities of lipoprotein lipase and hepatic lipase are substantially decreased during normal pregnancy and is attributed to the heightened insulin resistance and raised estrogen levels respectively. Physiological insulin resistance is exaggerated in preeclamsia. Gestational insulin resistance may accentuate the suppression of lipoprotein lipase activity and increase mobilisation of free fatty acid from visceral adipocytes. Genetic factors (apo E polymorphism) are also found to be related to the lipoprotein lipase activity. These facts explain the hypercholesterolemia in preeclampsia (Adiga Usha and Adiga Sachidananda, ?). In accordance with the studies done by Rubina Aziz *et al.* (2007) and Jayant De *et al*. (2006) PIH is associated with hypertriglyceridemia, increased VLDL-c and reduced HDL-c, but total cholesterol and LDL-c showed no statistical difference between patients and controls. In the present study there is a significant increase in serum triglycerides in patient group (295.3 ± 101.94) as compared to controls (203.07 ± 15.90) and serum VLDL-c also showed significant increase in patient group (59.05 ± 20.38) as compared to controls (40.46 ± 3.30) but, serum HDL-c is decreased in patient group (41.83 ± 7.62) as compared to controls (58.80 ± 6.80).

During the course of normal pregnancy, plasma triglyceride and cholesterol concentrations rise and as pregnancy progresses both become normal. Hormonal variations during pregnancy affect lipid metabolism. The endogenous female sex hormones have significant effect on serum lipids. 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,

whereas the decreased activity of lipoprotein lipase is responsible for the decreased catabolism at the adipose tissue level, the net effect of which will be an increase in circulating triglycerides and the second step of uptake of the remnant chylomicrons by the liver is delayed so it leads to accumulation of triglycerides (Rubina Aziz and Tabassum Mahboob, 2007).

On the other hand increased triglycerides play a part to decrease the HDL cholesterol .HDL particles carry cholesterol from peripheral tissue to liver. Impaired transport of cholesterol from peripheral tissue to the target area of utilization cause the decrease in HDL cholesterol in serum. There is a direct correlation between adipose tissue lipoprotein lipase activity and plasma HDL cholesterol. This direct correlation may be responsible for low levels of HDL cholesterol. Hypertriglyceridemia, leading to low HDL cholesterol is due mainly to the action of Cholestreryl Ester Transfer Protein (CETP) (Rubina Aziz and Tabassum Mahboob, 2007). We also calculated ratios between different lipids like LDLC: HDLC, TCHO: HDLC, TGL: HDLC, HDLC: VLDLC are stastistically significant compared to normal pregnant women. The relavence of these ratios in pregnancy and PIH is yet to be established the significance of altered TC: HDLC, TG: HDLC and HDLC: VLDLC ratios cannot be over looked as they indicate additional risk in PIH. Dyslipidemia mediated activation of the endothelial cells to the placentally derived endothelial disturbing factors like lipid peroxide and trophoblastic components or combination of placentally derived factors with the lipoproteins could be regarded as possible contributors for pathogenesis of PIH. Thus the assessment of blood lipids may be helpful in prevention of complications in PIH.

Conclusion

Women who develop pre-eclampsia had distributed lipid profile due to abnormal lipid metabolism. Increased triglyceride levels and delayed triglyceride clearance and high blood pressure are the reasons for the development of preeclampsia. This association may be significant in understanding the pathological process of pre-eclampsia and may help in developing strategies for prevention and early diagnosis of pre-eclampsia.

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