Original Research Article

Atherogenic index of plasma and dyslipidemia in preeclampsia- a risk factor for future maternal coronary arterial disease

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Abstract

Aim and Objective: To compare the serum lipid profile i.e. Total Cholesterol, Triglycerides, LDL-C, VLDL-C and HDL-C, atherogenic index (AI), and there correlation/association with Pregnancy induced hypertensioin (PIH) .**Methods:** We analysed the fasting blood sample for lipid profile and urine for protein in 60 PIH primigravida cases and in 60 normal ANC controls. In that we analysed Total Cholesterol (TC), Triglyceride (TG), High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C) and Very low density lipoprotein cholesterol (VLDL-C) by fully automated biochemistry analyser. **Results:** The mean value of atherogenic index TC/HDL-C in controls and cases are 3.42 ± 0.36 and 5.25 ± 0.97 respectively. AI (TC/HDL-C) was higher (twice the average risk) than normal in cases as compared to controls and the difference was highly significant ($p<0.001$).The mean value of atherogenic index LDL-C/HDL-C in controls (normal pregnant women) and cases (PIH women in third trimester) was found to be 1.76 ± 0.3 and 2.96 ± 0.74 respectively. There was significant increase in atherogenic ratio LDL-C/HDL-C in cases (PIH women) as compared to controls (normal pregnant women in third trimester) ($p<0.001$).**Conclusion:** PIH is associated with atherogenic dyslipidemia. Therefore estimation of lipid profile in primigravidae at antenatal visits may help in identifying high risk pregnancies that are more prone for developing cardiovascular diseases. Further prospective cohort studies in larger population are required to predict maternal future cardiovascular risk in women with history of PIH. It can be prevented by lifestyle modifications and therapy in PIH. Women with hypertensive disorders in pregnancy should therefore be monitored more closely for the future development of hypertension and the presence of other cardiac risk factors.

Keywords: Total Cholesterol, Triglycerides, LDL-C, VLDL-C. HDL-C, Atherogenic index (AI), PIH

Introduction

Human pregnancy is associated with numerous biochemicals, physiological and anatomical alterations. Pregnancy is a physiological stress in which many changes occur in the body. More stress is laid on the biochemical changes, which occur in the blood during the normal pregnancy and becomes exaggerated in complications of pregnancy, like Pregnancy Induced Hypertension (PIH). PIH was reported with incidence of about 10% of first pregnancies and 20% to 25% of women with previous chronic hypertension[1].According to WHO,[2] the world health report 1998, PIH is defined as ”hypertension after 20 weeks of pregnancy in a woman with or without edema and proteinuria without previous history of hypertension”. When associated with proteinuria, the disorder is termed preeclampsia/toxemia, and when present without protein in urine it is called transient hypertension or gestational hypertension[2]. Eclampsia is a dangerous complication of preeclampsia. Overall world wide incidence of Preeclampsia is 3-5%[3].But in India, overall incidence is 5-15%[4]. There is increasing evidence that endothelial cell dysfunction is the primary patho-physiological mechanism which causes preeclampsia[5,6]. However, the pathway mediating endothelial cell layer dysfunction still not clear . Multiple circulating factors may provoke endothelial changes, including altered lipoproteins[7].In normal pregnancy, there is physiological increase in plasma lipids but this event is not atherogenic,[8]as it is under hormonal control[7]. But in complicated pregnancy there may be a defect in mechanism of adjusting physiologic hyperlipidemia. The abnormal lipid metabolism seems important in the pathogenesis of pregnancy induced hypertension[8]. The role of abnormal lipid profile as a risk factor in pathophysiology of preeclampsia is controversial[9]. Estimation of Serum lipid profile during pregnancy in primigravidae may help in identifying high risk pregnancies that are more prone for developing PIH .Also serum lipid profile along with atherogenic index (TG/HDL-C, TC/HDL) may help to predict the future risk of cardiovascular diseases.

Material and methods

This was case control study, conducted in Department of Biochemistry of medical college with the help of Obstetrics and Gynaecology Department during period of May 2011 to October 2012.The study was approved by institutional Ethics Committee for

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research work. The diagnosis of PIH was done by Obstetrics and Gynaecology Department based on the definition of American college of obstetrics and gynaecologist. Systolic blood pressure > 140 mm Hg or diastolic blood pressure >90 mm Hg; systolic blood pressure increase of > 30 mm Hg or diastolic blood pressure increase of 15 mm Hg over first trimester of prepregnancy values (manifested on two occasion at least 6 hrs apart)and proteinuria ≥300 mg or greater in 24 hr urine collection or dipstick protein ≥ 1 + (on two occasion at least 6 hrs apart) is defined as PIH.

Study Groups-The study subjects were divided into two groups.

Group A: Control subjects

60 women having normal uncomplicated pregnancy without hypertension

Group B: Cases

60 pregnancy induced hypertension (PIH) patients (PIH) patient includes,Preeclampsia, Preeclampsia with convulsions (Eclampsia)

Pregnant women of age ge < 18 years and > 30 years, multigravida with more than one para, women with previous history of hypertension, DM, thyroid disorder, dyslipidemia, preeclampsia, renal disease, women on drug therapy except iron and calcium were excluded

Drug therapy that interferes with serum lipid levels such as

- Oral contraceptives
- Cimetidine / Ranitidine
- Oestrogens
- Progestins
- Non steroidal anti-inflammatory drugs.

2 ml of freshly voided urine specimen is collected in a bulb with aseptic precaution, proetein was measured by dipstic method and was graded on scale of 0 to 4 (0- none,1+ : 30 mg/dl, 2+ : 100 mg/ dL, 3+ 300 mg/dl, 4+ 1000). 5 ml of venous blood was collected in clean plain bulb after an overnight fast (after 8 to 12 hours) . Samples were collected between 7am to 9 am. The serum was separated by centrifugation at 4000 rpm for 10 min. Serum lipid profile was estimated on the same day. In this study, we measured serum levels of lipid profile comprising of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) by fully automated biochemistry analyser.

Result

Table 1: Comparison of lipid profile in PIH cases and controls

Parameter	Control (n=60)[mean ± SD]	Cases(n=60)[mean ± SD]	P value
TG	201.03±12.9	258.98±37.33	0.000***
TC	209.1±14.14	211.25±13	0.3877
HDL-C	61.87±8.45	41.4±6.81	0.000***
VLDL-C	40.21±2.58	51.8±7.47	0.000***
LDL-C	107.03±10.56	118.05±13.39	0.000***
TG/HDL-C	3.30±0.43	6.44±1.45	0.000***
TC/HDL-C	3.42±0.36	5.25±0.97	0.000***
LDL-C/HDL-C	1.76±0.3	2.96±0.74	0.000***

* = (p<0.05), **= (p<0.01), ***= (p<0.001)

The mean value of serum triglycerides in controls (normal pregnant women in third trimester) and cases (PIH women in third trimester) was found to be 201.03 ± 12.9 and 258.98 ± 37.33 respectively. Serum triglycerides level was higher in both cases and control but rise in TG was much more in cases (PIH women in third trimester) as compared to controls (normal pregnant women in third trimester) and the difference was highly significant.(p<0.001) The mean value of serum total cholesterol in controls and cases was 209.1 ± 14.14 and 211.25 ± 13 respectively. Serum total cholesterol was higher in both controls and cases. But there was no significant difference in serum total cholesterol between controls and cases (p value = 0.38).The mean value of serum high density lipoprotein cholesterol (HDL) in controls and cases was 61.87 ± 8.45 and 41.4 ± 6.81 respectively. There was significantly lower HDL-C in cases as compared to controls and the difference was highly significant between two groups (p<0.001).The mean value of serum very low density lipoprotein cholesterol (VLDL-C) in controls and cases was found to be 40.21± 2.58 and 51.8 ± 7.47 respectively. Serum VLDL-C level was higher in cases as compared to controls and the difference was highly significant between two group (p<0.001).The mean value of serum low density lipoprotein cholesterol (LDL-C) in controls and cases (PIH women in third trimester) were 107.03 ± 10.56 and 118.05 ± 13.39 respectively. There was significant higher levels of serum LDL-cholesterol observed in cases as compared to controls (normal pregnant women) and the difference was highly significant. P value = 0.00002.Atherogenic index like TG/HDL, TC/HDL and LDL/HDL were calculated in cases and controls to find out the risk ratio for cardiovascular diseases. The mean value of Atherogenic index TG/HDL-C in controls and cases was found to be 3.30 ± 0.43 and 6.44 ± 1.45 respectively. AI (TG/HDL-C) risk ratio was very high than normal in cases (PIH) as compared to controls and the difference was statistically highly significant (p<0.001).The mean value of atherogenic index TC/HDL-C in controls and cases was found to be 3.42 ± 0.36 and 5.25 ± 0.97 respectively. AI (TC/HDL-C) was higher (twice the average risk) than normal in cases as compared to controls and the difference was highly significant (p<0.001).The mean value of atherogenic index LDL-C/HDL-C in controls (normal pregnant women) and cases (PIH women in third trimester) was found to be 1.76 ± 0.3 and 2.96 ± 0.74 respectively. There was significant increase in atherogenic ratio LDL-C/HDL-C in cases (PIH women) as compared to controls (normal pregnant women in third trimester) (p<0.001).

Discussion

Worldwide diverse studies[10] have reported elevated lipid levels in PIH. Earlier study[11] reported that the major changes in the lipid profile in normal pregnancy as well as in PIH is serum hypertriglyceridemia, which may be as high as two to three folds in the third trimester over the levels in non pregnant women. Our study was conducted to find out what changes occur in lipid profile of PIH patients with respect to normal pregnant women and is there any correlation of lipid profile with the severity In our study, we compared serum triglyceride level in normal pregnant women (controls) and PIH. We found that, triglycerides level was above the normal level in both normal pregnancy and PIH cases. But in PIH cases, rise in triglycerides level was more and highly significant than normal pregnant women. Studies conducted by De J et al[10], Adiga U et al[12] and Sattar N et al[13] for lipid profile in PIH, showed of PIH.Normal pregnancy is state of hyperlipidemia and hyper-estrogenemia. Estrogen causes increase in HDL-C level and decrease in LDL-C level. Estrogen causes decline in hepatic lipase activity. It results into impaired clearance of lipoproteins from circulation[14].

The principle modulator of this hypertriglyceridemia is oestrogen as normal pregnancy is associated with hyperoestrogenaemia. Oestrogen induces hepatic biosynthesis of endogenous triglycerides, by raising the hepatic VLDL-C[15]. This process may be modulated by hyperinsulinism found in pregnancy[16]. Also activities of adipose tissue lipoprotein lipase and hepatic lipase are substantially decreased during normal pregnancy (due to insulin resistance and estrogen, respectively). This results into impaired removal of triglyceride rich lipoproteins from the circulation. Thus increased production and impaired removal of TG is responsible for rise of TG in normal pregnancy[17]. Preeclampsia is a state of hypoestrogenemia and exaggerated insulin resistance[10]. One of the reasons for dyslipidemia in PIH is hormonal imbalance.Decreased uteroplacental blood flow is the main pathophysiological event in preeclampsia. This leads to impairment in the formation of dehydroepiandrosterone sulphate (DHEA) by fetal adrenal glands by interfering with the uptake of lipids by the fetus. Ninety percent of estrogen in maternal circulation is from fetal DHEA.The state of hypoestrogenemia leads to decreased expression of VLDL-C receptors in the placenta that are essential for the lipid transport to the fetus. Resulting in reduced transport of VLDL-C to fetal compartment, which may be the reason for maternal hypertriglyceridemia in PIH. Further LDL-C taken up by the fetus for the synthesis of DHEA is decreased due to reduced fetoplacental perfusion. This leads to increased LDL-C in maternal circulation. The decreased catabolism of TG rich lipoproteins by reduced placental uptake results in the accumulation of TG rich lipoproteins in the maternal circulation[8].Therefore, the level of TG gets elevated in PIH. Increased triglycerides found in PIH are thought to be deposited in predisposed vessels. This contributes to the endothelial dysfunction, both directly and indirectly through generation of small, dense low density lipoprotein cholesterol[13]. In our study, levels of serum VLDL-C was significantly higher ($p<0.001$) in PIH cases in comparison to normal pregnant women (controls). There was highly significant difference in the VLDL-C level between PIH and normal pregnancy. Studies conducted by De J et al[10], Adiga U et al[12] and Sattar N et al[13]showed similar result in their study. This increase in VLDL-C levels in PIH may be due to hypertriglyceridemia. This leads to increased entry of VLDL-C that carries endogenous triglyceride into circulation[18,19].In our study, cholesterol level was raised above the normal range in both controls (normal pregnancy) and PIH cases. This elevation of cholesterol was more in PIH cases as compared to the normal pregnant women. But no significant difference (p value = 0.38) in total cholesterol value could be observed in both groups. This finding in our study was consistent with the findings of Sattar N et al[13]and Jayanta De et al[10]. However studies conducted by Khaliq F et al [8], Adiga U et al[12], Kocyight A et al[20] have found significant rise in serum cholesterol in PIH.

Conclusion

Human gestation is associated with "atherogenic" lipid profile that is further enhanced in PIHs and this profile may be potential contributor to endothelial cell dysfunction. PIH is characterized by abnormal increase in a triglyceride level beyond the physiological increase of normal pregnancy. The women who developed PIH had disturbed lipid profile due to abnormal lipid metabolism resulting in endothelial dysfunction. This association may be significant in understanding the pathophysiological process of PIH and may help in developing strategies for prevention and early diagnosis. Hence simple measurement of lipid profile can help in prevention of the complications of PIH and future cardio vascular risk of the mother.Both systolic and diastolic blood pressure was positively correlated with the level of TG. Thus risk of PIH is associated with increased TG concentration. PIH and atherosclerosis share common pattern of dyslipidemia such as increased TG, decreased HDL-C and increased LDL-C. Also elevation of atherogenic index TG/HDL-C was shown to be the single most powerful predictor for coronary heart disease among all the lipid variables. From these all above findings, it is clear that dyslipidemia in PIH will predispose mothers to future cardiovascular diseases.PIH is associated with atherogenic dyslipidemia. Therefore estimation of lipid profile in primigravidae at antenatal visits may help in identifying high risk pregnancies that are more prone for developing cardiovascular diseases. Further prospective cohort studies in larger population are required to predict maternal future cardiovascular risk in women with history of PIH. It can be prevented by lifestyle modifications and therapy in PIH. Women with hypertensive disorders in pregnancy should therefore be monitored more closely for the future development of hypertension and the presence of other cardiac risk factors.

References

1. Ghosh MK. Maternal mortality. A global perspective. J Reprod Med 2001 May;46(5):427-433.
2. World Health Organization. The World Health Report 1998. Life in the 21st century; a vision for all. Geneva: WHO 1998; p. 97.
3. Wang A, Rana S, Karumanchi SA. Preeclampsia: The Role of Angiogenic Factors in Its Pathogenesis: Physiology (Bethesda). 2009 ;24:147-158
4. Friedman SA, Taylor RN, Roberts JM. Pathophysiology of preeclampsia. Clin. Perinatol.1991;18(4):661-682.
5. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclamnpsia: an endothelial cell disorder. Am J Obstet Gynecol.1989;161(5):1200-1204.
6. Adiga U, D'souza V, Kamath A, Mangalore N. Antioxidant Activity and Lipid Peroxidation in Preeclampsia: J Chin Med Assoc. 2007 ;70(10): 435 -8.
7. Winkler K, Wetzka B, Hoffmann MM, Friedrich I, Kinner M, Manfred WB,et al.Triglyceride-rich lipoproteins are associated with hypertension in pre-eclampsia. The J Clin Endocrinol Metabol. 2003;88:1162-6.
8. Klhaliq F, Singhal U, Arshad Z, Hossain MM. Study of Serum lipid and Lipoprotein in pre-eclampsia with special reference to parity. Indian Journal of Physiology and Pharmacology. 2000;44(2):192-196.
9. Setareh A, Mitra MG, Sedigheh B, Shoaleh S, Vahid Y, Siroo s S. Maternalplasma lipid concentrations in first trimester of pregnancy and risk of sever preeclampsia: Pak J Med Sci. 2009;25(4):563-567.
10. De J, Mukhopadhyay A, Saha PK. Study of serum lipid profile in pregnancy induced hypertension. Ind J Clin Biochem. 2006;21(2):165-168.
11. Chiang AN, Yang ML, Hung JH, Chon P, Shyn SK Nq HT. Alterations of serum lipid levels and their biological relevance's during and after pregnancy.Life Sci.1995; 56 (26): 2367-75.
12. Adiga U, Adiga S. Dyslipidemia in pregnancy induced hypertension. Journal of Global Pharma Technology. 2010; 2(5):69-72.
13. Sattar N, Bendomir A, Berry C, Shepherd J, Greer IA, Packard CJ. Lipoprotein subfraction concentrations in preeclampsia: pathogenic parallels to atherosclerosis. Obstet Gynecol 1997;89(3):403-408.
14. Applebaum DM, Goldberg AP, Pykalisto OJ, Brunzell JD, And Hazzard WR .Effect of estrogen on post-Heparin lipolytic activity. Selective Decline In Hepatic Triglyceride Lipase. The Journal Of Clinical Investigation.1977;59(4):601-608.
15. Glueck, CJ, Fallet RW, Scheel D. Effects of oestrogenic compounds on triglyceride kinetics. Metabolism 1975; 24(4):537-45.

16. Adegoke, OA, Iyare EE, Gbenebitse SO. Fasting plasma glucose and cholesterol levels in pregnant Nigerian women. Niger Postgrad Med J.2003;10(1):32-36.
17. Alvarez JJ, Montelongo A, Iglesias A, Lasuncion MA, Herrera E. Longitudinal study on lipoprotein profile, high-density lipoprotein subclass, and postheparin lipases during gestation in women. J Lipid Res 1996;37(2):299–308.
18. Teichmann, AT, Wieland H, Cremer P, Kulow G, Mehle U. Serum lipid and lipoprotein concentrations in pregnancy and at onset of labour in normal and complicated pregnancies caused by hypertensive gestosis and fetal growth retardation. Geburtshilfe Frauenheilkd (Germany, West) 1998; 48(3):134-139.
19. Knopp, RH, Warth MR, Charles D, Childs M, Li JR, Mabuchi H, Van Allen MI. Lipoprotein metabolism in pregnancy, fat transport to the fetus and the effects of diabetes. Biol. Neonate.1986;50(6):297-317.
20. Kocyigit Y. Atamer A, Atamer A, Tuzcu A, Akkus Z. Changes in serum levels of leptin, cytokines and lipoprotein in pre-eclamptic and normotensive pregnant women. Gynecol Endocrinol. 2004;19(5):267-73.

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