<u>**Original Research Article**</u>

"A STUDY ON ATHEROGENIC INDEX OF PRE-ECLAMPSIA AS COMPARED TO NORMAL PREGNANT WOMEN"

Rajesh Bansal[1], Ruby Naz[2], Sadhana Joshi[3], Rinku Bansal[4]

[1]Assistant Professor, Department of Microbiology, Jhalawar Medical College, Jhalawar (Raj.)

[2]Associate Professor, Department of Microbiology, Jhalawar Medical College, Jhalawar (Raj.)

[3] Assistant Professor, Department of Microbiology, Jhalawar Medical College, Jhalawar (Raj.)

[4]Associate Professor, Department of Biochemistry, Jhalawar Medical College, Jhalawar (Raj.)

Corresponding Author: Dr. Rinku Bansal
Email: rinksbansal@gmail.com

Abstract

Introduction: Hypertensive disorders of pregnancy affect 10% of pregnancies and are defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as new-onset hypertension ($\geq$140 mmHg systolic or $\geq$90 mmHg diastolic) after 20 weeks' gestation[2]. Pre-eclampsia patients had significantly higher levels of TC, LDL, TG, and VLDL than normal pregnant women. Pre-eclampsia and atherosclerosis are associated with dyslipidemia, endothelial dysfunction, and an increase in the circulating levels of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α. An abnormal lipid profile is known to be strongly associated with atherosclerotic cardiovascular diseases and has a direct effect on endothelial dysfunction[13]

Materials and Methods: The study was conducted in the clinical Biochemistry laboratory, at Jhalawar Medical College, Jhalawar. In this present study, 50 primigravida women already diagnosed with pre-eclampsia in the third trimester of pregnancy in the age group 18-25 years as the case group and 50 age and gestational age-matched healthy normotensive primigravida women with normal pregnancy as a control was studied. All the data was collected through pre-designed Performa and data was entered in MS Excel software. Data was analyzed by SPSS 23.0 Software.

Result and Discussion: Most participants belong to the 20 to 29 years of age group in pre-eclampsia as well as normal pregnant women. The mean age of pre-eclampsia patients was 28.67 ± 4.32 and the mean age of normal pregnant women was 27.38 ± 3.69. In Pre-eclampsia, pregnant women had a 62% family history of hypertension while in normal pregnant women, only 36% had a family history of Hypertension. Pre-eclampsia women's lipid profiles were significantly higher than normal pregnant women's, except for high-density lipoprotein-cholesterol (HDL-C). Endothelial dysfunction is the main cause of the multiple-organ pathophysiology of preeclampsia-eclampsia.[15] In pregnancy, hormonal alterations modify the maternal metabolic environment, and significant hyperlipidemia is considered physiological. However, in pre-eclampsia, these changes in lipid metabolism are exaggerated and are a major cause of endothelial dysfunction.

Conclusion: Pre-eclampsia, being the prominent cause of maternal death and perinatal morbidity, the necessity for a dependable marker to identify the disease in its early stages is increasing gradually. In pre-eclampsia and other hypertensive diseases of pregnancy, dyslipidemia is exaggerated with associated endothelial dysfunction and increased oxidative stress, which is thought to increase the risk

of atherosclerosis and other CVDs. Pre-eclampsia patients had significantly higher levels of TC, LDL, TG, and VLDL than normal pregnant women. This is consistent with the findings in this study.

Keywords: Pre-eclampsia, hypertension, hyperlipidemia, endothelial dysfunction.

Introduction: Hypertensive disorders of pregnancy affect 10% of pregnancies[1] and are defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as new-onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) after 20 weeks' gestation[2].

This umbrella definition includes chronic hypertension, gestational hypertension, and preeclampsia (de novo or superimposed on chronic hypertension). Both of these conditions can significantly impact maternal and fetal health in the immediate and long term. For the mother, this includes a two- to four-fold increased risk of long-term hypertension, a doubling of the risk of cardiovascular mortality and major adverse cardiovascular events, and a 1.5-fold increased risk of stroke[3]. The precise origin of preeclampsia remains elusive, but it is believed to be likely multifactorial. A certainty is the central role played by the placenta in its pathology[4,5,6,7].

A long-standing hypothesis has been that preeclampsia develops as a consequence of some kind of immune maladaptation between the mother and the fetus during the very first weeks of pregnancy, leading to a 2-step disorder progression that can be summarized as follows: in a first–asymptomatic – step, local aberrant fetomaternal immune interactions within the uterine wall lead to impaired tissue and arterial invasion by trophoblast cells. This results in the failed transformation of the uterine spiral arteries and subsequently worsened placental perfusion. Chronic hypoxia or alternate periods of hypoxia/re-oxygenation within the intervillous space are expected to trigger tissue oxidative stress and increase placental apoptosis and necrosis[8,9]. The clinical disorder arises, in a second step, when the maternal vascular and immune systems cannot handle any longer the increased shedding of placental-produced debris and the aberrant expression of pro-inflammatory, anti-angiogenic and angiogenic factors, leading to systemic endothelial cell dysfunction and an exaggerated inflammatory response[10,11,12].

Pre-eclampsia and atherosclerosis are similar; both are associated with dyslipidemia, endothelial dysfunction and an increase in the circulating levels of proinflammatory cytokines, such as interleukin-6 and tumour necrosis factor-α. An abnormal lipid profile is known to be strongly associated with atherosclerotic cardiovascular diseases and has a direct effect on endothelial dysfunction[13]. Incorporation of specialist tests such as uterine artery pulsatility index and pregnancy-associate plasma protein A (PAPP-A) into clinical risk prediction models can also increase the positive predictive value for detecting women at risk of this condition[14].

Materials and Methods

Source of data: The study was carried out in the clinical Biochemistry laboratory, at Jhalawar Medical College, Jhalawar. In this present study, 50 primigravida women already diagnosed with pre-eclampsia in the third trimester of pregnancy in the age group 18-25 years as the case group and 50 age and gestational age-matched healthy normotensive primigravida women with normal pregnancy as a control was studied. **Study design:** The present study was designed to measure the level of total Cholesterol (TC), Triglyceride (TG), Direct LDL–cholesterol (dLDL-c), HDL-cholesterol (HDL-c), and VLDL in women diagnosed with pre-eclampsia as well as in women with normal pregnancy.

The Institutional Ethical Committee approved the study. Informed consent was obtained from all the women in the study or their legal representatives. Careful history was taken, and a clinical examination was done as per proforma.

Sample received in the Clinical Biochemistry lab for biochemical analysis of pregnant women were taken for study. Samples were allowed to clot and centrifuged at 3000rpm for 10 min and the serum separated. Lipid Profile was estimated using standard reagent kits after properly calibrating each method in Beckman fully automated analyzer. Total Cholesterol (TC) measurement based on the CHOD/PAP method, Triglyceride (TG) based on the GPO/PAP method, Direct LDL–cholesterol (dLDL-c) was estimated by kit based on the selective detergent method, HDL-cholesterol (HDL-c) by the method based on precipitation by Phosphotungstate and VLDL by Friedewald's formula.

Inclusion criteria:
1) Patients with a history and physical findings of pre-eclampsia.
2) Biochemical analysis suggestive of pre-eclampsia.
3) Pregnant females in age group 18-25 years.

Exclusion criteria:
1) Women with twin/multiple pregnancy.
2) Previous history of hypertension, diabetes mellitus, autoimmune disorders, renal, hepatic, or thyroid gland diseases, and intake of drugs that affect lipid metabolism.
3) Smoking and alcohol abusers.

Table: 1 Reference range of various parameters

Parameters (Unit)	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	Direct LDL (mg/dl)	HDL (mg/dl)	VLDL
Normal Range	150-240	50-200 (Male) 40-150(Female)	80-175	30-60 (Male) 35-75(Female)	Calculated by Friedewald's formula.

Results

One Hundred participants were recruited consisting of 50 pregnant women with pre-eclampsia and 50 pregnant women without pre-eclampsia.

Table 2: Socio-demographic data of pre-eclampsia women compared to normal pregnant women

Variable	Category	Pre- Eclampsia	Normal	P value
Age	< 20 Years	1(2%)	1(2%)	0.945
	20 – 29 Years	29(58%)	26(52%)	
	30-39 Years	14(28%)	16(32%)	
	> 40 Years	6(12%)	7(14%)	
Parity	Primi	19(38%)	21(42%)	0.683
	Multi	31(62%)	29(58%)	
Family History of Hypertension	Yes	31(62%)	18(36%)	0.009*
	No	19(38%)	32(64%)	

The sociodemographic characteristics of the research participants who were pregnant are displayed in Table 2. Age and parity differences between the two groups were not statistically significant. 1729

According to Table 2, most participants belong to 20 to 29 years of age group in pre-eclampsia as well as normal pregnant women. The mean age of pre-eclampsia patients was 28.67 ± 4.32 and the mean age of normal pregnant women was 27.38 ± 3.69. There was no significant difference found in mean age between case and control. Most of the female belongs to Multi gravida in both groups. On the other hand, notable variations of differing degrees were seen among pre-eclampsia pregnant women with a favourable family history of hypertension. In Pre-eclampsia, pregnant women had a 62% family history of hypertension while in normal pregnant women, only 36% had a family history of Hypertension.

Table: 3 **Comparison of lipid parameters between pre-eclampsia and normal pregnant women**

Lipid Profile	pre-eclampsia	Normal	P value
Total Cholesterol (mg/dl)	251.23 ± 14.23	220.36 ± 13.25	<0.0001*
Triglycerides (mg/dl)	166.36 ± 12.38	131.35 ± 11.39	<0.0001*
LDL (mg/dl)	181.96 ± 19.35	155.32 ± 18.36	<0.0001*
HDL (mg/dl)	36.39 ± 21.23	51.28 ± 15.21	<0.0001*
VLDL (mg/dl)	39.27 ± 10.27	20.26 ± 7.88	<0.0001*

The mean lipid profile of the patients is displayed in Table 3, which contrasts pre-eclampsia women with typical pregnant moms. Pre-eclampsia women's lipid profiles were significantly higher than normal pregnant women's, except for high-density lipoprotein-cholesterol (HDL-C).

Discussion
Pre-eclampsia, being the prominent cause of maternal death and perinatal morbidity, the necessity for a dependable marker to identify the disease in its early stages is increasing gradually. Endothelial dysfunction is the main cause of the multiple-organ pathophysiology of preeclampsia-eclampsia.[15] In pregnancy, hormonal alterations modify the maternal metabolic environment, and a significant hyperlipidemia is considered as physiological. But in pre-eclampsia, these changes in lipid metabolism are exaggerated and are a major cause of endothelial dysfunction that is reduced vasodilation and anticoagulant properties as well as increased adhesion molecule expression, cytokine release and reactive oxygen species production from the endothelium.

In pre-eclampsia and other hypertensive diseases of pregnancy, dyslipidemia is exaggerated with associated endothelial dysfunction and increased oxidative stress, which is thought to increase the risk of atherosclerosis and other CVDs. Dyslipidemia is a recognized feature of physiologic pregnancy and part of the biochemical response to a developing foetus.

The study found a substantial variation in blood lipid profile between pre-eclamptic women and those with normal pregnancies. Pre-eclampsia patients had significantly higher levels of TC, LDL, TG, and VLDL than normal pregnant women. This is consistent with findings from previous investigations.[4,5]

In the current investigation, a favourable family history was closely linked to the development of pre-eclampsia. Women having a positive family history of pre-eclampsia were found to be six times more likely to develop the condition than those without. Singh et al.[16] discovered similar connections in India. In a comprehensive evaluation of a controlled cohort study of pre-eclamptic and normal pregnancy, Bellamy et al.[17], in a systematic review and meta-analysis reported that women with a history of pre-eclampsia present an increased risk of hypertension (relative risk, RR= 3.7) [22], venous thromboembolism (RR = 1.79) and stroke (RR = 1.81). These findings confirm the possible association between hypertension during pregnancy and future cardiovascular disease.

Conclusion

Pre-eclampsia, being the prominent cause of maternal death and perinatal morbidity, the necessity for a dependable marker to identify the disease in its early stages is increasing gradually. In pre-eclampsia and other hypertensive diseases of pregnancy, dyslipidemia is exaggerated with associated endothelial dysfunction and increased oxidative stress, which is thought to increase the risk of atherosclerosis and other CVDs. Pre-eclampsia patients had significantly higher levels of TC, LDL, TG, and VLDL than normal pregnant women. This is consistent with the findings in this study.

Limitation: We had to study only 100 patients because we had a limited time duration. It was a single-centre study, but the results were not affected by the limitation.

References

1. Ananth C.V., Keyes K.M., Wapner R.J. Pre-Eclampsia Rates in the United States, 1980–2010: Age-Period-Cohort Analysis. *BMJ.* 2013;347:f6564. doi: 10.1136/bmj.f6564. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

2. Brown M.A., Magee L.A., Kenny L.C., Karumanchi S.A., McCarthy F.P., Saito S., Hall D.R., Warren C.E., Adoyi G., Ishaku S. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension.* 2018;72:24–43. doi: 10.1161/HYPERTENSIONAHA.117.10803. [PubMed] [CrossRef] [Google Scholar].

3. National Guideline Alliance (UK) Hypertension in Pregnancy: Diagnosis and Management (NG133) [(accessed on 3 October 2019)];2019 Available online: https://www.nice.org.uk/guidance/ng133.

4. Hahn S, Gupta AK, Troeger C, Rusterholz C, Holzgreve W. Disturbances in placental immunology: ready for therapeutic interventions? *Springer SeminImmunopathol.* 2006;27:477–493. [PubMed] [Google Scholar]

5. Jauniaux E, Poston L, Burton GJ. Placental-related diseases of pregnancy: Involvement of oxidative stress and implications in human evolution. *Hum Reprod Update.* 2006;12:747–755. [PMC free article] [PubMed] [Google Scholar]

6. Saito S, Shiozaki A, Nakashima A, Sakai M, Sasaki Y. The role of the immune system in preeclampsia. *Mol Aspects Med.* 2007;28:192–209. [PubMed] [Google Scholar]

7. Wen SW, Chen XK, Rodger M, White RR, Yang Q, Smith GN, Sigal RJ, Perkins SL, Walker MC. Folic acid supplementation in early second trimester and the risk of preeclampsia. *Am J Obstet Gynecol.* 2008;198:45–47. [PubMed] [Google Scholar]

8. Hung TH, Skepper JN, Charnock-Jones DS, Burton GJ. Hypoxiareoxygenation: a potent inducer of apoptotic changes in the human placenta and possible etiological factor in preeclampsia. *Circ Res.* 2002;90:1274–1281. [PubMed] [Google Scholar]

9. Soleymanlou N, Jurisica I, Nevo O, Ietta F, Zhang X, Zamudio S, Post M, Caniggia I. Molecular evidence of placental hypoxia in preeclampsia. *J ClinEndocrinolMetab.* 2005;90:4299–4308. [PMC free article] [PubMed] [Google Scholar

10. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science.* 2005;308:1592–1594. [PubMed] [Google Scholar].

11. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest.* 2003;111:649–658. [PMC free article] [PubMed] [Google Scholar].

12. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. *Am J Obstet Gynecol.* 1989;161:1200–1204. [PubMed] [Google Scholar].

13. De J, Mukhopadhyay AK, Saha PK. Study of serum lipid profile in pregnancy induced hypertension. *Indian Journal of Clinical Biochemistry.* 2006;21(2):165–68. [PMC free article] [PubMed] [Google Scholar].

14. Al-Rubaie Z., Askie L.M., Ray J.G., Hudson H.M., Lord S.J. The Performance of Risk Prediction Models for Pre-Eclampsia Using Routinely Collected Maternal Characteristics and Comparison with Models That Include Specialised Tests and with Clinical Guideline Decision Rules: A Systematic Review. *BJOG.* 2016;123:1441–1452. doi: 10.1111/1471-0528.14029. [PubMed] [CrossRef] [Google Scholar].

15. Schwartz RB. Preeclampsia-Eclampsia: Clinical and Neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. Radiology 2000; 217: 371-376.

16. Singh M, Pathak MS, Paul A. A Study on Atherogenic Indices of Pregnancy Induced Hypertension Patients as Compared to Normal Pregnant Women. J Clin Diagn Res. 2015 Jul;9(7):BC05-8. doi: 10.7860/JCDR/2015/13505.6241. Epub 2015 Jul 1. PMID: 26393117; PMCID: PMC4572947.

17. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis 2007. *BMJ*. 2007;335:974-77.