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A Study on Evaluation of Oxidative Stress in Association With Hypoxia Inducible Factor -1α Polymorphisms in Pre-Eclampsia

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ABSTRACT

Background:The prevalence rate of preeclampsia in India in isolation is stipulated at 8-10 percent amongst pregnant mothers. It normally occurs between the second part of the pregnancy. In preeclampsia, oxidative stress and inflammatory condition play a significant role in relation to involvement of NADPH oxidase, maternal, endothelial and leukocyte activation. Present study was aimed to evaluate oxidative stress in connection with pre-eclampsia and hypoxia-inducible factor-1α polymorphisms. Material and Methods:The current study was a single-center, prospective, comparative study of pregnant women with preeclampsia after the 20th week of gestation.Results: The prevalence of CC genotype is higher in normal pregnant (36.50%) than in PE (11.11%) and nonpregnant women (25.39%). The prevalence of the CT genotype was higher in normal gestating women (42.85%) and non-gestating women (46.39%) than in PE (34.92%) and the TT genotype was also higher in PE (53.96%) than in normal pregnant women (42.85%) and Non-pregnant women (46.39%). In non-pregnant women and in normal pregnant women, the frequency of the C allele was more (80.95% and 57.67%, respectively). However, lower in PE and the frequency of the T allele was higher in PE lower in normal pregnant women and nonpregnant women. The chi-square p-value of genotypes (CC, CT, and TT) and alleles (C, T) were highly significant. The association of Overall PE (OR= 13.91), sever PE (OR=13.22) and mild PE (OR= 15.65) with CC seen in the recessive model. In the dominant model, the connection was less with moderate form PE (OR = 2.24) compared to severe PE (OR = 2.931) and with PE in general (OR = 3.29).The relationship between intermediate form PE (OR = 2.24) and serious PE (OR = 2.931) and PE in general (OR = 3.29) was less in the dominant model.The increases in all oxidative stress markers were also significant in the preeclampsia group associated to the normotensive gestating women and non-gestating women. Conclusion:The current study found that in the dominant model, placental HIF1 α gene polymorphism is associated with PE, but not maternal polymorphism.

KEYWORDS: Maternal Hif1 A Gene, Gene Polymorphism, Preeclampsia, Oxidative Stress, Polymorphisms.

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INTRODUCTION

Preeclampsia/eclampsia, chronic hypertension, gestational hypertension, and chronic hypertensive development in preeclampsia/eclampsia are the several categories of hypertensive diseases of pregnancy (HDP).Irrespective of the classification, the significance of BP monitored in the course of pregnancy is emphasized. The rate of HDP is 4 to 25 percent, and It stands as the world's third most important cause of maternal sickness and mortality.[1]

Preeclampsia alone occurs at a frequency of 8-10 percent in pregnant women in IndiaUsually, it takes place during the second part of pregnancy.The primigravida women are more likely to experience pre-eclampsia than the second or later ones.[2] The result in fetal uterine growth limitation, premature birth, inflammation, maternal and fetal Morbidity can be minimized via early identification and care. Despite its frequency, its pathophysiology is little known, and its cause must be determined.[3]

It is also reported in various studies that there was an association between various diseases (diabetes, coronary disease and cancer) and HIF-1 α target genes. Thus, it is anticipated that the current investigation would identify a link between preeclampsia and HIF-1α genes.It is also reported that in preeclampsia, oxidative stress and inflammatory condition play a significant role in relation to involvement of NADPH oxidase, maternal, endothelial and leukocyte activation.[4] Thisresearch was aimed to assessthe oxidative stress in association with hypoxia inducible factor -1α polymorphisms in Pre-eclampsia.

MATERIAL AND METHODS

This research was done at the Department of Obstetrics and Gynaecology of RMC Govt. General Hospital, Kakinada, East Godavari District, India and was a prospective, single-center study and a comparative study. The study is of 4 years duration (August 2019 - August 2023). The institutional ethics committee gave the study its approval.

Inclusion criteria

- All pregnant women above the 20th week of gestation with preeclampsia conforming to the classification laid down by the National High Blood Pressure Education Programme working group (NHBPEP) who were admitted to our Hospital and were willing to participate in the present study.
- The Preeclampsia is diagnosed when a woman, after 20 weeks of gestation, presents for the first time with elevated blood pressure defined as systolic levels of ≥140 mmHg and/or diastolic levels of ≥90 mmHg on at least two separate readings taken six hours apart along with evidence of proteinuria, characterized by a protein excretion of ≥300 mg in a 24-hour urine collection or a reading of ≥1+ on a dipstick test in a random urine specimen, as per the NHBPEP guidelines.

Exclusion criteria

- Pregnant female with a past of cardiovascular illness, hypertensive encephalopathy, epilepsy, chronic high blood pressure,diabetes during pregnancy, thyroid disorders, kidney disease, or a high risk of anemia.

The study protocol was explained to all participants in their local language, and written informed consent was obtained. Blood samples were collected, consisting of 3 ml in heparinised tubes and 2 ml in EDTA tubes. Before use, sterile dry centrifuge tubes were rinsed with heparinised blood. Plasma was then separated by centrifugation at 3000 rpm for 10 minutes to obtain a clear sample.

The plasma was then separated and this was stored at -80oC until analysis. The remaining packed cell is used to prepare the hemolysate and stored in triplicates at -80^{O}C to use in the future for any other investigations. Whole blood was used for DNA extraction and PCR along with the genetically obtained informed consent form.

In present study, methods for detecting oxidative stress markers were damage of lipid by malondialdehyde (determined as a thiobarbituric acid reactive substance), protein damage by protein carbonyl level & DNA damage by 8-hydroxy-2-deoxyguanosine ELISA Kit. For Endothelial Dysfunction Markers, we studied Nitric oxide (determination by Griess Reagent Kit), Human Endothelial Selectin (E- selectin) (by ELISA Kit) & P-Selectin (by ELISA Kit -Abcam). For antioxidants determination as non-enzymatic antioxidants, we measured Vitamin C (L-Ascorbic acid), Vitamin E & Uric Acid. For enzyme antioxidants levels we measured Superoxide Dismutase, Glutathione Peroxidase, Glutathione Reductase, Catalase &Ferric reducing ability of plasma (FRAP).

Amplification of genomic DNA was conducted in a Bio-Rad C1000 Touch Thermal Cycler. The pairs of primers that were used were 5′-TCCTTCGATCAGTTGTCACCA-3′ (forward) 5′- GGCTGTCCGACTTTGAGTATC-3′ (reverse). 15µl reaction involved 4µl of master mix, 1µl of forward primer, 1µl of reverse primer and 8µl of deionized water. There were 5 minutes of preliminary denaturation at 95°C, thirty cycles of denaturation at 95°C for 30 seconds, annealing at 62°C for 30 seconds, extension at 72°C for 30 seconds, and final extension at 72°C for five minutes.The amplification product size of H1F1 α- rs11549467 (A/G) is 276bp length. The restriction fragment length polymorphism (RFLP) method was utilized to digest the PCR product using the Acl1(ssil) restriction enzyme overnight at 37 °C. The DNA size mark and the protein digest have been run on an agarose gel, which was electrophoresed with 3% agarose and examined after a safe stain.Gels were photographed under ultraviolet light to document the results.

The data obtained was analysed with the use of SPSS 23.0 version and compiled in Microsoft excel. Calculations were made for continuous variables (frequency, percentage, averages, and standard deviations (SD)) as well as for categorical variables (ratios and proportions). The chi-square test or Fisher exact test, if applicable, were used to test for variations in proportions in qualitative variables. P values below 0.5 were considered significant.

RESULTS

The prospective observational study involves 405 of study subjects that was administered in the RMC Govt. General Hospital, Kakinada, East Godavari District. The study subjects were divided into 3 groups of which 135 each. Group 1(n=135) containing of non-pregnant as the control people; Group 2 (n=135) non-hypertensive normal pregnant after 20th-week follow-up at successive intervals of 24th, 28th, 30th and 34th weeks before delivery and within 48 hours of delivery. Group 3 (n=135) pregnant with preeclampsia after 20th-week follow-up at successive intervals 24th, 28th, 30th and 34th weeks before delivery and within 48 hours of delivery depending on the progression of the disease.

The PE's clinical and demographic characteristics, Normotensive pregnant female and Nonpregnant women. There was no significance between age groups among both cases and controls (P- value 0.192). The PE group had noticeably higher systolic and diastolic blood pressures. A significant p-value was observed in systolic (< 0.0002) and diastolic (<0.0008) blood pressure. However, PE women had considerably greater neonatal birth weights and gestational ages.The chi-square p value was statistically significant in gestational age, total WBC (cells/cumm), and platelet count. There is not much difference between blood parameters like hemoglobin (HB),mean cell hemoglobin (MCH pg), RBC, mean cell volume (MCV fL), packed cell volume (PCV), mean cell hemoglobin concentration (MCHC gms%), lymphocytes, monocytes, eosinophils, basophils in three groups. The random

blood sugar (RBS) was also higher in PE groups and the chi-square p-value was also statistically significant.

Table 1: Baseline characteristics of study participants

Parameters	Preeclampsia (n=135)	Normal Pregnant Women (n=135)	Non-pregnant (n=135)	P-value
Age	23.25 ± 3.07	22.49±2.93	23.33±2.87	0.192
Systolic BP	146.19 ±17.99	109.68±8.22	110.47±8.43	< 0.0002
Diastolic BP	96.03 ±12.64	70.95 ± 9.10	71.74±8.07	<0.0008
Weight(Kg)	69.01 ± 18.88	61.90±9.75	62.38 ± 10.01	0.015
Height(cm)	4.90 ± 0.50	5.04 ±0.39	5.09±0.40	0.65
Gestational age	35.51± 0.50	40.20±1.07	NA	<0.0000001
HB%(gm/dL)	11.03 ± 1.83	11.01 ± 1.65	11.43±1.21	0.426
T. RBC mil/cumm	4.23 ± 0.54	4.08±0.53	4.25±0.40	0.683
T.WBC (cells/cumm	12055.56 ± 3378.527	11450.91 ± 3022.623	11467.86 ± 2678.693	<0.0004
PCV%	32.74 ± 4.47	33.56 ± 8.86	34.26±7.2714	0.138
MCV (fL)	78.33 ± 7.68	80.36± 10.63	78.37 ± 8.86	0.022
MCH pg	25.87±3.49	27.70±3.65	26.69±2.77	0.150
MCHC gms%	32.17 ± 3.15	33.78±4.71	33.96±5.03	0.139
PLT count	3398.84 ± 16277.94	2.379434 ± 0.756877	1675.083±12291.66	<0.0000001
P%	74.53 ± 8.79	70.76±8.03	71.75 ±9.40	0.022
L%	23.41 ±9.63	23.54±5.83	23.03 ± 7.64	0.156
M%	2.58 ± 4.30	2 ± 0	2 ± 0	0.662
E%	1.98± 0.12	2.38 ± 1.50	1.96±0.26	0.753
B%	0.031± 0.25	0±0	0.03±0.26	0.984
RBS	94.27 ± 21.45	87.00 ±21.87	84.26±12.83	0.006

The prevalence of CC genotype is higher in normal pregnant (36.50%) than in PE (11.11%) and nonpregnant women (25.39%). The prevalence of the CT genotype was higher in normal women who were pregnant (42.85%) and women with no pregnancy (46.39%) than in PE (34.92%) and the TT genotype was also elevated in PE (53.96%) than in normal pregnant women (42.85%) and Non-pregnant women (46.39%). The C allele was more often in normal pregnant women (57.67%) than non-pregnant women (80.95%). lower in PE, and the T allele frequency was greater in PE compared to normal pregnant and nonpregnant women.The chi-square p-value of genotypes (CC, CT, and TT) and alleles (C, T) were highly significant.

Table 2: H1F1- α Gene Polymorphism in the study Population

Genotypes	Preeclampsia (N=135)	Normal Pregnant Women (N=135)	Non-Pregnant (N=135)	Chi-square (P-value)	Degree of Freedom
CC	07 (11.11%)	23 (36.50%)	16 (25.39%)		
CT	22 (34.92%)	27 (42.85%)	29 (46.39%)	0.0003	20.4
TT	34 (53.96%)	13 (20.63%)	18 (28.57%)		
Alleles					
C	53 (28.04%)	109 (57.67%)	153 (80.95%)	<0.000	2
T	136 (71.95%)	80 (42.32%)	36 (19.04%)		

The association of Overall PE (OR= 13.91), sever PE (OR=13.22) and mild PE (OR= 15.65) with CC seen in recessive model. The domination model showed a stronger association with severe PE (OR= 2.931) and overall, PE (OR = 3.29) than the mild one (OR = 2.24). The odds ratio parameters of the onset of PE OR= 0.286 (95% CI = (0.1819-0.4489) and statistical tests were valued with a criterion of a severe and mild outcome.

Table 3: Evaluation of H1R1-α Genotype and allele associated with preeclampsia

Models	Overall	Severe	Mild
Dominant CC+CT Vs. TT	P= 0.006 OR= 2.931 95% CI = (1.319-6.571)	P= 0.008 OR=2.875 95% CI = (1.184-7.005)	P= 0.03 OR= 3.056 95% CI = (0.9536-9.824)
Recessive CT+TT Vs.CC	P= <0.000 OR= 13.91 95% CI = (5.086-41.34)	P= <0.000 OR=13.22 95% CI = (4.561-47.86)	P= 0.000 OR= 15.65 95% CI = (3.181-146.4)
Allele C Vs.T	P= 0.000 OR= 0.286 95% CI = (0.1819-0.4489)	P= 0.000 OR= 0.3032 95% CI = (0.1827-0.5003)	P=0.000 OR= 0.2502 95% CI = (0.1212 – 0.498

Comparing the preeclampsia group to the normotensive pregnant and non-pregnant women, all oxidative stress indicators showed a substantial increase.The nitric oxide levels were significantly reduced between normal pregnant and preeclampsia pregnant women. The levels of E selectin and P selectin were markedly increased in Preeclamptic females than in normal pregnant females.

There was a significant reduction in the non-enzyme antioxidant vitamin C levels among non-pregnant, normotensive women than preeclampsia women. Whereas Vitamin E levels were found to be higher in normotensive women than in preeclampsia. Uric acid levels were found to be increased in normotensive and preeclamptic females than in normal pregnant females.

Glutathione reductase and catalase were found to be remarkablyhigh in the preeclampsia group than in typicalexpectantfemales. However, related to healthy pregnant women, the levels of superoxide dismutase and glutathione peroxidase were much lower in preeclamptic women.Compared to pregnant women with normotension, preeclampsia patients had a considerably lower total antioxidant level.All the results were found to have an inverse relation with oxidative stress parameters.

Table 4: Comparison of oxidative stress markers between the groups

Parameters	Non-pregnant women (mean ± SEM)	Normotensive pregnant (mean ± SEM)	Preeclampsia (mean ± SEM)
Oxidative stress markers			
Malondialdehyde (µmoles/L)	5.09 ± 0.32	7.2 ± 0.21	17.3 ± 1.8
Protein carbonyl (nmol/L)	97.89 ± 4.3	141.28 ± 5.2	162.86 ± 17.9
DNA damage (Arbitrary units)	1.23± 2.9	15.43 ± 2.2	45.76 ± 4.2
Endothelial markers			
Nitric oxide (µmoles/L)	7.34 ± 3.4	6.52 ± 7.6	5.91 ± 6.2
E selectin (pg/ml)	07	11	23
P selectin (ng/ml)	30	20	152
Non-enzyme antioxidants			
Vitamin C (mg/dl)	1.01 ± 0.02	0.7 ± 0.03	0.5 ± 0.04
Vitamin E (mg/L)	9.6 ± 0.43	12.8 ± 1.8	9.2 ± 0.42
Uric Acid (mg/dl)	2.4 ± 0.12	3. 83 ± 0.21	7.5 ± 0.23
Enzyme antioxidants			
Superoxide dismutase (SOD) (U/ml)	6.7 ± 0.5	12.5 ± 0.45	7.5 ± 0.73
Glutathione peroxidase (U/L)	534.6 ± 52.4	601.23 ± 32.1	435 ± 54.89
Glutathione reductase (U/L)	28.7 ± 4.2	10.23 ± 2.3	20.3 ± 6.85
Catalase (U/ml)	112.5 ± 9.2	35. 6 ± 6.5	65.5± 3.2
FRAP (µmoles/ml)	1786 ± 78.96	1021 ± 13.5	786 .4 ± 76.4

DISCUSSION

One of the primary characteristics of preeclampsia (PE), a systemic condition, is insufficient trophoblast invasion, which results in partial spiral artery remodeling, decreased uteroplacental perfusion, and placental hypoxia.Maternal endothelial dysfunction can be common in hypoxic environments, which can lead to PE symptoms. It has been demonstrated that placental growth factor, vascular endothelial growth factor (VEGF), and other factors are important in the pathophysiology of PE.An increasing amount of attention is being paid to the biology of HIF-1α as it is the primary controller of the angiogenic/antiangiogenic elements,which are overexpressed in preeclamptic women.

The importance of HIF-1alpha in the pathogenesis of PE was initially reported by Caniggia et al. The findings support the view that HIF-1 alpha has increased expression when the oxygen in the placenta level is defective during early gestation.[5] The findings also demonstrate that HIF-1 -apollo in placental functions and development is significant.[6] Ex vivo, it has been shown that both HIF1-alpha C1772T and G1790A polymorphism exhibit greater transcriptional capacity normoxia and hypoxia conditions resulting in protein over-expression, compared to the wild-type allele.[7]

There are few data on the potential implications of fetal variations on PE risk, and the majority of genetic research have exclusively examined maternal genes. [8, 9] The current investigation assessed the relationship between PE and mother's and placental HIF1-α polymorphisms: rs11549465 and rs11549467.

The aforementioned findings requires us to look into the increase of HIF1-α gene susceptibility in maternal plasma and the placentas of women with PE. In the first trimester, there was no expression of the gene H1F1 α- rs11549467 (A/G) in PE women and then second trimester H1F1-α rs11549467 (A/G) gene expression was slightly increased with PE as well as in the condition of third trimester H1F1 α- rs11549467 (A/G) gene expression was higher in PE susceptibility. However, in the dominant model, PE susceptibility was linked to the HIF1-α rs11549465 polymorphism. The synergistic impact of these genotypes was linked to a 2.2-fold increased risk of PE, and the united impact of placental HIF1-α rs11549467 gene polymorphism revealed that the AA/GG combination genotypes were considerably higher in PE women.

In the study of Hein *et al.*,[10] no connection was found between H1F1 α- rs11549467 (A/G) gene polymorphism and PE in Finish women. Based on the studies and Nava- Salazar *et al.*[11] found there was a relation between H1F1 α- rs11549467 (A/G) gene polymorphism and PE in the Korean and Mexican inhabitants.The gene frequencies of H1F1 α- rs11549467 (A/G) was very low in the Mexican population and had no association with PE in the Korean and Mexican population.

In contrast, Andraweera et al.[12] investigated the relationship between maternal HIF1-α rs11549465 and rs10873142 polymorphisms and PE in Sinhalese women, but they did not find any correlation in either the dominant or recessive models.The

study of Mahdiyeh Harathi Sadegh *et al.*,[13] identified the connection between placental but not maternal HIF1 α gene polymorphism and PE in the dominant modal among the Iranian population.

The HIF-1 alpha gene expression patterns of placenta samples in the HIF1 gene signaling pathway were compared between preeclampsia and controls by Xun Yang et al.[14].The present study was correlated with Mahdiyeh Harathi Sadegh *et al.*,[12] study. We have also identified the connection between placental but not maternal HIF1- α gene polymorphism and PE in the dominant modal in the Indian population.

In the present study, oxidative stress parameters are evaluated with a special focus on endothelial dysfunction activity along with antioxidant status and also to know the impact of oxidative stress on placental hypoxia-inducible factor 1 alpha gene polymorphism in pre and post-delivery of normotensive and preeclamptic pregnant women.

MDA levels were elevated in preeclamptic pregnant women and therefore, increased lipid peroxidation is considered to be a causative factor for preeclampsia. Increased protein carbonyl content and decreased antioxidant capacity indicate high levels of oxidative stress in female with preeclampsia which serves a crucial role in the endothelial dysfunction initiation and expression of preeclampsia. Therefore, intake of adjuvant antioxidants supplementation can minimize the progression of preeclampsia.

DNA damage is elevated in preeclamptic pregnant women which can be considered as a marker in preeclampsia. Increased uric acid content is seen in preeclamptic women. Increased catalase activity represents a contending action against oxidative stress. Reduction of nitric oxide level in preeclampsia indicates endothelial dysfunction. Decreased oxidative stress post-delivery within 48 hours in preeclampsia indicates placental abnormality. The levels of E and P selectins were remarkably high in Preeclampsia pregnant women and post-delivery P selectin levels were decreased in normal pregnancy and preeclampsia but are not significant.

CONCLUSION

The current study discovered a correlation between placental, but not maternal, HIF1 1-alpha gene polymorphism and PE, in a dominant model.The significance of hypoxia in trophoblast invasion and maturation during gestation has been well established. This research was able to determine that HIF-1alpha activation in late pregnancy could contribute to the pathogenesis of preeclampsia.

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