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STUDY OF HOMOCYSTEINE LEVELS IN PREECLAMPSIA ATTERTIARYCAREHOPITAL

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ABSTRACTBACKGROUND

Preeclampsia is one of the major conditions causing maternal morbidity and mortality throughout the world.Though the exact cause of preeclampsia is still unknown, endothelial dysfunction with associated intensevasospasm has been implicated in its causation. Elevated homocysteine levels comprise an independent riskforvasculardisease,directendothelialtoxicity,failureofnitricacidoxidereleaseand plateletabnormalities.Hence topreventthe vascularrelated pregnancy complications,our aim istoestimatehomocysteinelevelsinpreeclampsia.

AIM

To compare the levels of serumhomocysteine and lipid profileinpreeclampticindividuals andinnormalpregnantwomen

METHODS

The study was conducted at Government Medical College /Government General Hospital ,NalgondafromJanuary2020 to December 2020. A total of 50 cases of preeclamptic women were taken for the study aftersatisfying the inclusion and exclusion criteria. Fifty healthy pregnant women were included in the studyunder the control group. All patients were evaluated in detail and serum homocysteine andlipidprofilewereassayed.

RESULT

Serumhomocysteinelevelswassignificantlyhigh incasescomparedtocontrols.(Pvalue0.001).

CONCLUSION

There was significant increase in serum homocysteine in preeclamptic patients compared to the controls.Thisstudyexploresthepossibilityoffindingserum homocysteineasa

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markertoexplaintheendothelial dysfunctionin preeclampstic patients. This valuable information would be helpful in propermedicalintervention.

KEYWORDS: Homocysteine,Normotensive,Preeclampsia

INTRODUCTION

Preeclampsia,apregnancyspecificdisordercharacterizedbyvasospasmandendothelialdys functionandcomplicates 7 to10% of all gestations with serious feto- maternal morbidity andmortality.Aetiology ofpreeclampsia is still obscured but one of the most favoured hypothesis is the endothelial dysfunction secondaryto the peroxidation of membrane lipids. Decreased antioxidant activity and increased lipid peroxides was shownclearlyinpreeclamptics[1,2]

Preeclampsia is defined as a blood pressure of at least 140 mmHg systolic pressure and 90mmHg diastolicpressure measured on two occasions 6 hours apart, accompanied by proteinuria of at least 300 mg per 24 hours,oratleast1+ondipsticktestingafter20weeks[3].

It is a serious manifestation that is associated with increased risk of mortality and morbidity in the pregnantwomen and poor perinatal outcomes. The incidence of pre-eclampsia/eclampsia in hospital practice varieswidely from 5-15%, in primigravidae is about 10% and in multigravidae 5%[4]. In developing countries, theincidence is expected tobe higher; comparativelow figures are reported in thehospital statistics due toinclusionofonlysevere degrees ofthesyndrome,theminorbeingignored[5].

The main cause of preeclampsia is unknown, however abnormal placentationis thought to be responsible to aninflammatory type response with endothelial dysfunction. Different etiologies have been known in preeclampsiainclude immunologic factors, genetic, nutrition, race, increased insulin resistance, oxidative stress and imbalance ofprostaglandins oxidativestress byfreeradicals[6].

The definitive treatment of preeclampsia/eclampsia is delivery to preventdevelopment of maternal or fetalcomplications from disease progression. Whether or not to deliver the fetus is based upon severity of pre-eclampsia, gestational age, maternal and fetal condition[7]. Patients at term are delivered, but preterm delivery isnot always in the best interests of the fetus. In preterm pregnancy, aggressivemanagement to deliver may resultinhighneonatalmortality whileexpectantmanagementmaybeassociatedwith-maternalcomplications.Expectantmanagementbeyond37weeksoffersnobenefittothemoth

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erandfoetus,deliveryisadvised[8].

It is recognized that the source for the underlying pathophysiology of the disease is poorly understood, butcurrentlyEndothelialdysfunctionismostpopularlyhypothesizedtobethefeature of preeclampsia.Thehomocysteinemediatedvascular changesaresimilartothoseassociatedwithpreeclampsia,therefore,ahypothesishasbeenproposedthathyperhomocysteinemiamaybe associatedwithpreeclampsia[9].

Elevated circulating homocysteine is a risk factor for endothelial dysfunction and vascular disease such asatherosclerosisand occlusivevasculardisorders.Itissulphurcontainingaminoacidrequiredforthegrowthof cells and tissues in the human body. It is hypothesized that hyperhomocysteinemia might damage the vascularendothelium of the developing placenta by promoting oxidative stress, thereby increasing contractile responseandtheproductionofpro-coagulantsandvasoconstrictor[10].Plasmahomocysteineisnormallylowerthroughout pregnancy than in the non-pregnant state[11]. Homocysteine concentrations are directly correlatedwith albumin concentration, which decrease during pregnancy and decrease further in pregnant women takingfolic acid supplements. Studies reported that hyperhomocysteinemia may also be an important biologicalmarker for adverse outcome of pregnancy and even possibly a cause of or a contributor to the complications ofpregnancy. An increased risk of preeclampsia, premature delivery, very low birth weight, neural tube defectsand clubfootoccursinthose womenwhoare sufferingfromhyperhomocysteinemia[12].

Materialsandmethods

Fiftypregnantwomenclinicallydiagnosedwithpreeclampsia(BP>140/90mmhg, proteinuria>300mg/day, with or without pathological edema) attendingGynaecology and ObstetricsOP atGovernment Medical College/Government GeneralHospital, Nalgonda, between January toDecember2020 were included in the study,and fifty normal pregnant women of more than 20 weeksofgestationduringthesameperiodwereincludedinthestudyunderthecontrolgroup.

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Inclusioncriteria

1. Pregnantwomenwhohavebeenclinicallydiagnosedwithpreeclampsia(bothprimigravidaandmultigravida).
2. Normalpregnantwomenofmorethan20weeksofgestation,primigravidaandmultigravidawithnobadobstetrichistory.

Exclusioncriteria

1. PregnantwomenwithH/Osmokingandalcoholism.
2. Pregnantwomenwithotherconditionslikegestationaldiabetes,diabetesmellitus,hypertension,cardiovasculardisease,chronicliverandkidney disease,anemia,multiplepregnanciesand otherchronic diseasesthatinterfere withthe study.
3. Pregnantwomenonantioxidantlikevitamin Eand vitaminsupplementation.
4. Pregnantwomenonanyothermedicationexceptironandcalciumsupplementation

Informedconsentwastakenfrom allcasesandcontrol subjects.Baselinedataincludingage,detailedmedicalhistoryincludingconventionalriskfactors,clinicalexaminationsandrelevant investigationswere included as part of the methodology. Serum samples were collected underaseptic precautions .Serum Homocystein and lipid profileestimation was done on Abbott Architectci4100inbiochemistrydepartment.

Recording of blood pressure: BP was recorded in lying down position using sphygnomanometer. Tworecordingsweretakenat6hours apart.

StatisticalAnalysis

Itisacrossectionalstudy

Studentttest(twotailed,independent)hasbeenusedtofindthesignificanceofstudyparametersoncontinuousscale betweentwogroups(Intergroupanalysis)onmetricparameters.

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Chi-square/FisherExacttesthasbeenusedtofindthesignificanceofstudyparameterson categoricalscalebetweentwoormoregroups.

RESULTS

TABLE–1:DETAILSOFTHESUBJECTSTUDIED

	Casesgroup	Controlgroup
Variablen=100	**Mean±SD**	**Mean±SD**
Age(yrs)	23.38±3.31	22.40±2.58
POG (wks)	33.74±3.82	36.18±1.78
SBP(mmHg)	151.12±8.56	114.00±5.53
DBP(mmHg)	106.56±11.34	73.68±4.49

Thistableisshowingthedetailsofthesubjectstudies,i.e.,Ageinyears,Periodofgestation ,SystolicbloodpressureandDiastolicbloodpressureincases andcontrolgroups.

Table2:Agewisedistributionofcasesandcontrols

Agein years	**Cases**		**Controls**	
	No	**%**	**No**	**%**
18-20	14	28.0	13	26.0
21-30	35	70.0	37	74.0
>30	1	2.0	0	0.0
Total	50	100.0	50	100.0
Mean± SD	23.38±3.31		22.40±2.58	

Themeanageinthecontrolwas22.4yearsandindiagnosedPEcases

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(studygroup)was23.3 years.

Majority of them belonged to age group of 21-30years. In the control group,74% belonged to age group 21-30 years and in study group 70% belonged to agegroup21-30years.

In control group 26% belonged to age group 18-20 years and none in the groupof>30years.

Instudygroup28%belonged to18-20years,2% belonged to>30 years.

Table3:PeriodofGestationintwogroupsstudied

Periodof Gestation	Cases		Controls	
	No	%	No	%
22-28	8	16.0	0	0.0
28-32	7	14.0	1	2.0
32-37	29	58.0	33	66.0
37-40	6	12.0	16	32.0
Total	50	100.0	50	100.0
Mean± SD	33.74±3.82		36.18±1.78	

Themeanperiodofgestationinthecontrolwas36.18±1.78andindiagnosedPEcases(st udygroup)was33.74±3.82years.

Majorityofthembelongedto32-37weeksofgestation.Inthecontrolgroup66%andinstudygroup58%belongedto32-37weeksofgestation

Table5:Gravidadistributionintwogroupsstudied

Gravida	Cases		Controls	
	No	%	No	%
Primi	32	64.0	35	70.0
Multi	18	36.0	15	30.0

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Total	50	100.0	50	100.0

Inourstudy,primigravidaincasesandincontrolswere64%and70%respective ly,multigravida were36%incasesand 30%incontrols.

Table6:ComparisonofBloodpressure intwogroupsstudied

	Cases	**Controls**	**Pvalue**
SBP(mmHg)	151.12±8.56	114.00±5.53	<0.001**
DBP (mmHg)	106.56±11.34	73.68±4.49	<0.001**

Inourstudy,systolicbloodpressureanddiastolicbloodpressurevalueswerecomparedi ncasesandcontrolsandP-valuewassignificant.

Table6:UrineAlbumindistributionincasesstudied

Urine Albumin	**No.of patients**	**%**
1+	15	30.0
2+	17	34.0
3+	17	34.0
4+	1	2.0
Total	50	100.0

Urinealbumin:1+wasfoundin30%ofcases,both2+and3+ineach34%ofcasesand4+inonly 2%ofcases.

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Table7: ComparisonofLipidparametersin twogroupsstudied

	Cases	Controls	Pvalue
TGL(mg/dl)	247.78±107.48	143.92±43.46	<0.001**
TotalCholesterol(mg/dl)	195.92±47.89	111.48±28.39	<0.001**
LDL(mg/dl)	109.84±26.66	100.34±15.89	0.033*
HDL(mg/dl)	44.74±12.01	63.12±19.83	<0.001**

Triglycerides: Themeanserumtriglycerides(mg/dL)incasesandcontrolswere

247.78±107.48and143.92±43.46andwashighlysignificant.(P< 0.001)

Totalcholesterol:Themeanserumtotalcholesterol(mg/dL)incasesandincontrolswere195.92± 47.89and111.48±28.39respectivelyanditwashighlysignificant.(P<0.0001)

Lowdensitylipoprotein: Themeanlowdensitylipoprotein(mg/dL)incaseswere109.84±26.66andincontrols were100.34±15.89whichwasmoderatelysignificant.(P < 0.033)

Highdensitylipoprotein: Themeanserumhighdensitylipoprotein(mg/dL)incasesandcontrolswere 44.74±12.01and63.12±19.83andwas highlysignificant.(P<0.001).

Table8:SerumHomocysteine(µmol/L)intwogroupsstudied

SerumHomocysteine(µmol/L)	Cases		Controls	
	No	%	No	%
<15	23	46.0	49	98.0
>15	27	54.0	1	2.0

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Total	50	100.0	50	100.0
Mean± SD	16.24±8.22		8.58±3.02	

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Meanserumhomocysteinelevelsincaseswere16.24±8.22andincontrolswere 8.58±3.02,and itisstatistically highlysignificant.(P<0.001).

Table12:Comparisonofbaselinevariables accordingtolevelsofHomocysteine(µmol/L)

Variables	Homocysteine(µmol/L)		Total	Pvalue
	Normal (<15)	High (>15)		
Ageinyears	23.04±3.00	22.50±3.00	22.89±2.99	0.419
POG	35.18±3.08	34.39±3.51	34.96±3.21	0.273
SBP(mmHg)	124.72±17.00	152.71±10.93	132.56±19.98	<0.001**
DBP (mmHg)	82.53±15.06	109.64±11.20	90.12±18.62	<0.001**

Comparing Homocysteine levels in less than <15 µmol/L and more than >15µmol/L,systolicbloodpressureanddiastolicbloodpressurewerebothsta tisticallysignificant.

DISCUSSION

Hypertensive disorders of pregnancy which frequently manifest as Preeclampsia continuestoexertanenormoustollindevelopingcountrieslikeIndiaandalsoindeveloped countries. Despite progress in its prevention, detection and treatment, it continues to be theleadingcauseofmaternaldeath.Itisrecognizedthatthesourcefortheunderlyingpatho physiology of the disease is poorly understood, but currently endothelial dysfunctionis most popularly hypothesized to be the feature of preeclampsia. Various traditional andnewerbiomarkersweresuggestedfordiagnosis

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andprognosisofpreeclampsia.Thehomocysteine mediated vascular changes are similar to those associated with preeclampsia(PE)

Therefore, thepresentstudyhasbeentakenuptoassess clinicalutilityofsomeofthepromisingbiochemicalmarkerslikehomocysteine andlipidprofilewhichare

simpleandcanbeofsomediagnosticandprognostic significance.

In this present Study, 100 women were selected and divided into 2 groups, the controlgroup comprised of 50 healthy pregnant women and the study group comprised of 50diagnosedPEcases.

Inpreeclampticpatients,systolicbloodpressureanddiastolicbloodpressure showedsignificantincrease.

In the present study, the mean serum homocysteine levels in the control group (normotensivepregnant women) is 8.58±3.02 μmol/l. The review article of Ueland et al[13] showed that thevaluebetween5and15mmol/Linfastingsubjectsare normal.

Our study is supported by various other studies viz., Singh Urmila et al[14]., showed that thevalue

inthenormotensivepregnantwomenis11.5±4μmol/l,Hoqueetal.,6.86±2.47μmol/l[15]

In the study group comprising of 50diagnosed PE cases the mean serum homocysteine levelis 16.24±8.22 μmol/l which when compared to normotensive pregnant women is elevated,whichishighlystatisticallysignificant($p<0.001$).Thisshowsthatthedecreaseinho mocysteinelevelswhichoccursinnormalpregnancydo notoccurinpre-eclampsia.Therefore it can be stated that increase in homocysteine concentration in preeclampsia isrelated to the defect in the mechanism that usually decreases homocysteine during normalpregnancy.

Our study is supported by the study conducted by Singh Urmila et al., who found that themean value in preeclamptic pregnant women was statistically significant comparing withnormotensive pregnant women[14]. In other studies, conducted by Shahid A. Mujawar et al[16].,mean serum homocysteine levels in pre- eclamptic pregnant women was 16.4 ± 3.26 μmol/land Khosrowbeygi A et al[17]., found it in the range 14.05±1.43 μmol/l where both the studiesshowedstatisticallysignificantvalues.

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It is possible thatin pre-eclampsia,theelevated homocysteinelevel injures the vascularendothelium which contribute to the pathogenesis of PE. In addition vascular endothelium inpregnant women may be more sensitive to injury. Therefore, elevation in homocysteine levelsmay lead to endothelial injury with subsequent activation of various factors that eventuallyresultsinpreeclampsia.

In our study there was a positive correlation between Preeclampsia and lipid parameters.

Theserumtriglycerideconcentrationshowedverysignificant(P<0.001)increaseinthepreeclampsia thanin the normalpregnancy.

Theprinciplemodulatorofthishypertriglyceridemiaisoestrogenaspregnancyisassociatedwithhyperoestrogenaemia.Oestrogeninduceshepaticbiosynthesisofendogenous triglycerides, which is carried by VLDL. This process may be modulated byhyperinsulinismfoundinpregnancy.IncreasedTG,foundinpregnancyinducedhypertension, is likely to be deposited in predisposed vessels, such as the uterine spiralarteries and contributes to the endothelial dysfunction, both directly and indirectly throughgeneration of small, dense LDL. Moreover, this hypertriglyceridemia may be associatedwithhypercoagulability[18].

In ourstudy a significantdecreasein HDL-Cwere observedinpreeclamptic thaninnormotensivepregnantwomen.

Oestrogen is responsible for induction of TG and HDL and suppression of serum LDL andoestrogen level falls in preeclampsia. The Low level of HDL in pre-eclampsia is howevernotonlybecauseofhypooestrogenaemiabutalsodue toinsulinresistance[18].

A significant fall in LDL-C level in normal pregnancy as observed in present study may beattributedtohyperestrogenaemia,whileLDL-Clevelincreasedsignificantlyinpreeclampsia.

In presentstudy,significantalterationin TotalCholesterollevelcouldbeobservedinpreeclampsiathaninnormalpregnancy.

ThesefindingsaresimilartopradnyaPhalaketal[19].,Gohil et al[20]., and Usha Adiga et al[21]., they have found significant increase in serum TC inpreeclampsia comparingwith normotensive pregnantwomen. However others have foundnosignificanceintotalcholesterolmeanvalues[22].

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CONCLUSION

Elevated levels of homocysteine can be due to genetic or nutritional deficit or a combinationofboth.Nutritionaldefectsinvolveinadequateintake offolic acid andvitaminB12.

The findings of our study suggest that abnormal levels of lipid profile especially TG, TC,LDL and HDL may contribute in the pathophysiology of preeclampsia. This association mayhelptoinvestigatethe underlyingpathologicalprocess ofpreeclampsia.

Early detection is the corner stone for proper managementof preeclampsia,which willreduce the maternal mortality rate and infant mortality rate. For early detection a reliablesimple laboratory test is essential. Serum homocysteiene and lipid profile can be used for thispurpose and itmay help in developing strategies forprevention and early diagnosis ofpreeclampsia.

Furtherstudiesarerequiredtoknowthecauseofhyperhomocysteinemiaobservedinpregnant women with preeclampsia, which may help in pharmacological management ofpregnantwomenatriskforPE.

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