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ORIGINAL RESEARCH

A study of insulin resistance in women with preeclampsia

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ABSTRACT

Background: Preeclampsia isa state of insulin resistance. Insulin resistance features like Hypertension, hyperinsulinemia, glucose intolerance, and lipid abnormalities are associated with pregnancy-induced Hypertension.

Aimsandobjectivesofthestudy:

1. **Tostudyinsulinresistanceinwomenwith pre-eclampsia.**
2. **TocompareandevaluatetheroleofmeasuringIR amongwomenwith preeclampsiaandnormalpregnancy.**

Methodology: AProspectiveandobservational one year study conducted in GovernmentGeneralHospital.Kurnool. Atotalof 50Womenwith preeclampsiaand50women withnormalpregnancy. Women were instructed for 12hrs overnight fasting about 2ml of venous blood was collected in a fluorideethylenediaminetetraacetic acid vial using proper aseptic precautions. Plasma was separated by centrifugationand usedforestimationof plasmaglucoseandplasmainsulinlevels. Values are presented as mean ± standard deviation (SD) and the statistical analysis was done using SPSS 17.0software. Student's unpaired t-test was used for comparison of parameters between two groups. The p-value oflessthan0.05was consideredas statistically significant.

Results: Pre-eclampticwomenhadsignificantlyhigherFPIlevels(n=50,mean12.17µIU/ml)thencontrols(n=50,mean 2.95 µIU/ml, p=<0.001vhs) and higher IR levels (mean = 2.54) then controls (mean 0.65) and levels of FPIand IR was directly proportional to severity of disease (mean FPI=8.60µIU/ml in mild PE, 12.85µIU/ml insevere, and 20.51µIU/ml in eclampsia, p < 0.001vhs, and mean IR 1.71 in mild, 2.74 in severe, 4.26 ineclampsia).

Conclusion: Fasting plasma insulin levels are increased during the normal pregnancy with the levels maximum during thirdtrimester.Endothelialdysfunctionandinflammatoryimbalanceinpreeclampsialeadto developmentofIRwiththeresultanthyperinsulinemia. Thisstudyalsoshows thatIRwasdirectlypropotionaltoseverityof preeclampsia.

Keywords:Preeclampsia,Fastingplasmaglucose,Fastingplasmainsulin,Insulinresistance, Hyperinsulinemia, Normotensives,Pregnancy.

INTRODUCTION

Preeclampsia is best described as a pregnancy specific syndrome that can affect virtuallyeveryorgansystem.Classically,itwasdefinedasahypertensionandproteinuriainawomen

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withnopriorincidenceofthesesequencesandthat,whichresolveafterdelivery.Itisdangeroustoboth motherandbaby ofunknowncause.[1]

Insulin produced by the β-cells of the pancreatic islets, is a polypeptide hormone formedaftereliminationofCpeptidebyhydrolysisA(21aminoacids)andB(30aminoacids) chainsofinsulinbeingconnectedby disulfidebonds.

Pregnancyisassociatedwithbetacellhyperplasiaresultsinincreasedseruminsulinlevelsin both fasting and fed states. Early pregnancy is associated with slightly improved insulin sensitivitybutaspregnancyprogresses,womenbecomeincreasinglyinsulinresistant.Theinsulinres istanceis due to effects of increased levels of several hormones including cortisol, growth hormone andhumanchorionicsomatomammotropin(HCS,alsoknownas humanplacentallactogen,HPL).[2,3]

Adequate invasion of trophoblasts into uterine spiral arterioles is necessary for properfunctioning of placenta. Impaired invasion leads to narrowing of uterine arterioles and placentalischemia. Placental ischemia becomes a causative factor for reduced expression of placentalgrowth factor, vascular endothelial growth factor, nitric oxide, and prostacyclin from vascularendothelium.[4] Expression of antiangiogenic factors, such as soluble Fms-like tyrosine kinase 1,interleukins (ILs), tumor necrosis factor- (TNF- α), etc., is increased on the other side. Thisangiogenic imbalance causes widespread endothelial dysfunction all over the body. IncreasedlevelsofTNF-αandILscausealterationsintheinsulinsignalingpathwayleadingtoIR.That'swhyin preeclamptic women have an associated hyperinsulinemia as reflected by the higher plasmalevelsofinsulinascomparedtowomen withnormalpregnancy.

MATERIALSANDMETHODS

SAMPLESIZE

Hundred pregnant women (50 cases and 50 controls) admitted to Government General Hospitalduringthestudyperiod(september2019toAugust2020)wasenrolledforthestudy,whosatis fiedtheinclusioncriteria.

SAMPLETYPE

Prospectivestudy

STUDYPERIOD

Oneyear

METHODOFCOLLECTIONOFDATA

A prospective study was done on 100 pregnant women who were enrolled in the study ascases and controls. Fasting plasma insulin (FPI) and fasting plasma glucose (FPG) level and their co-relation with the severity of the disease based on their age, gestational age, parity, BMI and severity ofhypertension wasstudied.

All the women in the study were subjected to detailed history, examination and all weresurveyedfortheuseofiron,folicacid,vitaminsandanyotherdrugs.Besidesroutineantenatalinv estigations in all pregnant women and special investigations in pre eclamptic women, all of them weresubjectedtofasting plasmainsulinlevelsandfastingplasmaglucose.

For the measurement of fasting plasma insulin levels, 3 ml of blood from the antecubital vein inthe fasting state was taken after overnight fasting. All the specimens were transported to the laboratorywithin2hoursofcollection.Thereafterthespecimenswerecentrifuged5to7minutesat20 00rpm.Clearserum obtained was transferred in a plastic vial and stored in a refrigerator until analysis. The sampleswere then subjected to Chemiluminescent Immunoassay (CLIA)

ISSN 2515-8260 Volume 09, Issue 03, 2022

technique using the FDA approvedreagentsandkitwithBACKMANCOULTERequipment,USA Insulin resistance (IR) was estimated by using HOMA MODEL (Homeostatic Model Assessment).Unpairedstudent t- testwas usedforcomparison.
Formulatocalculate IRbyusingHOMAMODEL:
Fastingplasmaglucoseinmg/dl× Fastingplasmainsulininμ IU/ml405
Thesubjectisconsideredtohave insulinresistanceifHOMA-IRvalueismorethan 2.7.

PLANFOR DATA ANALYSIS:
Statisticanalysis ofthe collecteddatawasdoneby‘t’test,
Fischer’s testchi-squaretest
$p<0.05$wastakenasstatisticallysignificant

INCLUSIONCRITERIA
Afterthewrittenandinformedconsent,womendiagnosedaspreeclampsiaweretakenascasesandthe controlgroupwerethehealthy pregnantwomen.
Allantenatalpregnantwomenbetween20-40weeks
- Normotensives(Control)
- Hypertensives(Cases)

EXCLUSIONCRITERIA
- Multiplegestation
- Molarpregnancy
- H/OPCOS
- Gestationalorprediabeticwomen
- Liverdisorders
- Renaldisorders
- Addictionormedicationaffectingbloodglucoseandinsulinlevels.

Inwomenwhosepregnanciesarecomplicatedbyhypertensionthereappearstobeanexaggerationofi nsulinresistanceandtheassociated metabolic changes.
Fromtheareaofcardiovascularresearchthereisincreasedevidencethathyperinsulinemia cancauseincreasedendothelial damage.
Thisstudywasdonewithanaimtotestthehypothesisthatfastingplasmainsulinlevelsareincreasedin womenwithpreeclampsiacomparedtonormotensivewomen.

RESULTSANDANALYSIS
Table1:Numberofwomen inthestudy

Group	Number
Normotensive	50
Preeclampsia	50
Total	100

Thepresentstudywasconductedon100womenoutofwhich50controlwhowerenormotensive and50cases whowerepreeclamptic.

Table2:Severityofpreeclampsia

Group	Number	Percentage
MILD	7	34%
SEVERE	**28**	**56%**

ISSN 2515-8260 Volume 09, Issue 03, 2022

ECLAMPSIA	**5**	**10%**
TOTAL	**100**	**100%**

According to the NHBPEP 2000 classification the cases was further classified into mild pre-eclampsia, severe preeclampsia and eclampsia. Among the cases in the study 34% (17) were inmild preeclampsia group, 56% (28) were in severe pre- eclampsia group and 10% (5) were ineclampsiagroup.

Table3: Patientprofile

	AGE	**PARITY**	**GESTATIONALAGE**	**BMI**
CASES(n=50)	Mean24.4(18 to35years)	Primi52%(26) Multi48%(24)	22to 40 weeks	24.08
CONTROLS(n=50)	Mean23.88(18 to35 years)	Primi56%(28) Multi44%(22)	28to 40 weeks	23.92

Table4:AgeDistribution

AGE		**<20**	**20-25**	**26-30**	**31-35**	**TOTAL**
CONTROL	No.(%)	8(16%)	24(48%)	14(28%)	4(8%)	50(50%)
MILD	No.(%)	-	11(22%)	4(8%)	2(4%)	17(17%)
SEVERE	No.(%)	1(2%)	18(36%)	7(14%)	2(4%)	28(28%)
ECLAMPSIA	No(%)	3(6%)	1(2%)	1(2%)	-	5(5%)
TOTAL	No.	12	54	26	8	100

Themeanageofthewomeninthecontrolgroupandthestudygroupwas23.88and24.4years respectively which was comparable with both groups. In the present study maximum no. ofwomenwereinagegroupbetween 20-25yrs(54%),incontrolandstudygroups.

Table 5:Paritydistribution

Parity	**Group**		**Total**
	Control	**Study**	
Primicount(%)	28(56%)	26(52%)	54(54%)
Multicount(%)	22(44%)	24(48%)	46(46%)
Totalcount(%)	50(100%)	50(100%)	100(100%)

Number of primigravida was 56% in the control group and 52% in the study group whereas themulti'swere44%inthecontrolgroupand48%inthestudygroupandtheresultsobtainedwerestatis ticallynotsignificant.

Table6:Gestationalageatthetimeof sampling

Group	**<28**	**28-32**	**33–37**	**>37**
Control	-	2	17	31
Mild	-	1	9	7
Severe	6	5	6	11
Eclampsia	1	-	3	1

62% women in control, 36% with preeclampsia were at term at the time of sampling.38%ofwomenincontroland64%ofwomenwith preeclampsiaweresampled atearlier gestationalage.

Table 7:BMI

	N	**MeanBMI**	**SD**

Normotensive	50	23.92	
Mild	17	24.58	
Severe	28	23.32	
Eclampsia	5	22.28	

ThemeanBMIinthenormotensivegroupwas23.92andthatinmildpreeclampsia,severepreeclampsiaandeclampsiagroupwas24.6,23.3and22.3 respectively.

Table8:FastingInsulinlevelsamongcontrolandcases

	N	Mean	SD
Normotensive	50	2.95	
Preeclampsia	50	12.17	

Inthepresentstudy,themeanfastinginsulinlevelsinnormotensivegroupwas 2.95µIU/mland in preeclamptic group was 12.17µIU/ml. The results obtained shows that fasting insulin levelswas more in preeclamptic group in comparison to normotensive pregnant women and the resultswerestatistically significant,p=<0.001vhs

Table9:Fastinginsulinlevelsdependingonvariousgroups

	N	Mean	SD
Normotensive	50	2.95	
Mild	17	8.60	
Severe	28	12.85	
Eclampsia	5	20.51	

Themeanfastinginsulinlevelsinmildpreeclampsiawas8.60µIU/ml,insevereeclampsiaitwas12.85 µIU/ml and ineclampsiaitwas20.51µIU/ml.

Table: 10Insulinresistanceinvariousgroups

	N	MEAN	SD
NORMOTENSIVES	50	0.65	
MILDPE	17	1.71	
SEVEREPE	28	2.74	
ECLAMSIA	5	4.26	

The mean insulin resistance in controls is 0.65 and where as in mild preeclampsia was1.71, severepreeclampsia2.74andin eclampsiaitwas4.26

Allthethreegroupsofcaseshadhighervaluesoffastinginsulinlevelsascomparedtothenormotensives(2.95µIU/ml),anddifferenceamongthegroupwasstatisticallysignificantwithp = <0.001vhs and it was noted that among the study group ,the fasting insulin levels was higherinseverepre-eclampsiaandeclampsiagroupincomparisontomildpreeclampsia.

DISCUSSION

Hypertension and preeclampsia during pregnancy, making this disorder one of the leading causes of maternal and perinatal morbidity and mortality worldwide. It has been estimated that preeclampsia complicates 2 – 8% of pregnancies daily. Women in low-resource countries are at high risk of developing PE.

The leading cause of PE is placental ischemia due to impaired trophoblastic invasion of uterine spiral arterioles. The ischemic placenta releases various inflammatory mediators that cause widespread endothelial dysfunction and cause alterations in the insulin signaling pathway leading to IR. Women with preeclampsia, independent of obesity and glucose

intolerance, exhibit insulin resistance during pregnancy. It is believed placental hormones are the most critical factors responsible for a change in insulin resistance.

The present study analyzes insulin resistance in preeclampsia compared to normal healthy pregnant women at tertiary care hospitals. This study comprises 50 preeclampsia and 50 normotensive women. Several studies are done to show the relation between insulin resistance and preeclampsia.

The present study shows that patients with preeclampsia were not statistically significantly different from the control group in terms of average age. Similar to other tasks conducted by Lakshmi Praba et al. [1], Sonagra et al. [2], Chen et al. [3],

The present study also following**Manjeerika and Nanda et al. (2012)[4], Hauth et al. (2011)[5]** mean age in years were not statistically different in both the groups of normotensives and preeclamptics.

The present study shows mean age in between severity of PE was no statistically different, according toSamaira et al. (2015)[6].

The present study number of primigravida was 28 in the control group and 26 in the study group. In contrast, the multi was 22 in the control group and 24 in the study group. Even though PE incidence was high in primigravida, there is no statistically significant difference between the study and control group regarding parity. **Samaira et al. (2015)[6], FaridehAbhari et al. (2014)[7],** are found that there was no significant difference regarding parity in both groups.

BMI is slightly elevated in preeclamptic women than in control, but it is not statistically significant. Which is similar to Lakshmi Praba et al. [7] (2019), Farideh et al. (2014)[7], and Sierra et al. (2007)[8] are also found that no significant difference in BMI between preeclamptic women and normal pregnant women.

The present study mean GA no statistically significant difference between study and control group which following Amit D Sonagra et al. [9] (2017), FaridehAbhari et al. [7]

The present study shows no statistically significant difference in mean GA between severity of PE. Still, other studies like **Samaira et al. (2015)[6] and Lazar et al. (2009)[10]** show a significant difference in mean gestational age between PE severity.

The increase in the fasting plasma insulin levels was directly proportional to the severity of the disease. As the severity of PE increases, plasma insulin levels also increases, i.e., FPI levels were higher in severe PE than mild PE.In the present study, the mean FPI levels higher in severe PE were 31.09 than mild PE (mean FPI 9.98). The difference was very much statistically significant.

Similar studies like **Samaira El Mallah et al. (2015)[6]** also found a significant difference in FPI levels in between severe PE (7.75) compared to mild PE (5.44).

In the present study, IR was higher in the preeclamptic group (mean IR 4.92), compared to normotensive pregnant women (mean IR 0.65), and the difference was very much statistically significant (P-value 0.01).

Similar to other study conducted by **Lakshmi Praba et al. (2019)[1],** found that in preeclamptic women, IR (mean IR 12.46) was highly elevated, nearly twice as that of a control group(mean IR 5.69), and so suggests that insulin resistance can be very well be used as a biomarker in the diagnosis of preeclampsia.

A study conducted by **Samaira El Mallah et al. (2015)[6]**also found that statistically significant difference in IR between mild and severe PE and concluded that plasma insulin should be considered an indicator of PE and may act as a pathophysiological relevant factor in the development of PE.

Insulin resistance was directly proportional to the severity of preeclampsia. As the severity of PE increases, insulin resistance also increased. The present study shows insulin resistance was higher in severe preeclampsia.
Like other studies like Samira El Mallah et al (2015), [6] also shows a statistically significant difference between insulin resistance and the severity of PE.

CONCLUSION

The present study shows that preeclamptic women have higher fasting hyperinsulinemia and insulin resistance than normotensive pregnant women, and the relationship between insulin resistance and preeclampsia is independent of BMI, age, and parity.
The present study signified that fasting plasma insulin levels and insulin resistance were increased in women with preeclampsia compared to normotensives. It also found that fasting insulin levels and insulin resistance were directly proportional to the disease's severity. IR and FPI levels were higher in severe preeclampsia than a mild one.
The present study also signified that insulin resistance is higher in PIH women, especially those with early-onset preeclampsia. The association between preeclampsia and insulin resistance may be significant in understanding the pathological process and may help develop strategies for the prevention and early diagnosis of preeclampsia.

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CONFLICT OF INTEREST

None

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