DISCUSSION

Pre-eclampsiaisamulti-systemdisorderthatcausessubstantialmaternalandfetalmorbidityandmortality.Itisdefinedassuddenonsetofhypertensionpresentingafterthe20thweekofgestation(≥140/90mmHg)accompaniedbyabnormaledemaand/orproteinuria***(Sharonetal.,2008).***

Althoughpre-eclampsiaremainsadiseaseoftheories,previousstudieshaveindicatedthatpreeclampsiaisassociatedwithendothelialdysfunction,ahypercoagulablestate,metabolicabnormalities,aninflammatoryresponseandatherosclerosis***(Kauretal.,2010).***Theetiologyofthesecondi tionsremainselusiveandmultiplefactorsareimplicatedinpathogenesisofpre-eclampsiaamongthesemechanisms,insulinresistance.Manystudieshavebeenperformedtoelucidatetheprecisemechanismofexaggeratedinsulinresistanceinpre-eclampsia,focusingonidentifyingcirculatingadipokinessuchasleptin,adiponectinandresistininthepathogenesisofpre-eclampsia***(Akdenizetal.,2011)***.

Resistinisapeptidehormonethatisspecificallysecretedbyhumanadipocytesandmononuclearcells**.**Itisapotentregulatorofglucosehomeostasisthatisthoughttoopposetheactionofinsulininperipheraltissues;itimpairsglucoseintakebyadipocytes,increasesplasmaglucoseconcentration,andthusdecreasesinsulin***(Hivertetal.,2009)***.

Resistinisexpressedinthehumanplacentaanditsserumleveli senhancedinthethirdtrimesterofpregnancy;suggestingitspivotalr oleinthestateofinsulinresistanceduringpregnancy.Recentstudiess uggestresistinmayplayanimportantroleinthepathogenesisofpre-eclampsiathroughtheirroleinlow-gradesystemicinflammation,atherosclerosis,andinsulinresistance .Therefore,itisreasonabletosupposethatresistinmaydirectlyorindi rectlyinfluencethefunctionofplacentalendothelialcells*(Nandaeta l.,2012)*.

HOMAwasfirstdevelopedin1985byMatthews.HOMAdesc ribesglucose–insulinhomeostasisbymeansofasetofsimple,mathematicallyderiv ednonlinearequations.TheapproximatingequationforIRhasbeensi mplifiedandusesafastingplasmasampleinwhichglucose(fastingbl oodglucose;FBG)andinsulin(fastinginsulin;FI)aremeasured,toge therwithaconstant*(Nandaetal.,2012)*.

TheproductofFBG×FIisanindexofIR.HOMA-IR=(glucose×insulin)/22.5.InsulinconcentrationisreportedinμU/ Landglucoseinmmol/L.Theconstantof22.5isanormalizingfactor,i .e.normalFIof5μU/mL×thenormalFBGof4.5mmol/Ltypicalofa'n ormal'healthyindividual=22.5*(Nandaetal.,2012).*

Inthelightofthepreviouspostulation,Theaimofthepresentst udywastoinvestigatetheclinicalutilityofmaternalserumresistinin womenwithpre-eclampsiacomparedtothoseinnormalpregnantwomenandnormaln

on-
pregnantwomen,andtoinvestigatethepotentialroleofresistinasam
ediatorofinsulinresistance.

Ourstudywasconductedonsixety(60)pre-
eclampticpatientsTheiragesrangedfrom20to39yearswithameana
geof25.00±4.50.Thirty(30)patientswithmildpre-
eclampsia,andthirty(30)patientswithseverepre-
eclampsiawomenwithsingletonpregnancybetween24and31week
sofgestation.TheywereattendingtheObstetricsout-
patientclinicsufferingfrompre-
eclampsiaduringthethirdtrimesterofpregnancy.Inadditiontofiftee
n(15)healthypregnantcontrolsofthesamegestationalageandageof
patientgroupandfifteen(15)healthynon-
pregnantfemalesofthesameageofpatientgroup.

Allthestudiedindividualsweresubjectedtofullhistorytaking
andcompleteclinicalexamination.Bloodsampleswerecollectedfor
determinationofALT,AST,RBS,creatinine,CBC,FBG,fastingins
ulinandserumresistin,while24hoursurinesampleswerecollectedfo
rdeterminationoftotalurinaryproteins.Assayofserumresistinands
erumfastinginsulinwascarriedoutusinganenzymelinkedimmunos
orbentassaytechnique.

Theresultsofthepresentstudyrevealedthatpregnantcontrols
hadastatisticallysignificanthigherserumlevelsofresistinandHOM
A-IRwhencomparedtonon-
pregnantcontrols.Ourresultsagreedwiththoseof***Yuraetal.,2003,***w

horeportedthatresistinexpressionwasgreaterintermplacentasthani nchorionicvilliofearlypregnancy,Headedthatbloodresistinlevelw assignificantlyhigherinnormaltermpregnantwomenthaninage-matchedhealthynon-pregnantwomen,however,theexactmechanismsbehindtheincreas einserumresistinduringpregnancyhavenotbeenclarified.

Basedonthefindingsof***Yuraetal.,2003,***andthefactthattherei sanincreaseinplacentalmasswithgestation,itisreasonabletospecul atethatresistinproductionbytheplacentaisthemaincauseoftheincre aseinserumresistin.

Thesecondhalfofpregnancyisastateofinsulinresistance***(See lyetal.,2003).***Resistin,alongwithhumanplacentallactogen,prolact in,steroidhormonesandotherhormones,decreasesinsulinsensitivit y,whereasleptinincreasesinsulinsensitivity.Theincreaseinserumr esistininthethirdtrimesterofpregnancyisinaccordancewithinsulin resistanceinnormalpregnancy***(Sharmaetal.,2002)***.

Thisimpliesthatresistinmayparticipateintheregulationofm etabolisminpregnancy.Duringpregnancy,changesinmaternalmet abolismoccurinresponsetothegrowingfetusandplacentaandtheiri ncreasingmetabolicneeds.Pregnancyisassociatedwithalterationsi ntheregulationofglucosemetabolismcausedbytheactionsofhuman placentalgrowthhormone,prolactin,cortisol,andprogesterone;the sehormonesantagonizetheactionofinsulin,particularlyduringthe2 ndand3rdtrimesters,leadingtoastateofrelativeinsulinresistanceaspr egnancyprogresses***(Seelyetal.,2003).***Themother'sbodyadaptstot

henewmetabolicenvironmentsothatthetransferofglucosetothefetu sisadequate.

Ourstudyalsorevealedahighlystatisticallysignificantincrea seinserumlevelsofresistinandHOMA-IRinpre-eclampticwomenwhencomparedtotheirmatchedcontrols.Thisco mesinaccordancewith***Haugenetal.,2006,***and***Seol etal.,2010,***whodemonstratedthatSerumresistinlevelsweresignific antlyelevatedinwomenwithpre-eclampsiacomparedtonormalpregnantwomen.Althoughtheexactf unctionofresistininthepathophysiologyofpre-eclampsiaremainsunclear,theelevatedserumresistinlevelsmightb eassociatedwithexaggeratedinsulinresistanceviatheextensivesyst emicinflammatoryresponseinpre-eclampsia***(Sonagraetal.,2012)***.Extensivesystemicinflammationi sawellknowncharacteristicofpre-eclampsia,andmonocyteactivationisoneoftheassociatedfeatureso fsystemicinflammation***(Demircietal.,2011)***.Monocytesmaybeth esourceoftheincreasedserumresistinconcentrationsinpre-eclampsia.Unfortunately,wedidnotinvestigatemononuclearcellac tivationorotherproinflammatoryadipokines,suchasTNF-αandIL-6,inthisstudy.Futureinvestigationisneededtodeterminewhetherth edifferentgeneticexpressionofmonocytesisrelatedtocirculatingre sistinconcentrationsinwomenwithpre-eclampsia.

Resistinimpairsglucoseintakebyadipocytes,andincreasespl asmaglucoseconcentrations,thusdecreasinginsulinsensitivity***(So nagraetal.,2012)***.

Onthecontrary,***Chenetal.,2003,***observedthatinwomenwith PE,resistinlevelsweresignificantlylowerthanincontrols,owingtha ttoareductionintheplacentaproductionofthispeptide.Thisviewissu pportedbythedetectionofresistinmRNAexpressioninthehumanpl acenta,togetherwiththeabsenceofsignificantchangesinresistinexp ressioninadiposetissueduringgestation.

Ourstudyalsoshowedastatisticallysignificantincreaseofresi stinandHOMA-IRlevelsinseverepre-eclampsiaincomparisontomildpre-eclampsia.Onthecontrary***AL-Refai,2012,***whofoundnostatisticallysignificantincreaseofresistin andHOMA-IRlevelsinseverepre-eclampsiaincomparisontomildpre-eclampsia.

Ourcorrelationstudyrevealedasignificantpositivecorrelation betweenbothresistinandHOMA-IRandSBPaswellasDBP.Theresultsareconsistentwiththefindings of***Haugenetal.,2006,***and***Seoletal., 2010,***whoalsoreportedasignificantpositivecorrelationbetweenme ansystolicbloodpressureandmeandiastolicbloodpressure,theindic esofpre-eclampsia,andthebothresistinandHOMAIRlevelsinpre-eclampticgroups.

Ourcorrelationstudyalsoshowedanonsignificantcorrelation betweenbothresistinandHOMA-IRandBMI.Thiscomesinaccordancewith***Silhaetal.,2003***and***Heil bronn etal.,2004,***whoreportednorelationshipbetweenresistinserumlevel

sandpercentagebodyfat,visceraladiposityandBMI.Onthecontrary ***Azumaetal.,2003,*** whoreportedahigherserumresistinlevelsinobesesubjectscomparedwithleansubjects,whichpositivelycorrelatedwiththechangesinBMIandvisceralfatarea.

Thebestdiagnosticcutofflevelofresistinfordiscriminatingpre-eclampticpatientsversushealthypregnantcontrolswas10ng/mL.Thishadadiagnosticsensitivityof88.33%,specificity96.67%positivepredictivevalue98.1%andnegativepredictivevalue80.6%.Thissensitivityandspecificityissupportedbytheresultsof***AL-Refai,2012,*** whopublishedsensitivityandspecificityof90%and98%respectivelyforresistinatcutofflevel12ng/mL.

AssessmentofthediagnosticperformanceofHOMA-IRinpre-eclampticpatientsversushealthypregnantcontrolsrevealedthatthebestdiagnosticcutofflevelwas2.05.Thishadadiagnosticsensitivity98.3%,specificity86.67%positivepredictivevalue93.7%andnegativepredictivevalue96.3%.Thissensitivityandspecificityissupportedbytheresultsof***Haugenetal.,2006,*** whopublishedsensitivityandspecificityof90%and80%respectivelyforresistinatcutofflevel3.2.

Furthermoreassessmentofthediagnosticperformanceofresistinand HOMA-IRfordiscriminatingseverepre-eclampticpatientsfromthosewithmildpre-eclampsiafoundthatthebestcutoffvalueofresistinwas17ng/mL.Thishadadiagnosticsensitivityof96.70%andspecificity70%positivepred

ictivevalue76.30%andnegativepredictivevalue95.50%.Thissensiti vityandspecificityissupportedbytheresultsof***AL-Refai,2012***,whopublishedsensitivityandspecificityof98%and85%r espectivelyforresistinatcutofflevel19ng/mL.

Thebestdiagnosticcutofflevelof HOMA-IRfordiscriminatingseverepre-eclampticpatientsfromthosewithmildpre-eclampsiawas3.7.Thishadadiagnosticsensitivityof93%andspecif icity40%positivepredictivevalue60.90%andnegativepredictivev alue85.70%.Thissensitivityandspecificityissupportedbytheresult sof***Seoletal.,2010***,whopublishedsensitivityandspecificityof82%a nd55%respectivelyforresistinatcutofflevel3.5.

Theresultsofthisstudydemonstratedincreasedserumresistin concentrationsinwomenwithpreeclampsiacomparedtothelevelsfo undinwomenwithnormalpregnancies.Thisfindingsuggeststhatele vatedserumresistinlevelsmayrepresenttheexaggeratedinsulinresi stanceinpreeclampsia.

SUMMARYANDCONCLUSION

Pre-eclampsiaisapotentiallyseriousconditionthatstillaccountsforsignificantmorbidityandmortalityforthemotherandtheneonate,complicating5-7%ofallpregnanciesandexposingthemtoa3-to25-foldincreasedriskofsevereobstetriccomplications.Although,thepathogenesisisnotfullyunderstood,itisnowwidelyacceptedthatvascularendothelialdysfunctionisthemostastonishingandtheprincipaleventinthepathophysiologyofthedisease.

Researchersinvestigatedthefactthatpreeclampsiaisassociatedwithendothelialdysfunction,ahypercoagulablestate,metabolicabnormalities,aninflammatoryresponseandatherosclerosis.Theetiologyoftheseconditionsremainselusiveandmultiplefactorsareimplicatedinpathogenesisofpre-eclampsiaamongthesemechanisms,insulinresistance.

Resistinisadipose-specificsecretedhormone,whichbelongstothefamilyofcysteine-rich,c-terminalproteins.Itisapotentregulatorofglucosehomeostasisthatisthoughttoopposetheactionofinsulininperipheraltissues;itimpairsglucoseintakebyadipocytes,increasesplasmaglucoseconcentration,andthusdecreasesinsulin.Resistinisexpressedinthehumanplacentaanditsserumlevelisenhancedinthethirdtrimesterofpregnancy;suggestingitspivotalroleinthestateofinsulinresistanceduringpregn

ancy.Recentstudiessuggestresistinmayplayanimportantroleinthe pathogenesisofpre-eclampsiathroughtheirroleinlow-gradesystemicinflammation,atherosclerosis,andinsulinresistance .Therefore,itisreasonabletosupposethatresistinmaydirectlyorindirectlyinfluencethefunctionofplacentalendothelialcells.

Inthisregard,thisstudyaimedtoinvestigatetheclinicalutility ofmaternalserumresistininwomenwithpre-eclampsiacomparedtothoseinnormalpregnantwomenandnormalnon-pregnantwomen,andtoinvestigatethepotentialroleofresistinasamediatorofinsulinresistance.

Thisstudywasconductedonsixety(60)pre-eclampticpatients.Thirty(30)patientswithmildpre-eclampsiaandthirty(30)patientswithseverepre-eclampsia.Inadditiontofifteen(15)healthypregnantcontrolsandfifteen(15)healthynon-pregnantfemales.

Allthestudiedindividualsweresubjectedtofullhistorytaking andcompleteclinicalexamination.Bloodsampleswerecollectedfor determinationofALT,AST,RBS,creatinine,CBC,FBG,fastingins ulinandserumresistin,while24hoursurinesampleswerecollectedfo rdeterminationoftotalurinaryproteins.Assayofserumresistinands erumfastinginsulinwascarriedoutusinganenzymelinkedimmunos orbentassaytechnique.

Theresultsofthepresentstudyrevealedthatpregnantcontrols hadsignificantlyhigherserumlevelsofresistinandHOMA-

IRwhencomparedtononpregnantcontrols.Ourstudyalsorevealeda highlysignificantincreaseinserumlevelsofbothresistinandHOMA IRinpre-
eclampticwomenwhencomparedtotheirmatchedcontrols.

AsregardstherelationofresistinandHOMA-IRtotheseverityofpre-eclampsia,ourstudyshowedastatisticallysignificantincreaseofresistinandHOMA-IRlevelsinseverepre-eclampsiaincomparsiontomildpre-eclampsia.Moreover,significantpositivecorrelationwasalsofound betweenbothresistinandHOMA–IRandbothSBPandDBP,whichareconsideredamongtheindicesofseverityofpre-eclampsia.

Recevieroperatingcharacteristic(ROC)curveanalysiswasappliedtoassessthediagnosticutilityofresistinandHOMA-IRfordiscriminatingseverepre-eclampticpatientsfromthosewithmildpre-eclampsia.Itwasfoundthatthebestcutoffvalueofresistinwas17ng/mL.Thishadadiagnosticsensitivityof96.7%,specificity70%positivepredictivevalue76.30%andnegativepredictivevalue95.50%..Thebestdiagnosticcutofflevelfor HOMA-IRwas3.7whichhadadiagnosticsensitivityof93%,specificity40% positivepredictivevalue60.90%andnegativepredictivevalue85.70%..

Inaddition,thediagnosticperformanceofresistinandHOMA-IRinpre-eclampticpatientsversushealthypregnantsubjectstoassesstheirutilityasearlyindicatorsofpre-eclampsia..Thebestdiagnosticcutofflevelforresistinwas10ng/mL. Thishadadiagnosticsensitivityof88.33%,specificity96.67%,positivepredictivevalue98.1%andnegativepredictivevalue80.6%.Thebestdiagnosticcutofflevelfor HOMA-IRwas2.05.Thishadadiagnosticsensitivityof98.33%,specificity86.67%positivepredictivevalue93.7%andnegativepredictivevalue96.3%.

CONCLUSION

- Serumresistincanbeconsideredapromisingmarkerindiagnosis ofPEwithanexcellentdiagnosticefficiency.
- ResistincanalsobeusedindiscriminatingpatientswithmildPEfr ompatientswithseverePE,thereforeitiscloselyrelatedtotheprog ressofthedisease.
- Elevatedserumresistinlevelsmayrepresenttheexaggeratedinsu linresistanceinpreeclampsia.