

## DISCUSSION

**P**re-eclampsia is a multi-system disorder that causes substantial maternal and fetal morbidity and mortality. It is defined as sudden onset of hypertension presenting after the 20th week of gestation ( $\geq 140/90$  mmHg) accompanied by abnormal edema and/or proteinuria (*Sharon et al., 2008*).

Although pre-eclampsia remains a disease of theories, previous studies have indicated that pre-eclampsia is associated with endothelial dysfunction, a hypercoagulable state, metabolic abnormalities, an inflammatory response and atherosclerosis (*Kaure et al., 2010*). The etiology of these conditions remains elusive and multiple factors are implicated in pathogenesis of pre-eclampsia among these mechanisms, insulin resistance. Many studies have been performed to elucidate the precise mechanism of exaggerated insulin resistance in pre-eclampsia, focusing on identifying circulating adipokines such as leptin, adiponectin and resistin in the pathogenesis of pre-eclampsia (*Akdeniz et al., 2011*).

Resistin is a peptide hormone that is specifically secreted by human adipocytes and mononuclear cells. It is a potent regulator of glucose homeostasis that is thought to oppose the action of insulin in peripheral tissues; it impairs glucose intake by adipocytes, increases plasma glucose concentration, and thus decreases insulin (*Hivert et al., 2009*).

Resistin is expressed in the human placenta and its serum level is enhanced in the third trimester of pregnancy; suggesting its pivotal role in the state of insulin resistance during pregnancy. Recent studies suggest resistin may play an important role in the pathogenesis of pre-eclampsia through their role in low-grade systemic inflammation, atherosclerosis, and insulin resistance. Therefore, it is reasonable to suppose that resistin may directly or indirectly influence the function of placental endothelial cells (*Nanda et al., 2012*).

HOMA was first developed in 1985 by Matthews. HOMA describes glucose-insulin homeostasis by means of a set of simple, mathematically derived nonlinear equations. The approximating equation for IR has been simplified and uses a fasting plasma sample in which glucose (fasting blood glucose; FBG) and insulin (fasting insulin; FI) are measured, together with a constant (*Nanda et al., 2012*).

The product of  $FBG \times FI$  is an index of IR.  $HOMA-IR = (\text{glucose} \times \text{insulin}) / 22.5$ . Insulin concentration is reported in  $\mu\text{U/L}$  and glucose in  $\text{mmol/L}$ . The constant of 22.5 is a normalizing factor, i.e.  $\text{normal FI of } 5 \mu\text{U/mL} \times \text{the normal FBG of } 4.5 \text{ mmol/L typical of a 'normal' healthy individual} = 22.5$  (*Nanda et al., 2012*).

In the light of the previous postulation, The aim of the present study was to investigate the clinical utility of maternal serum resistin in women with pre-eclampsia compared to those in normal pregnant women and normal

on-pregnant women, and to investigate the potential role of resistin as a mediator of insulin resistance.

Our study was conducted on sixty (60) pre-eclamptic patients. Their ages ranged from 20 to 39 years with a mean age of  $25.00 \pm 4.50$ . Thirty (30) patients with mild pre-eclampsia, and thirty (30) patients with severe pre-eclampsia women with singleton pregnancy between 24 and 31 week of gestation. They were attending the Obstetrics outpatient clinics suffering from pre-eclampsia during the third trimester of pregnancy. In addition to fifteen (15) healthy pregnant controls of the same gestational age and age of patient group and fifteen (15) healthy non-pregnant females of the same age of patient group.

All the studied individuals were subjected to full history taking and complete clinical examination. Blood samples were collected for determination of ALT, AST, RBS, creatinine, CBC, FBG, fasting insulin and serum resistin, while 24 hours urine samples were collected for determination of total urinary proteins. Assay of serum resistin and serum fasting insulin was carried out using an enzyme linked immunosorbent assay technique.

The results of the present study revealed that pregnant controls had a statistically significant higher serum level of resistin and HOMA-IR when compared to non-pregnant controls. Our results agreed with those of *Yura et al., 2003*, w

horeportedthatresistinexpressionwasgreaterintermplantasthani nchorionicvilliofearlypregnancy,Headedthatbloodresistinlevelw assignificantlyhigherinnormaltermpregnantwomenthanin age- matchedhealthynon- pregnantwomen,however,theexactmechanismsbehindtheincreas ein serumresistinduringpregnancyhavenotbeenclarified.

Basedonthe findings of *Yura et al., 2003*, and the fact that there is an increase in placental mass with gestation, it is reasonable to speculate that resistin production by the placenta is the main cause of the increase in serum resistin.

Thesecondhalfof pregnancy is a state of insulin resistance (*See ly et al., 2003*). Resistin, along with human placental lactogen, prolactin, steroid hormones and other hormones, decreases insulin sensitivity, whereas leptin increases insulin sensitivity. The increase in serum resistin in the third trimester of pregnancy is in accordance with insulin resistance in normal pregnancy (*Sharma et al., 2002*).

This implies that resistin may participate in the regulation of metabolism in pregnancy. During pregnancy, changes in maternal metabolism occur in response to the growing fetus and placenta and their increasing metabolic needs. Pregnancy is associated with alterations in the regulation of glucose metabolism caused by the actions of human placental growth hormone, prolactin, cortisol, and progesterone; these hormones antagonize the action of insulin, particularly during the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters, leading to a state of relative insulin resistance as pregnancy progresses (*Seely et al., 2003*). The mother's body adapts to

hewnewmetabolicenvironmentsothatthetransferofglucosetothefetusisadequate.

OurstudyalsorevealedahighlystatisticallysignificantincreaseinserumlevelsofresistinandHOMA-IRinpre-eclampticwomenwhencomparedtotheirmatchedcontrols.Thiscomesinaccordancewith**Haugenetal.,2006**,and**Seol et al.,2010**,whodemonstratedthatSerumresistinlevelsweresignificantlyelevatedinwomenwithpre-eclampsiacomparedtonormalpregnantwomen.Althoughtheexactfunctionofresistininthepathophysiologyofpre-eclampsia remains unclear, the elevated serum resistin levels might be associated with exaggerated insulin resistance via the extensive systemic inflammatory response in pre-eclampsia (**Sonagraetal.,2012**). Extensive systemic inflammation is a well known characteristic of pre-eclampsia, and monocyte activation is one of the associated features of systemic inflammation (**Demircietal.,2011**). Monocytes may be a source of the increased serum resistin concentrations in pre-eclampsia. Unfortunately, we did not investigate mononuclear cell activation or other proinflammatory adipokines, such as TNF- $\alpha$  and IL-6, in this study. Future investigation is needed to determine whether the different genetic expression of monocytes is related to circulating resistin concentrations in women with pre-eclampsia.

Resistin impairs glucose intake by adipocytes, and increases plasma glucose concentrations, thus decreasing insulin sensitivity (**Sonagraetal.,2012**).

On the contrary, *Chen et al., 2003*, observed that in women with PE, resistin levels were significantly lower than in controls, owing to a reduction in the placental production of this peptide. This view is supported by the detection of resistin mRNA expression in the human placenta, together with the absence of significant changes in resistin expression in adipose tissue during gestation.

Our study also showed a statistically significant increase of resistin and HOMA-IR levels in severe pre-eclampsia in comparison to mild pre-eclampsia. On the contrary *AL-Refai, 2012*, who found no statistically significant increase of resistin and HOMA-IR levels in severe pre-eclampsia in comparison to mild pre-eclampsia.

Our correlation study revealed a significant positive correlation between both resistin and HOMA-IR and SBP as well as DBP. The results are consistent with the findings of *Haugen et al., 2006*, and *Seo et al., 2010*, who also reported a significant positive correlation between mean systolic blood pressure and mean diastolic blood pressure, the indices of pre-eclampsia, and the both resistin and HOMA-IR levels in pre-eclamptic groups.

Our correlation study also showed a non-significant correlation between both resistin and HOMA-IR and BMI. This comes in accordance with *Silha et al., 2003* and *Heilbronn et al., 2004*, who reported no relationship between resistin serum level

sand percentage body fat, visceral adiposity and BMI. On the contrary *Azuma et al., 2003*, who reported a higher serum resistin levels in obese subjects compared with lean subjects, which positively correlated with the changes in BMI and visceral fat area.

The best diagnostic cutoff level of resistin for discriminating pre-eclampsic patients versus healthy pregnant controls was 10 ng/mL. This had a diagnostic sensitivity of 88.33%, specificity 96.67% positive predictive value 98.1% and negative predictive value 80.6%. This sensitivity and specificity is supported by the results of *AL-Refai, 2012*, who published sensitivity and specificity of 90% and 98% respectively for resistin at cutoff level 12 ng/mL.

Assessment of the diagnostic performance of HOMA-IR in pre-eclampsic patients versus healthy pregnant controls revealed that the best diagnostic cutoff level was 2.05. This had a diagnostic sensitivity 98.3%, specificity 86.67% positive predictive value 93.7% and negative predictive value 96.3%. This sensitivity and specificity is supported by the results of *Haugen et al., 2006*, who published sensitivity and specificity of 90% and 80% respectively for resistin at cutoff level 3.2.

Furthermore assessment of the diagnostic performance of resistin and HOMA-IR for discriminating severe pre-eclampsic patients from those with mild pre-eclampsia found that the best cutoff value of resistin was 17 ng/mL. This had a diagnostic sensitivity of 96.70% and specificity 70% positive pred

ictive value 76.30% and negative predictive value 95.50%. This sensitivity and specificity is supported by the results of *AL-Refai, 2012*, who published sensitivity and specificity of 98% and 85% respectively for resistin at cutoff level 19 ng/mL.

The best diagnostic cutoff level of HOMA-IR for discriminating severe pre-eclamptic patients from those with mild pre-eclampsia was 3.7. This had a diagnostic sensitivity of 93% and specificity 40%, positive predictive value 60.90% and negative predictive value 85.70%. This sensitivity and specificity is supported by the result of *Seo et al., 2010*, who published sensitivity and specificity of 82% and 55% respectively for resistin at cutoff level 3.5.

The results of this study demonstrated increased serum resistin concentrations in women with preeclampsia compared to the levels found in women with normal pregnancies. This finding suggests that elevated serum resistin levels may represent the exaggerated insulin resistance in preeclampsia.

## SUMMARY AND CONCLUSION

Pre-eclampsia is a potentially serious condition that still accounts for significant morbidity and mortality for the mother and the neonate, complicating 5-7% of all pregnancies and exposing them to a 3- to 25-fold increased risk of severe obstetric complications. Although, the pathogenesis is not fully understood, it is now widely accepted that vascular endothelial dysfunction is the most astonishing and the principal event in the pathophysiology of the disease.

Researchers investigated the fact that pre-eclampsia is associated with endothelial dysfunction, a hypercoagulable state, metabolic abnormalities, an inflammatory response and atherosclerosis. The etiology of these conditions remains elusive and multiple factors are implicated in pathogenesis of pre-eclampsia among these mechanisms, insulin resistance.

Resistin is an adipose-specific secreted hormone, which belongs to the family of cysteine-rich, C-terminal proteins. It is a potent regulator of glucose homeostasis that is thought to oppose the action of insulin in peripheral tissues; it impairs glucose intake by adipocytes, increases plasma glucose concentration, and thus decreases insulin. Resistin is expressed in the human placenta and its serum level is enhanced in the third trimester of pregnancy; suggesting its pivotal role in the state of insulin resistance during pregnancy.

ancy. Recent studies suggest resistin may play an important role in the pathogenesis of pre-eclampsia through their role in low-grade systemic inflammation, atherosclerosis, and insulin resistance. Therefore, it is reasonable to suppose that resistin may directly or indirectly influence the function of placental endothelial cells.

In this regard, this study aimed to investigate the clinical utility of maternal serum resistin in women with pre-eclampsia compared to those in normal pregnant women and normal non-pregnant women, and to investigate the potential role of resistin as a mediator of insulin resistance.

This study was conducted on sixty (60) pre-eclamptic patients. Thirty (30) patients with mild pre-eclampsia and thirty (30) patients with severe pre-eclampsia. In addition to fifteen (15) healthy pregnant controls and fifteen (15) healthy non-pregnant females.

All the studied individuals were subjected to full history taking and complete clinical examination. Blood samples were collected for determination of ALT, AST, RBS, creatinine, CBC, FBG, fasting insulin and serum resistin, while 24-hour urine samples were collected for determination of total urinary proteins. Assay of serum resistin and serum fasting insulin was carried out using an enzyme-linked immunosorbent assay technique.

The results of the present study revealed that pregnant controls had significantly higher serum levels of resistin and HOMA-

IR when compared to nonpregnant controls. Our study also revealed a highly significant increase in serum levels of both resistin and HOMA-IR in pre-eclamptic women when compared to their matched controls.

As regards the relation of resistin and HOMA-IR to the severity of pre-eclampsia, our study showed a statistically significant increase of resistin and HOMA-IR levels in severe pre-eclampsia in comparison to mild pre-eclampsia. Moreover, significant positive correlation was also found between both resistin and HOMA-IR and both SBP and DBP, which are considered among the indices of severity of pre-eclampsia.

Receiver operating characteristic (ROC) curve analysis was applied to assess the diagnostic utility of resistin and HOMA-IR for discriminating severe pre-eclamptic patients from those with mild pre-eclampsia. It was found that the best cutoff value of resistin was 17 ng/mL. This had a diagnostic sensitivity of 96.7%, specificity 70%, positive predictive value 76.30% and negative predictive value 95.50%. The best diagnostic cutoff level for HOMA-IR was 3.7 which had a diagnostic sensitivity of 93%, specificity 40%, positive predictive value 60.90% and negative predictive value 85.70%..

In addition, the diagnostic performance of resistin and HOMA-IR in pre-eclamptic patients versus healthy pregnant subjects to assess their utility as early indicators of pre-eclampsia. The best diagnostic cutoff level for resistin was 10 ng/mL. This had a diagnostic sensitivity of 88.33%, specificity 96.67%, positive predictive value 98.1% and negative predictive value 80.6%. The best diagnostic cutoff level for HOMA-IR was 2.05. This had a diagnostic sensitivity of 98.33%, specificity 86.67% positive predictive value 93.7% and negative predictive value 96.3%.

## CONCLUSION

- ➔ Serum resistin can be considered a promising marker in diagnosis of PE with an excellent diagnostic efficiency.
- ➔ Resistin can also be used in discriminating patients with mild PE from patients with severe PE, therefore it is closely related to the progress of the disease.
- ➔ Elevated serum resistin levels may represent the exaggerated insulin resistance in preeclampsia.