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DETERMINATION OF GLUCOSE, INSULIN AND HOMA-IR IN PATIENTS WITH PREECLAMPSIA IN EGYPTIAN WOMEN

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ABSTRACT

Background: Preeclampsia is characterized pregnancy-induced hypertension and proteinuria complicates 3 – 4% of pregnancies and thus is a leading cause of maternal and fetal morbidity and mortality. **Objective:** To determine the frequency of the glucose, insulin and HOMA-IR level in mild preeclampsia (MPE) and severe preeclampsia (SPE) at second trimester and to verify if the severity of preeclampsia would be associated with HOMA-IR level and to examine whether insulin resistance identifies subtypes of preeclampsia**. Method:** Case-control study included 60 women with Preeclampsia and 30 no preeclampsia normotensive women as control. Three groups were chosen; mild preeclampsia group consisted of 30 women, severe preeclampsia group 30and control group 30 women. All groups were matched strictly for gestational age at second trimester. Maternal blood samples for glucose and insulin collected from the patients at second trimester and compared. **Results:** Diagnosis criteria for the participants included blood pressure above 140/90 and proteinuria above 300mg. Mean ages of participants, gestational week and weight were similar. Homa-Irand rate of insulin resistance was calculated by HOMA-IR and patients were followed up. Homeostatic model assessments [HOMA-IR] revealed that the average insulin resistance increased during pregnancy among both the case and control groups. There was a significant difference between insulin resistances of these two groups after developing preeclampsia [P < 0.001]. **Conclusion:**

Insulin-resistance of the groups with preeclampsia was higher compared to natural pregnancy under similar conditions. Measurement of insulin resistance may be useful in predicting the risk of preeclampsia. **Recommendation:** It is tempting to consider that improving insulin sensitivity in high-risk women before and during early pregnancy may reduce the risk of preeclampsia taking into consideration other metabolic syndromes; however, the power calculation of the sample was low, suggesting that a larger sample needed.

KEYWORDS: Preeclampsia, glucose, insulin, HOMA-IR.

INTRODUCTION

Preeclampsia, which is characterized by pregnancy-induced hypertension and proteinuria, complicates3–4% of pregnancies and thus is a leading cause of maternal and fetal morbidity and mortality.[1] There are no early gestation screening tests available to predict the occurrence f preeclampsia, and the only effective therapy for established preeclampsia is delivery. Prophylactic strategies, including calcium supplementation and aspirin therapy, have been mostly unsuccessful.[2,3] Novel therapeutic targets, identified preferably during early gestation when there is time for therapeutic modification, are needed for future clinical trials aimed at preventing preeclampsia. Mild preeclampsia is associated with the lowest maternal and neonatal mortality and morbidity rate, while severe preeclampsia before 35 weeks into pregnancy is associated with significant maternal and prenatal complications. Severe preeclampsia occurs when blood pressure reaches over 160/110 and proteinuria is above 5 g in 24-hour urine collection.[4]

Insulin is a hormone that facilitates the transport of glucose from the bloodstream into cells. In response to increased blood sugar after a meal, pancreas secretes insulin into the bloodstream. When insulin resistance occurs, the normal amount of secreted insulin is not sufficient in order to deliver glucose into the cells. Pancreas subsequently increases its production of insulin to deliver blood sugar into the cells. Obesity and pregnancy are among the factors which can create insulin resistance. For these conditions there are theories that can explain etiology. Obesity is a cause of insulin resistance in modern societies. Obesity is often accompanied by an increase in fat cell size. This causes changes in adipocytes, including a reduction in adiponectin and an increase in tumor necrosis factor alpha and free fatty acids which increase insulin resistance.[5] Many metabolic changes during pregnancy increase adipose tissue and subsequently insulin resistance. Various placental hormones, in addition, alter maternal physiology to supply embryonic requirements. There is also a 30-fold increase

inhuman placental lactogen [hPL] which leads to the secretion of insulin from pancreas.[6] Studies show that hPL plays a role in insulin resistance.[7] 6-fold increase in human chorionic growth hormone is another factor causing insulin resistance.[8]

Blood glucose and insulin levels were measured 2hours after a 75 g oral glucose use in pregnant women; results showed that people with high blood insulin levels have higher risk for preeclampsia.[9] However, other studies found no relationship between elevated insulin and risk of preeclampsia.[9,10] Considering the serious complications of preeclampsia on the mother and fetus and value of predicting insulin resistance in preeclampsia, the present study suggests a process for the prediction of preeclampsia before the onset of the condition and its prevention.

METHODOLOGY

Study participants

Sixty patients with Preeclampsia were collected from the gynecological and Obstetric Department, Mansoura University, Egypt (mean age: 30.7.±4.3 years) between August 2015 and September 2016. Three strictly, gestational age matched groups were constructed. The first group consisted of 30women who were diagnosed as mild preeclampsia (MPE) during routine prenatal visits at second trimester. The second group consisted of 30 women who were diagnosed as severe preeclampsia(SPE)and the third group consisted of30 healthy control pregnant whose blood samples were taken during prenatal visits at second trimester of the gestational week that matches the other two groups and these women were followed up to delivery. Ages of women, gravidity, pregnancy outcomes, blood pressure values, maternal weights and height were recorded. Body-mass indexes were calculated. Participants were excluded if they had a pregnancy termination, a major anomaly, a twin pregnancy, or if the pregnancy outcome was unknown (i.e. if they did not deliver at our hospital). Thirty other pregnant women were put in the control group. Controls were women who entered University Hospital, Mansoura University, Mansoura, Egypt Obstetric Maternal Study cohort within2 wk of each case and who remained normotensive and non proteinuric throughout pregnancy. Women with a history of diabetes; thyroid, liver, or chronic renal disease; or preexisting chronic hypertension (defined as blood pressure >140/90 or need for antihypertensive medications before pregnancy or before 20 wk gestation) were excluded.

Ethical approval

All study participants have provided a written informed consent, and the study protocols have been approved by the Coordinating Ethics Committee of the Internal Medicine University Hospital, Mansoura University, Mansoura, Egypt Obstetric Maternal Study cohort. All experiments were performed in accordance with the approved guidelines.

The 30 women were assigned to the control group who were matched according to Weight, BMI, maternal age, and gestational age after assessing their files in the center and choosing most similar women to form healthy group to preeclamptic groups(Table 1). 12-hour fasting blood samples were taken from cases and control groups to determine blood insulin and glucose.

METHODS

Insulin levels were measured by radioimmunoassay from samples taken from mothers in the second trimester of pregnancy. Glucose was measured by glucose oxidase colorimetric assay (Pointe Scientific, Inc.). Intranasal CV averaged 0.6 and inter-assay CV averaged 1.9. Insulin was measured by ELISA (Linco, St. Charles, Missouri) with intra-assay CV 6.0, inter-assay CV 10.3, and sensitivity was 2 μU/ml.

Calculation of Insulin Resistance

Insulin resistance was measured by hemostasis model assessment [HOMA-IR] formula.[11]

Consider

$$\text{HOMA-IR} = \frac{\text{fasting insulin } [\mu\text{U/mL}] \times \text{fasting glucose [mg/dL]} \times 0.0551}{22.5}$$

Statistical analysis

Data analysis was done by Statistical package for social science (SPSS) version 16. The data were collected and entered to the computer. Statistical analysis was done using Statistical Package of Social Science (SPSS) Version 16 (Chicago, USA), IL 60606-6307. The quantitative data was presented in the form of mean and standard deviation. One way ANNOVA f test was used for quantitative data of the three groups followed by Bonferroni test to compare between each two groups. Pearson correlation coeffient was used to study relation between groups. Significance was considered at p value less than 0.05.

RESULTS

The maternal characteristics of each of the outcome groups are compared in (**Table 1).** The patients with preeclampsia were not significantly different from the control group in terms of average age and gestational age [Table 1 and 2].

Table 1: Case and control matching.

Parameters	Control (n = 30)	Mild Preeclampsia (n = 30)	Severe Preeclampsia (n = 30)
Age (year)	29.53± 4.36	30.03± 5.5	31.83± 3.69
Weight(Kg)	81.1± 12.73	81.4 ± 12.11	86.53 ± 12.98
Gestational age(Week)	20.72± 4.66	21.2± 3.57	19.83± 3.93
Body mass index (kg/m2)	25.95 ± 3.56	27.30 ± 4.03	28.57 ± 2.92
Diastolic blood pressure (mmHg)	76.26 ± 3.37	94.33 ± 3.27	105.6 ± 3.23
Systolic blood pressure (mmHg)	114.30± 6.2	149.13± 5.5	167.2± 6.3

Table 2: Characteristics of subjects.

Parameters	Control (n = 30)	Mild Preeclampsia (n = 30)	Severe Preeclampsia (n = 30)	*P* value
Age (year)	29.53	30.03	31.83	NS
Weight (Kg)	81.1	81.4	86.53	NS
Gestational age (wk)	20.72	21.2	19.83	NS
Body mass index (kg/m2)	25.95	27.30	28.57	0.021
Diastolic blood pressure (mmHg)	76.26	94.33	94.9	< 0.001
Systolic blood pressure (mmHg)	114.30	149.13	149.25	< 0.001

NS, Not statistically significant.

Levels of fasting insulin and glucose were substituted into the formula and resistance to insulin was studied among the case and control groups after the development of preeclampsia. Significant difference was found among fasting glucose among the two groups of preeclampsia and control group [$P < 0.001$] [Table 3] [Figure 1].

When we studied each group versus control group, we found Significant difference between group of mild preeclampsia and control group [$P = 0.017$] and for group with severe preeclampsia [$P < 0.001$]. The average fasting insulin increased for both case and control groups. Mean score for the level of fasting insulin among people with preeclampsia was higher than that of control group [$P < 0.001$] [Table 3][Figure 2].

Table 3: Glucose, Insulin and The average HOMA-IR.

Parameters	Control (n = 30)	Mild Preeclampsia (n = 30)	Severe Preeclampsia (n = 30)	*P* value
Glucose (mg/dl)	94±10.74	106±19.22	146±19.49	<0.001
Insulin(µIU/mL)	3.96±1.32	5.39±1.99	9.40±5.19	<0.001
HOMA-IR	0.87±0.31	1.30±0.41	3.43±1.87	<0.001

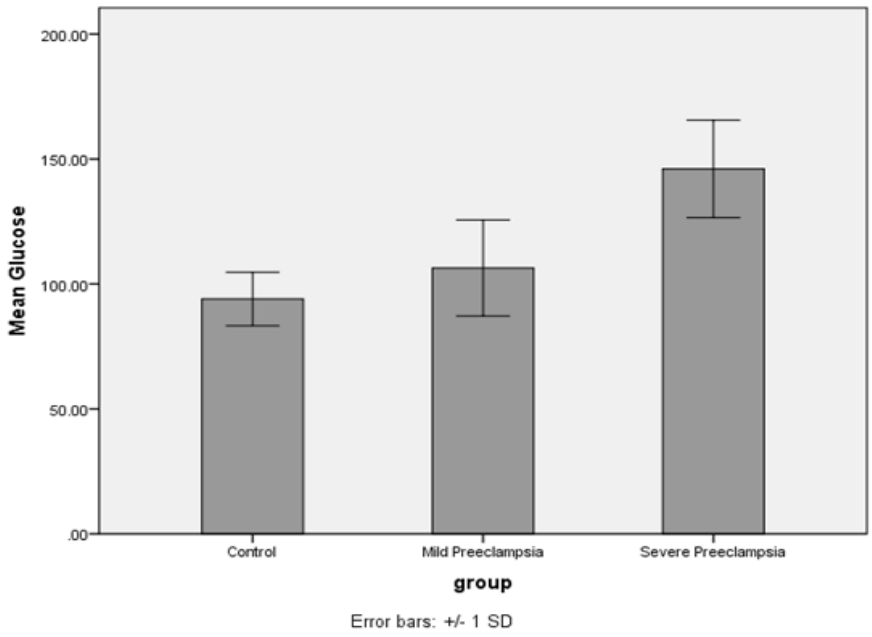

Figure 1: Bar chart illustrates mean (±2SD) of fasting glucose among studied groups.

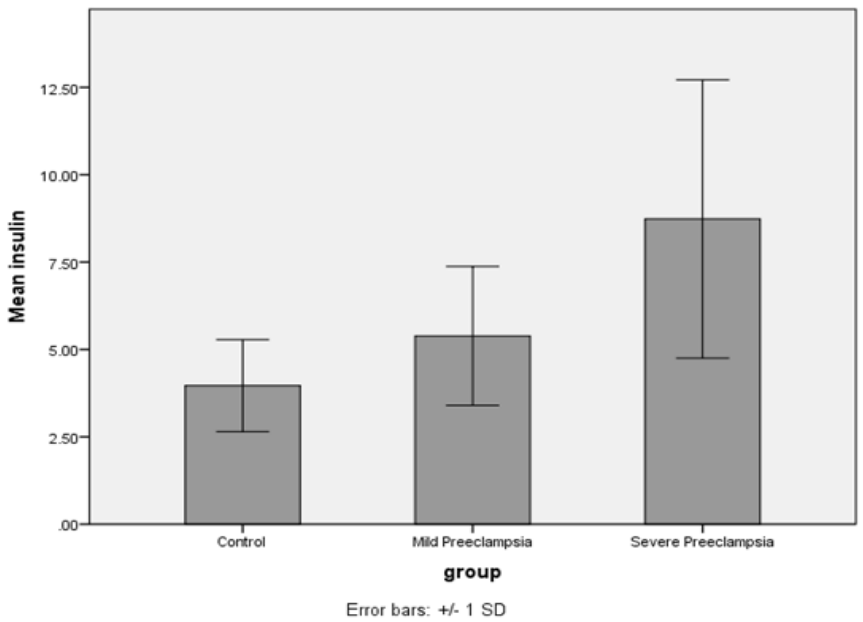

Figure 2: Bar chart illustrates mean (± SD) of fasting insulin among studied group.

According to results of f-test, changes in insulin level were significant for both groups during pregnancy [*P*< 0.001] but there was no significant difference between group of mild preeclampsia and control group [*P*=0.410] [Table 4]; therefore, insulin rate increased in both groups. HOMA-IR was calculated for both groups at the second trimester; in both cases, there was a significant difference between insulin resistances [Table 3] [Figure 3]. No significant difference between group of mild preeclampsia and control group [*P* = 0.294] [Table 4].

Table 4: Post hoc test between each two group.

	Glucose (mg/dl)	Insulin (µIU/mL)	HOMA-IR
(*P* value)Group I versus II	0.017	0.294	0.410
Group I versua III	<0.001	<0.001	<0.001
Group II versus III	<0.001	<0.001	<0.001

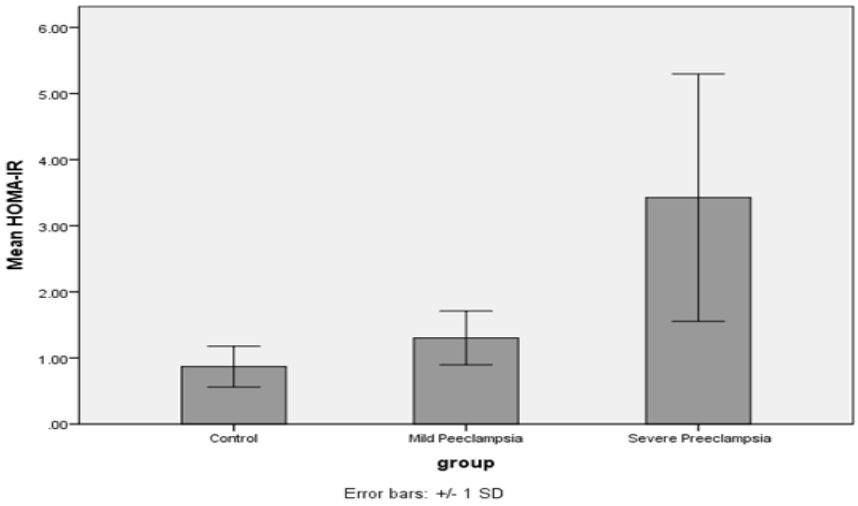

Figure 3: Bar chart illustrates mean (± SD) of HOMA-IR among studied groups.

DISCUSSION

Insulin resistance is described as inability of cells to respond to natural function of insulin hormone. Rate of insulin resistance naturally increases during pregnancy. It is believed placenta-derived hormones are the most important factors with the ability to change insulin resistance.[12] The metabolic syndrome that occurs during preeclampsia is typically associated with insulin resistance and endothelial dysfunction.[13,14] Insulin resistance is defined as impairment of the action of insulin on glucose and lipid metabolism, while endothelial dysfunction is defined as inadequate endothelial-mediated vasodilation. Recently, it was reported that insulin resistance is higher as inflammation increases in preeclampsia.[15] Furthermore, insulin resistance and endothelial dysfunction represent early events in individuals at high risk of developing cardiovascular disease later in life.[16]

The present study used indirect HOMA-IR which measures glucose and insulin after 12-hour fasting. Glucose homeostasis depends on its production by liver and insulin secretion from pancreatic beta cells. HOMA-IR shows this dependency in terms of an equation.[11] Our study suggested that insulin resistance during the second trimester among the members of the groups which consequently developed preeclampsia was significantly different from the control group. This finding is consistent with other findings in which mid trimester maternal insulin resistance is associated with subsequent preeclampsia.[17,18] Other studies did not find such relationship.[19] Several studies have reported an association between preeclampsia and insulin resistance as characterized by higher glucose and/or insulin levels when compared with normotensive women, but an association between direct measurements of insulin resistance and preeclampsia has not been demonstrated.[20,22]

Although insulin resistance is associated with preeclampsia, the majority of evidence comes from cross-sectional and retrospective studies. For example, in studies those examined surrogate markers of insulin resistance; women with established preeclampsia displayed elevated levels of glucose[23], uric acid[24], triglycerides[25], leptin[26], and plasminogenactivatinginhibitor-1[27] and reduced high density lipoprotein levels[25] In other cross-sectional studies, women with established preeclampsia had higher fasting and post glucose loading insulin levels and lower insulin sensitivity than controls.[28] Two prospective studies support an association between insulin resistance and subsequent preeclampsia.[29,30] Sowers *et al.*[31] showed that among African-American women, fasting insulin levels were significantly increased at20 wk gestation in those who ultimately developed preeclampsia. The role of insulin resistance contributing to the etiology of preeclampsia has yet to be determined. Metabolic studies in women with GDM, a subgroup that has been associated with an increased preeclampsia risk, did not find any correlation between multiple measures of insulin resistance and β-cell function with the subsequent development of preeclampsia during pregnancy.[32] Metabolic origins are implicated by differences in preeclampsia compared to normal pregnancy. Maternal hyperinsulinemia and insulin resistance which support the growing conceptus in normal pregnancy are accentuated in preeclampsia. Preeclamptic pregnancies demonstrated 37% lower insulin sensitivity and 70% higher free fatty acid concentration at 29 to 39 weeks gestation than was present in control women.

Moreover, women entering pregnancy with metabolic syndrome are more likely to develop preeclampsia. Obesity triples the risk of preeclampsia, yet 90% of obese pregnant women do

not develop the disease. Insulin resistance also occurs in non-obese metabolic syndrome. Although inflammation and insulin resistance commonly are associated, lack of correlation between these processes has been found in studies of hypertensive disorders of pregnancy.[15,33]

In the present study, there was a statistically significant difference between the groups of women with preeclampsia compared to the control group; Levels of fasting insulin and glucose were substituted into the formula and resistance to insulin [$P< 0.001$]. When we studied the patients with MPE or SMP separately, statistical difference was found between severe preeclampsia group and control group and between SPE group and MPE group [$P< 0.001$]. No statistical difference between mild preeclampsia group and control group in case of Levels of fasting glucose, insulin and resistance to insulin [$P = 0.017$, $P = 0.294$ and $P = 0.410$] respectively. Control group was carefully selected among pregnant women who remained normotensive and non-protein uric throughout pregnancy. The results may refer to there is a relation between insulin resistance and the mechanism and severity of the disease. It is important to keep in mind that the study was performed in a special group of patients. These findings dictate further mechanistic studies of insulin resistance and the metabolic syndrome in the pathophysiology of preeclampsia and indicate confirmatory tests for the predictive value of insulin resistance in other populations.

CONCLUSION AND RECOMMENDATION

In conclusion, it is possible that the excess insulin resistance we detected, in the form of HOMA-IR, in cases may have been present at baseline, predating pregnancy. This point has important therapeutic implications. It is tempting to consider that improving insulin sensitivity in high risk women before and during early pregnancy may reduce the risk of preeclampsia taking into consideration other metabolic syndromes; however, the power calculation of the sample was low, suggesting that a larger sample is needed.

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