Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Increased Insulin Levels Independent of Gestational Overweight in Women with Preeclampsia

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OBJECTIVE: To evaluate whether increased insulin levels are independent of gestational overweight in women with preeclampsia.

STUDY DESIGN: The patients studied were selected at the Zeynep Kamil Woman and Children's Hospital during their 29th and 40th week of pregnancy. The patients were evaluated in the four groups according to the diagnosis of preeclampsia (PE) and body mass index (BMI), group 1 overweight patients with mild preeclampsia (n=20), group 2 overweight patients without preeclampsia (n=20), group 3 non-overweight patients with mild preeclampsia (n=20), and group 4 non-overweight patients without preeclampsia (n=20). The serum fasting glucose and immunorective insulin levels were determined, and Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated.

RESULTS: The results show that there is no relation between high and normal BMI values and insulin resistance in patients with preeclampsia. Although, it was found that the HOMA-IR values of the patients with PE were higher than without PE.

CONCLUSIONS: The results indicate that there was no relation between the increased insulin resistance and the weight gain. Increased insulin resistance should be developed as a result of the pathophysiology of the preeclampsia itself.

Key Words: Preeclampsia, Insulin resistance, Weight gain

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Introduction

Preeclampsia is defined as the rise of the blood pressure after twentieth week of pregnancy which accompanied by proteinuria, edema, neurologic, hematologic, hepatologic and renal pathologies. It is specific to pregnancy and life threatening clinical condition.

The conflicting results of various researches on preeclampsia caused to this illness to be called as the illness of theories. The studies until now indicate that hypertension, diabetes, increased insulin resistance, higher testosterone levels, black race, elevated homocystein levels are predisposing factors for the preeclampsia.[1] Understanding the causes of the disease is accepted as an important step for treatment.

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Insulin resistance is known as the corrupted biologic response for exogen or endogen insulin. Insulin resistance deteriorates the endothel functions, carbohydrate and lipid metabolisms, liquid-electrolyte balance, myocardial contractility, vessel resistance, and causes to increased oxidative stress and visceral obesity. It is observed that preeclamptic patients have increased insulin resistance.[2-4]

It is controversial that insulin resistance is the result of weight gaining or preeclampsia itself. The purpose of this study was to examine the relation between weight gaining and insulin resistance in preeclamptic and non-preeclamptic pregnants.

Material and Method

The survey resulting the study was conducted at Zeynep Kamil Woman and Child Hospital between July 2007 and April 2008 on pregnants of their pregnancies between 29-40 weeks. Before the study, non-medical research permission has been granted from the ethic council of the hospital. All surveyed pregnants have been briefed and requested to sign an approval form.

Eighty pregnants between the ages of 18 to 38 were included to the study. Pregnants were selected between 29-40 weeks referred to their last period dates and obstetric ultra-

sound measurements. The gestational age, parity, maternal age, body weight and height measurements, weights before pregnancy and preeclampsia criterias have been recorded.

The study groups consist of the patients with normoglycemia at fasting, having diabetes, chronic hypertension or renal disease are excluding criterias. Pregnants gestational diabetes or gestational hypertension were also excluded. All patients did not use any medication.

Because of antihypertensive treatment may affect the insulin levels and the risk of premature birth in heavy preeclamptic patients, we included the mild preeclamptic patients to the study.

Pregnants over 20 weeks with a blood pressure between ≥140/90 mmHg and <160/100 mmHg, and with proteinuria were defined as light preeclamptic patients. ≥0.3 gr. in 24 hours or ≥300mg proteinuria in spot urea test without urinal infection has been determined as criterion of mild preeclampsia. Patients with blood pressure over ≥160/100 mmHg, ≥2 gr. proteinuria in 24 hours, or +2 in dipstick test, <500ml/24 hours urinal volume, increased serum creatin levels (>1,2mg/dl), thrombocytopenia (<100,000), persistent headache, cerebral or visual dysfunction, pulmonary edema, cyanosis, epigastric or upper quadrant ache, elevated liver enzymes, intrauterine growth retardation are accepted as heavy preeclamptic patients and kept out of the study.

Before pregnancy body mass index (BMI) values are ranging between 20-25 have been accepted as normal weight The BMI values were more than 25 kg/m^2 have been accepted as overweight pregnants. The weight gaining as 1-1,5 kg per month during pregnancy has been accepted as normal. However, monthly weight gaining more than 1,5 kg has been accepted as high.

Blood pressure has been checked every for hours twice or more while the patients were sitting. Urinary protein measurement has been made with 24 hours urine or spot urine. Gestational age has been determined according to the last period dates and checked with ultrasound. Blood glucose and immunoreactive insulin levels have been measured at the same time. Dimension RXL Dade Behring device and hexokinase method have been used for blood sugar levels, and to determine blood insulin levels E170 (ROCHE) and chemiluminescent method have been used.

The HOMA formula which is developed to show the effects of glucose and insulin levels over pancreatic β cell function and insulin sensitivity is used to calculate the insulin resistances of patients. The HOMA formula is [HOMA-IR = insulin (mU/ml) X glucose (mgr/dl) /405].

Patients have been classified into four groups for the statistical studies using their BMI normal/high, preeclampsia mild/none situations. Each group includes 20 patients. Age, BMI before pregnancy, height, total gained weight during pregnancy of each patient have been statistically analyzed over insulin HOMA factors and the cross relation between the groups have been analyzed.

The groups are categorized as shown in the following scheme, and kept as the same during the flow of the study.

Group 1: BMI high and mild preeclampsia (PE) exist
Group 2: BMI high and no PE
Group 3: BMI normal and mild PE
Group 4: BMI normal and no PE

The data analysis software's Mat lab and SPSS were used to statistical analyzes and visualize the results. Data were presented as mean±SD, Pearson's correlation and student's t tests were used where appropriate, and a $p \leq 0.05$ was considered as statistically significant.

Results

The demographic data of the patients are shown in table 1.

The HOMA-IR values were found as 55±94.8, 37.5±42.8, 63±107.7, 27.9±37.7 for groups 1 to 4 respectively. It found that preeclamptic patients have higher HOMA-IR levels as compared to pregnants have no preeclampsia (75.50±115, n=40, and 27.09±36.22, n=40, respectively, p=0.042).

When the BMI, PE and HOMA parameters of the patients were analyzed, remarkable results have been noticed. As mentioned before, there was a relation between preeclampsia and insulin resistance. On the other hand, there was no significant correlation between the preeclampsia and the BMI. The BMI value of the pregnants without PE was 23.74±5.0 kg/m^2,

Table 1: The demographic parameters of the patients (ns: no significant)

Group	Age (Year)	BMI (kg/m^2)	Gestational age (weeks)	Homa-ir	Weight gain during pregnancy (kg)
1	27.95±5.41	28.79±4.51	35.65±3.28	55.4±94.8	16.55±10.62
2	26.90±5.48	28.05±3.24	32.4±7.87	37.5±42.8	13.50±8.30
3	26.55±7.08	20.17±1.80	34.65±3.99	63±107.7	13.15±9.34
4	24.4±3.65	19.43±1.36	34.20±3.59	27.9±37.7	7.55±4.26
	ns	p<0.05	ns	p<0.05	P<0.05

(ns: no significant)

whereas the BMI value of the pregnants with PE was 24.48±5.5, (p>0.05).

There was no significant correlation between the Homa-ir value and weight gain in our cases.

A positive correlation was found between the patient's ages and Homa-ir values. (r=0.238, p=0.036). This correlation is shown in Figure 1.

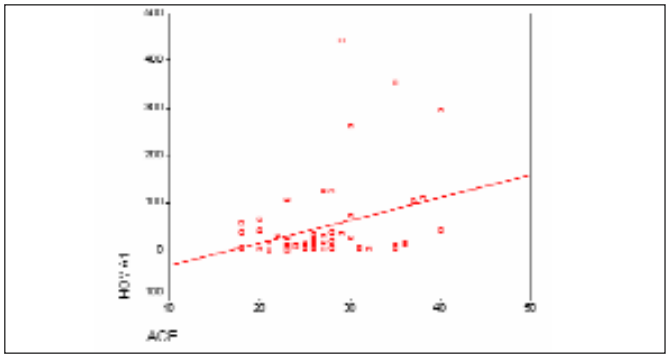

Figure 1: The correlation between the age and homa-ir

The pregnants with PE were gained more weight as compared with who have not PE (14.85±10.02 kg, n=40, and 10.53±7.18 kg, n= 40, p=0.03 respectively).

No significant difference was found for weight gain between the group 1 and 3 (16.55±10.62 kg and 13.15±9.34 kg, p>0.05 respectively).

The group with high BMI (group 2) gained more weight than the group with normal BMI (group 4) in pregnants without PE, (13.50±8.30 kg and 7.55±4.26 kg, p=0.05 respectively).

Also, the group 2 had slightly higher Homa-ir value than group 4, however, this difference could not achieve to statistical significance in pregnants without PE (37.5±42.8 and 27.9±37.7, p>0.05 respectively).

A positive correlation was observed between the age and weight gain. (r=0.375, p=0.04) as shown in Figure 2

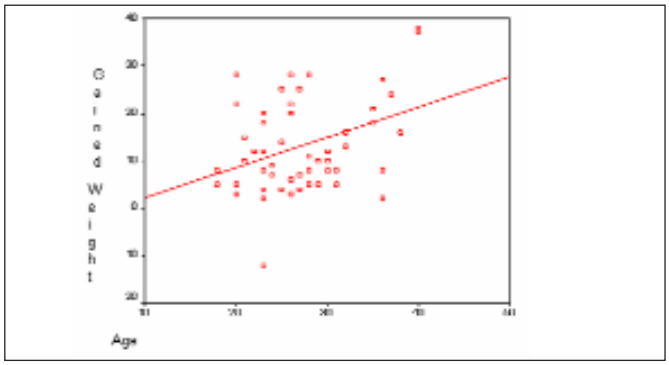

Figure 2: The correlation between the weight gain at pregnancy and age

A positive correlation was found between the Homa-ir and the gestation week. (r=0.290, p= 0.01) as shown in Figure 3

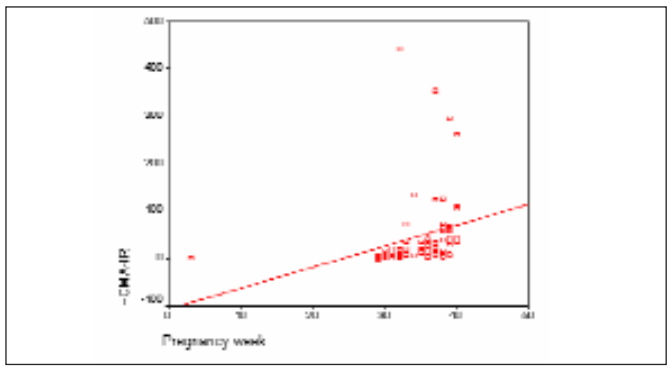

Figure 3: The correlation between the gestational age week and Homa-ir

Discussion

We observed that HOMA-IR values in patients with preeclampsia were greater than patients without preeclampsia. But, there was no significant correlation between BMI and insulin resistance in preeclamptic patients. In addition, BMI levels were similar in comparison of PE and non PE groups. These findings suggest that preeclampsia has no connection with BMI in pregnancy or have a weak relation.

In our research we observed that preeclamptic patients gained more weight than non preeclamptic patients. Furthermore, weight gaining rate in PE patients was similar regardless of their BMI status before pregnancy. On the other hand, non PE patients with overweight before pregnancy have gained more weight than who have normal BMI. The overweight group without PE has slightly higher homa-ir values than those within BMI normal, but not significant. This result may be explained by the limited number of the cases. It is well known that obesity increases the insulin resistance. Although our findings showed that the insulin resistance is an indepented risk factor for weight gaining rate in non PE patients, however, there is no correlation between insulin resistance and weight gaining rate in PE patients.

Similar results were found in previous researches. For example, Sowers et al. studied 140 African-American nullipar pregnant between 18-25 weeks. They have investigated the role of hyperinsulinemia in development of preeclampsia in a prospective study, with observation of the pregnants until delivery. Insulin levels were statistically analyzed with respect to gestational age and pre pregnancy BMI. In this research, similar to our findings, it was showed that blood pressure might be independent from BMI, and high second trimester insulin level have a role in preeclampsia pathogenesis.[5]

Although physiopathology process of preeclampsia is not fully explained, basic vasospasm is considered as the common

pathology.[6] In the mentioned vasospasm depending on the decrease in NO synthesis, increase in VCAM-1, e-selectin, ICAM-1 and increase in the effects of TNF-alpha, NF-kB are related to insulin resistance.[7] We found a remarkable correlation between insulin resistance and preeclampsia. Also, we found a positive correlation between pregnancy week and insulin resistance. Preeclampsia is seen after the mid second trimester. Increasing insulin resistance after the beginning of the second trimester should be seen as the most probable cause of the preeclampsia. Our study showed that there is a positive correlation between insulin resistance and pregnancy week.

In addition to HPL, progesterone, cortisol and prolactin, placental growth hormone decreases the insulin sensitivity. These diabetogenic hormones and placental steroids show linear increment in 2nd and 3rd trimester and they cause to the tissue resistance against the maternal insulin activity. There is no decrease in number of the insulin receptors during pregnancy, although 44% decrease in insulin sensitivity is determined. Physiopathologic cause is considered to be in post receptor level.[8]

The role of hyperinsulinemia in preeclamptic patients can be explained by the effects of insulin in cardiovascular and renal system. Increase in insulin levels is connected with sympathetic nerve activation, increased catecholamine concentration and peripheral vasoconstriction.[9-11] It is known that insulin increases the tubular sodium reabsorption in proximal tubulus.[10,11] Pregnant women are in tendency to sodium retention physiologically, and hyperinsulinemia increases this effect.[12]

There are numerous studies that suggest insulin resistance has a role in preeclampsia pathogenesis.

Martinez Abundis et al researched hyperinsulinemia and preeclampsia relation in 10 preeclamptic patients without diabetes and glucose intolerance and a control group. Although fasting and glucose loading plasma glucose levels are normal in two groups, in preeclamptic group fasting insulin level seems to be slightly higher than control group.[13]

Fuh et al loaded 75 gr glucose to postpartum 2nd month 26 patients of which 13 out of them preeclamptic and the remaining 13 normal, they found fasting and after glucose loading levels are normal in each groups but high insulin levels in preeclamptic group.[14] In a similar study by Nisell et al 21 PE and 22 normal pregnant patients are studied during postpartum and high insulin level has been observed in PE group.[15] The findings of these studies are suggestive of the insulin resistance plays a substantial role in the PE pathogenesis

In contrast to these studies, other researchers have not found any correlation between insulin resistance and preeclampsia in other studies. For example in a study of 11 preeclamptic and 11 control group pregnants, Robert et al found that there was an inverse correlation between insulin sensitivity and average blood pressure in normotensive pregnant group. But, they could not found any relation at the preeclamptic group. We suspect that relatively small number of patients and the study method may have affected the result of this study.[16] Caruso et al evaluated 26 pregnant women about the insulin resistance over preeclampsia. In their study 10 patients were preeclamptic, 10 patients were gestational hypertensive, and 6 patients were chronic hypertensive. Insulin resistance has been determined by using hyperinsulinemic euglisemic clamp technique. However, they found that preeclampsia and chronic hypertension are not correlated with insulin resistance.[17] This result may be explained with both of preeclampsia and hypertension are consequences of same physiopathologic disturbance which is insulin resistance. Because insulin resistance and the resultant hyperinsulinemia are considered to raise blood pressure through sympathetic nervous system activation, renal sodium retention, renin-angiotensin system stimulation, and intracellular calcium accumulation in vascular smooth muscle.[18]

Bartha et al have studied the 18 gestational hypertensive and 20 preeclamptic pregnant to evaluate the insulin levels and insulin resistance. They found that gestational hypertensive patients had increased insulin resistance, but they did not found insulin resistance in preeclamptic patients.[19] Different results might be resulted in pregnancy to without evaluating the effects of weight gaining, the effects of medications over insulin secretion, and separating the preeclampsia from the diseases with hypertension induced by pregnancy. We have included only the patients with mild preeclampsia because it is necessary to start antihypertensive treatment for heavy preeclamptic patients.

There are some studies showing that there is a relation between insulin resistance and weight gaining. Moran et al have studied to investigation the relationship between overweight and insulin resistance.[2] In their study, 140 pregnant women were separated according to have preeclampsia and overweight. The insulin resistance status has been evaluated. After loading glucose they were found that preeclampsia per se has associated with hyperinsulinemia, and it was independent of being overweight during pregnancy. In our study, we found that preeclamptic groups gained more weight than the non PE groups in overweight and normal patients. These findings are suggestive of the insulin resistance independent of BMI, and preeclampsia and insulin resistance are in close relation in pregnancy. Our results are compatible with the studies of Sower, Martinez, Fuh and Nisell.[5,13-15] However, it is well known that BMI is strongly correlated with insulin resistance in the common people. Our study showed that high BMI group has higher HOMA-ir levels than the normal BMI in non-preeclamptics although statistically not significant. This

result may be related to the small number of the cases.

A retrospective study carried out by Smith et al indicated that weight gaining during pregnancy was related with a number of pregnancy complications and preeclampsia development.[20]

Mostella et al carried out a similar study and showed overweight was highly related to preeclampsia.[21]

In conclusion, our results showed that pregnant patients with preeclampsia have higher insulin levels than those without. These findings may suggest that insulin resistance plays an important role at the physiopathology of preeclampsia, but not solely cause for weight gaining in preeclampsia. However, its role in the genesis of preeclampsia remains to be determined.

Preeklampsili Kadınlarda Artmış İnsülin Seviyeleri Gebelik Kilo Fazlalığından Bağımsızdır

AMAÇ: Bu çalışmanın amacı fazla kilolu eklampsili hastalarda artmış insülin düzeylerinin kilo fazlalığı ile ilgisi olup olmadığını araştırmaktır.

GEREÇ ve YÖNTEM: Bu amaçla Zeynep Kamil Kadın ve Çocuk Hastanesine başvuran 29-40 gebelik haftaları arasındaki gebeler çalışmaya dahil edilmiştir. Gebeler preeklampsi olup olmadığı ve fazla kilolu olup olmadıklarına gore 4 gruba ayrıldı; grup1 fazla kilolu ve hafif-orta eklampsili (n=20), grup 2 fazla kilolu normal (n=20), grup 3 normal kilolu hafif orta preeklampsili (n=20), grup 4 normal kilolu normal gebelerden oluşturuldu. Vakaların açlık glikoz ve immünoreaktif insülin seviyeleri ölçüldü, insülin direnci HOMA-IR formula ile hesaplandı.

BULGULAR: Preeklampsili hastalarda insülin direnci fazla kilolu ve normal kilolu vakalar için benzer bulunduğu halde preeklampsili hastaların HOMA-IR değerleri normal gebelerden yüksek idi.

SONUÇ: Eklampsili hastalarda kilo alımının insülin seviyelerinden bağımsız olduğu ve bu hastalarda insülin direnci eklampsiye yol açan ana fizyopatolojinin bir sonucunda gelişmiş olmalıdır.

Anahtar Kelimeler: Preeklampsi, İnsülin direnci, Kilo alımı

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