INSULIN RESISTANCE AND C-REACTIVE PROTEIN IN PREECLAMPSIA

Milan Stefanović*, Predrag Vukomanović, Mileva Milosavljević, Ranko Kutlešić, Jasmina Popović, Aleksandra Tubić-Pavlović

Clinic of Gynecology and Obstetrics, Clinical Center Niš,
Bul. Zorana Đinđića 48, 18000 Niš, Serbia

* Corresponding author

Abstract

Preeclampsia is referred to as the "disease of the theories" because of the multiple hypotheses proposed to explain is occurrence. Despite considerable research, the causes of preeclampsia remain unclear. Preeclampsia is likely to be multifactorial in origin, and recent research has focused on endothelial dysfunction as a central abnormality in preeclampsia. Insulin resistance and inflammation may contribute to the onset of preeclampsia. They could also be correlated. The aim of the study was to evaluate the presence and relationship between insulin resistance and its markers and C-reactive protein as a marker of inflammation. During their third trimester, 17 preeclamptic women and 20 normotensive controls underwent oral glucose tolerance test, basic biochemical analyses and SHBG. Preeclamptic women were more insulin resistant (p=0,004), and they had higher triglycerides levels (p=0,006), uric acid (p=0,002). However, the study groups did not differ in C-reactive protein (CRP), sex hormone–binding globulin (SHBG), high and low-density lipoproteins (HDL-cholesterol and LDL-cholesterol). In multiple regression analysis only SHBG (p=0,014) and triglycerides (p=0,003) were associated with insulin sensitivity independently of the body mass index (BMI), weight gain, HDL and LDL, and CRP. Preeclampsia is a state of increased insulin resistance, and CRP as the marker of inflammation was not increased in our research, and not associated with established preeclampsia.

KEY WORDS: preeclampsia, insulin resistance, C-reactive protein.

Introduction

Preeclampsia is a complication of late pregnancy characterized by hypertension and proteinuria (1). It is a major cause of perinatal and maternal morbidity and mortality, affecting 5% to 8% of all pregnancies (1). The etiology of this disease is still unknown, and there are multiple factors implicated in its pathogenesis (2). Among the many proposed causes are immunologic derangements (a maternal immune reaction to paternal antigen in placenta), genetic factors, increased insulin resistance (an associated elevations in the levels of the insulin, free fatty acids, and triglycerides), dietary calcium deficiency, increased oxidative stress, and prostaglandin imbalance (an increased ratio of tromboxan levels to prostacyclin levels) (3). Both insulin resistance and inflammation have been reported to contribute to the onset of hypertension and coronary artery disease, as a part of metabolic syndrome (4), and they may be present in hypertensive disorders of pregnancy (5). Normal pregnancy can be considered as a state of insulin resistance. Fasting insulin concentration rising during the pregnancy with peak in third trimester rapidly returns to pre-pregnancy levels after delivery (6). In preeclamptic pregnancies, metabolic changes similar to metabolic syndromes are also present (7). Insulin resistance, present in milder form in late pregnancy has long been ascribed to rises in cortisol and placental hormones, including human placental lactogen, progesterone, and estrogen. Causes of further enhancement in hypertensive pregnancies remain unknown (8). One explanation could be inflammation, and indeed the rises in some inflammatory markers predict the onset of insulin resistance in pregnant subjects (9, 10). Among these candidates, tumor necrosis factor α (TNF-α and leptin are known to be produced besides adipose tissue, also in the placenta and could therefore play a central role in insulin resistance in pregnancy (10). The aim of current study was to determine levels of insulin resistance and its markers (uric acid, lipids, lipoproteins, SHBG) and possible link between inflammation and its specific marker CRP.

Material and Methods

The study, designed as a prospective one, was carried out in the Obstetric Department of the Clinical Center Niš, from January to October, 2008. We studied 37 nulliparous women between 29 and 39 weeks of gestation (Table 1). Seventeen patients were women with established preeclampsia, and the controls, were 20 healthy nulliparous women with singleton pregnancy, similar age and body mass index (BMI), who were studied at the same gestational week. Informed consent had been obtained from each patient before investigations were undertaken. Preeclampsia was defined as blood pressure ≥140/90 mmHg, measured at least 2 times 6 hours apart and proteinuria ≥300mg/dm^3 after 20 weeks of gestation. All the subjects underwent 2-hour oral glucose tolerance test (OGTT, 75 g) after overnight fast. Only women whose glucose tolerance was normal (fasting ≤4,5 mmol/dm^3; 2 hours ≤7,8 mmol/dm^3 according to the World Health Organization criteria) were accepted for the study. Blood sample for OGTT was taken from a finger. The homeostasis model assessment (HOMA), is a mathematical formula that permits clinical evaluation of insulin resistance, calculated using fasting glycemia and insulin concentrations [IShoma=GoxIo/22,5] (11). Log-transformed HOMA (log-HOMA) has been reported as a reliable test with high correlation coefficients with the hyperinsulinemic euglicemic clamp (12). Baseline blood samples were also assessed for uric acid, lipid, lipoproteins, SHBG, and CRP. Blood glucose levels and biochemistry analysis were measured by Olympus AU 680. Insulin and C-peptide levels were analyzed by RIA-IRMA methods on Clinigama-Compugama LKB, and SHBG by fluoroimmunoassay method on Fluorimeter Arcus LKB. The material was analyzed at the Central University Laboratory.

Statistical analysis

We compiled all data in a database, which was analyzed by using NCSS 2000 (NCSS Kaysville, Utah). Continuous variables are presented as the mean ±SD. Paired or, where appropriate, unpaired Student's t test was used for comparisons. Multiple regression analysis was used with insulin sensitivity as the dependent variable and BMI, weight gain, serum triglycerides, serum HDL-cholesterol, LDL-cholesterol and CRP, as independent variables.

Results

There was no difference in age, pre-pregnancy BMI, weight gain, and gestational age between groups. Preeclamptic women had significantly higher blood pressure: both systolic and diastolic. Women with preeclampsia had shorter gestation period, lower birth and placenta weight and higher rate of cesarean delivery (Table 1). Biochemical determination of the preeclamtic and control women is shown in Table 2. The preeclamtic group had higher levels of fasting glucose, and insulin concentrations. Log-HOMA was significantly higher in women with preeclampsia than in the

Characteristic	Women with preeclampsia (n=17)	Normotensive pregnant women (n=20)	p value
Age (yr)	30,4±1,0	31,5±1,1	NS
Week of gestation	34,1±0,5	34,7±0,7	NS
Pre-pregnancy BMI (kg/m^2)	23,4±0,5	22,6±0,6	NS
BMI at study (kg/m^2)	27,8±0,6	27,2±0,7	NS
Proteinuria (g/24h)	1,88±0,50	-	
Uric acid ($mmol/dm^3$)	0,38±0,01	0,26±0,01	0,002
Systolic blood pressure (mm Hg)	148±2	122±4	0,0001
Diastolic blood pressure (mm Hg)	98±2	75±2	0,0001
Weeks of gestation of delivery	38,1±0,2	40,2±0,3	0,0003
Infant's birth weight (g)	2668±130	3428±79	0,0001
Placental weight (g)	520±30	610±25	0,03

TABLE 1. Clinical characteristics of the study population

Characteristic	Women with preeclampsia (n=17)	Normotensive pregnant women (n=20)	p value
Fasting Glucose ($mmol/dm^3$)	4,43±0,56	3,88±0,41	0,002
Fasting Insulin ($\mu UI/cm^3$)	7,79±4,38	5,26±2,75	0,024
Log-HOMA	0,31±0,56	-0,16±0,56	0,004
C-Peptide	0,76±0,50	0,56±0,04	0,03
Triglycerides ($mmol/dm^3$)	3,65±0,97	1,95±0,77	0,006
HDL ($mmol/dm^3$)	1,48±0,24	1,38±0,20	0,16
LDL ($mmol/dm^3$)	2,88±1,17	3,05±1,04	0,6
SHBG ($nmol/dm^3$)	440,3±95,2	425,4±93,8	0,7
CRP (mg/dm^3)	4,14±0,46	3,75±0,64	0,7
Infant's birth weight (g)	2668±130	3428±79	0,0001
Placental weight (g)	520±30	610±25	0,03

TABLE 2. Biochemical characteristics

control group. C-peptide levels in preeclamptic women were higher than in control. Preeclamptic women had higher levels of uric acid and triglyceride, while the HDL and LDL cholesterol levels were similar. There was no difference between groups in CRP concentration (Table 2). In multiple regression analysis, only triglycerides and SHBG emerged as independent mediators of insulin resistance (Table 3).

Risk factor	Univariate analysis P	R^2	Multivariate analysis P
BMI	0,016	0,15	0,13
Weight gain	0,071	0,91	0,061
Triglycerides	0,002	0,23	0,0033
HDL	0,78	0,0014	0,26
LDL	0,86	0,016	0,31
CRP	0,15	0,65	0,98
SHBG	0,31	0,026	0,014

NOTE: R^2 after multiple regression: 0,61.

TABLE 3. Contribution of different risk factors to the insulin sensitivity

Discussion

Changes in endothelial function and vasoactive agents have been proposed as possible pathogenic mechanisms of preeclampsia (13). The insulin resistance syndrome has been linked to this alteration, and hyperinsulinemia promotes oxidative stress, which is related with inactivation of nitric oxide and endothelial dysfunction (14). There are increasing data supporting the role of insulin resistance in preeclampsia (8), although this evidence has not been seen in all studies (15). Our research confirms decreased insulin sensitivity and increased insulin resistance in preeclamptic women. It is known that insulin resistance associated with low SHBG in the first trimester, is relatively good marker to predict development of preeclampsia (16). In our study, SHBG showed no significant difference between preeclamptic and normotensive women, although in multivariate analysis SHBG emerged as a significant factor in insulin resistance. Higher pre-pregnancy BMI (≥30 kg/m^2) and substantial weight gain during pregnancy have been associated with increased risk of developing preeclampsia particularly in the presence of positive correlation between BMI and HOMA levels (17). Visceral fat tissue produces proinflammatory cytokines, such as TNF-α and interleukin-6 (IL-6), which are involved in endothelial dysfunction, and have higher concentrations in women with preeclampsia (18). Our research observed no statistical difference in HDL and LDL concentrations between case and control groups, while trygliceryds and acidum uricum values were statistically different between the groups. Contradictory findings have been reported concerning the role of CRP, another inflammatory marker as a predictor of preeclampsia (19). In established preeclampsia, CRP has been reported to be higher than in normotensive controls, although this association was lost after adjustment for maternal weight (20). Although the newest data support that increases in CRP and endothelial dysfunction precede the clinical manifestation of preeclampsia (21), we did not find any difference in CRP levels between preeclamptic and control women. The presence of association with insulin resistance in univariate analysis (p=0,06) vanishes in multivariate analysis (p=0,9).

Conclusion

1. Patients with preeclampsia are less insulin sensitive and more insulin resistant, which is reflected through the increased insulin and C-peptide values.
2. Acidum uricum and triglyceride values are increased, but there is no statistical difference in HDL and LDL concentrations between the examined groups.
3. CRP, as an inflammatory marker, is not statistically significantly increased compared to the control group.

List of Abbreviations

CRP	-	C-reactive protein
SHBG	-	Sex hormone–binding globulin
BMI	-	Body mass index
OGTT	-	Oral glucose tolerance test
HOMA	-	The homeostasis model assessment

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