Acta Clin Croat 2022; 61:574-580
doi: 10.20471/acc.2022.61.04.02

Original Scientific Paper

CARDIOVASCULAR RISK IN WOMEN WITH PREECLAMPSIA

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SUMMARY – In this study, possible biochemical and functional cardiovascular markers were assessed in women with preeclampsia. Fifty-five pregnant women with manifest moderate (mild) preeclampsia (PE) and fifty healthy women as a control group were included in this prospective study. Laboratory tests including lipid panel, C-reactive protein (CRP), and homocysteine levels as biohumoral markers of atherogenesis, as well as ergometry and the main cardiovascular risk factor markers were performed in all women during pregnancy and six months after delivery. In our study, cholesterol and LDL levels in the PE group did not differ from those in the control group. Triglyceride levels in the PE group were higher than the corresponding values found in normal pregnancies, while HDL levels were significantly lower in the PE group than in the normal pregnancy group ($p<0.001$). The values of total cholesterol, LDL, HDL, and triglycerides in the PE group were higher compared to those in the same group six months after delivery ($p<0.001$). The effect of PE as an inflammatory disease could be confirmed to a certain extent by elevated CRP levels ($p<0.001$). A very high percentage of negative exercise stress tests indicated a good cardiovascular response to the current PE in the otherwise healthy pregestational women. It could be concluded that the development of possible cardiovascular comorbidities in preeclamptic pregnant women is a long process, but also due to etiologic factors of coexistent metabolic disorders such as dyslipidemia, as well as elevated inflammatory markers and homocysteine, PE can be considered even an early predictor of cardiovascular disease.

Key words: *Preeclampsia; Cardiovascular risk; Atherogenesis*

Introduction

Preeclampsia (PE) due to multiple organ disorders and consequential vasoconstriction, as well as fetomaternal tissue hypoperfusion, presents a major factor in maternal and fetal morbidity and mortality. The risk of thrombotic, cardiovascular and cerebrovascular incidents increases continuously and with the blood pressure values that are significantly lower than those that are nowadays assigned as arterial hypertension[1-4]. According to MacMahon *et al.*, every increase of 5 mm Hg in diastolic pressure is associated with a 34% increase in cerebrovascular and 21% increase in cardiovascular risk. Thus, maternal mortality after one eclamptic seizure is 5%, and after more than five seizures it amounts to approximately 40%[5]. Many biochemical predictors of PE are associated with short- and long-term adverse outcomes for the health

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Received December 10, 2018, accepted February 18, 2020

of pregnant women. Moreover, 25% of women with PE in pregnancy will develop arterial hypertension. Fibrin degradation products correlate with the severity of PE. Elevated concentrations of activin A, inhibin A, leptin and adiponectin, as well as increased C-reactive protein (CRP) and homocysteine levels, which all are markers of endothelial damage, along with hypercalciuria, hyperuricemia, alteration of pregnancy-associated plasma protein A (PAPP-A), and hyperlipidemia, are associated with the development of atherosclerosis and subsequent long-term postpartum morbidity[1,6,7].

Hypertension in pregnancy is a disease of early pregnancy with symptom expression in the second trimester, the major cause of which is wrong placentation with pathologic changes on the cytotrophoblast and consequential development of ischemic placental circulation[3,8]. Today, endothelial dysfunction is considered a key factor in the pathogenesis of PE, with a multietiologic imbalance of angiogenic factors such as lipid peroxidation of oxidant/antioxidant imbalance (oxidative stress), thrombophilic polymorphisms, gene polymorphism of angiotensinogen, inflammation, apoptosis (tumor necrosis factor alpha, interleukin-1 and interleukin-2), nitric oxide synthesis disturbance, prostacyclin and thromboxane A2 level disorder, alteration of serotonin, activation of the renin-angiotensin-aldosterone system, vascular endothelial growth factor, endothelin, neuropeptide Y, vasointestinal peptide, calcitonin gene-related peptide, neurokinin B, and platelet activating factor[8-11]. Therefore, PE in medical history of young women presents a serious cardiovascular morbidity, and should ensure an appropriate diagnostic and therapeutic approach during pregnancy.

In this study, the possible biochemical and functional cardiovascular markers were assessed in women with PE and six months after childbirth.

Patients and Methods

Fifty-five pregnant women with manifest moderate (mild) PE (blood pressure measurements on at least two occasions at a minimum 4-h interval in the range of ≥140/90 to 160/110 mm Hg, with positive proteinuria after the 20th week of gestation) as the PE group and fifty healthy women as the control group were included in this prospective study. All women read and signed an informed consent form previously approved by the Ethics Committee of the Osijek University Hospital Center. Pregnant women with PE diagnosed before the 20th week of pregnancy, with hypertension known before pregnancy, or with isolated hypertension and negative proteinuria, were not included in this study, nor were intellectually disabled persons and minors. The following basic data were assessed: parity, age, average gestational age, and comorbidities during pregnancy.

Laboratory tests that included lipid panel and CRP and homocysteine levels as biohumoral markers of atherogenesis, as well as the main cardiovascular risk factors, were done in all women during pregnancy and six months after delivery.

An Olympus AU400 device with Olympus reagents was used to determine CRP levels by immunoturbidimetric method. An AxSYM device (Abbott Laboratories) was used to determine homocysteine levels by Fluorescence Polarization Immunoassay (FPIA) technology with Abbott Laboratories reagents (TESTKIT Code No. 5F51-20). Cholesterol values were determined using the Olympus AU400 device with Olympus reagents (OSR TESTKIT Code No. 6216) by enzymatic CHOD color PAP method, in which the intensity of the resulting product is measured at 540 nm and is proportional to the cholesterol concentration in serum. Triglycerides were determined using the Olympus AU400 device with Olympus reagents (OSR TESTKIT Code No. 6133) by enzymatic color GPO PAP method in which the intensity of the resulting product is measured at 520 nm and is proportional to the triglyceride concentration in serum. HDL cholesterol was determined by the immunoinhibition method (autoantibodies against human beta-lipoprotein block LDL, VLDL, and chylomicrons; residual HDL cholesterol was determined by enzymatic color test) using the Olympus AU400 device with Olympus reagents (OSR TESTKIT Code No. 6156). LDL cholesterol values were determined by a test in which LDL-cholesterol was determined directly, without prior preparation of the sample, and with prior elimination of chylomicrons, VLDL cholesterol, and HDL-cholesterol. Cholesterol was released from residual LDL-cholesterol with the use of detergent, and measured by enzymatic color method, using the Olympus AU400 device with Randox reagents (TESTKIT Code No. 2657 CH).

Exercise stress testing was performed according to the Bruce protocol. The test started with an initial power output of 50 W in the first phase, which was increased by 25 W every 3 minutes. The study participants were continuously electrocardiographically monitored and their blood pressure was measured at the end of each stage. The test was conducted until the patient's request for termination, achievement of the target heart rate (80% of predicted maximum in terms of age), occurrence of angina, arrhythmias, changes in the ST segment or T wave, or signs of exhaustion. The test was considered positive in the following circumstances: occurrence of horizontal or downward ST segment depression by more than 1 mm for at least 0.08 seconds in at least three successive contractions of the heart, inability of raising the systolic blood pressure above 120 mm Hg, drop in systolic blood pressure by 10 or more mm Hg, ST segment elevation, occurrence of angina at low workload, inability of reaching 75% of the maximum heart rate, and occurrence of ventricular tachycardia lasting for 30 seconds or longer[12].

On statistical analysis, SPSS and Statistica programs and Shapiro-Wilk test, Mann-Whitney-Wilcoxon test, and χ^2-test were used. Differences at the level of $p<0.05$ were considered statistically significant.

Results

More than 90% of participants from both groups were pregnant for the first time, with a mean age of 29.97 years in the PE group *vs*. 27.88 years in the control group, both statistically nonsignificant. The mean gestational age was 35.5 weeks in the PE group *vs*. 39.1 weeks in the control group ($p<0.0001$). Three cases of deep venous thrombosis and three cases of gestational diabetes were observed in the PE group, and none in the control group.

Table 1 shows an overview of biochemical markers during pregnancy in the control group, and during pregnancy, as well as six months after delivery in the PE group.

The mean homocysteine level was 6.758 mmol/L in the women with PE and 6.014 mmol/L in the control group, yielding a difference of 0.744 mmol/L. Six months after delivery, the mean homocysteine level in the PE group was 7.636 mmol/L ($Z=-3,604$, $p<0.0001$).

The mean cholesterol value in the PE group was 7.762±1.414 mmol/L, which was lower than the mean cholesterol value in the control group (7.821±1.348 mmol/L). Six months after delivery, it was 6.167 mmol/L in the PE group ($t=9.138$, $p<0.0001$).

Table 1. C-reactive protein and homocysteine values and lipid panel in pregnant women without and with preeclampsia during pregnancy and 6 months after delivery

Marker	Healthy pregnant women	Pregnant women with mild preeclampsia	p value	6 months after delivery in PE group	p value
CRP (mg/L)	4.950	7.420	p<0.0001	4.793	p<0.0001
Homocysteine (μmol/L)	6.014	6.758	NS	7.636	p<0.0001
Triglycerides (mmol/L)	3.044	4.065	p<0.0001	2.919	p<0.0001
LDL cholesterol (mmol/L)	4.380	4.237	NS	3.422	p<0.0001
HDL cholesterol (mmol/L)	2.057	1.873	p<0.0001	1.638	p<0.0001
Cholesterol (mmol/L)	7.821	7.762	NS	6.167	p<0.0001
Ergometry (preeclamptic women) - negative - positive - contraindications				 83.64% 3.64% 12.73%	

CRP = C-reactive protein; LDL = low-density lipoprotein; HDL = high-density lipoprotein; NS = nonsignificant

The mean triglyceride value was higher by 1.021 mg/dL in the PE group compared to the mean value in the control group (Z=-4,029, p<0.0001). The mean value of HDL was by 0.184 mmol/L lower in the PE group than the mean value of HDL in the control group (t=-2.122, p=0.036). The results showed a mean LDL value of 4.237±1.423 mmol/L in the PE group, which was by 0.143 mmol/L lower than the mean value of LDL in the control group (4.380±1.047 mmol/L), but below the level of statistical significance (t=-0.59, p=0.557). The mean value of triglycerides in the PE group was by 1.146 mg/dL higher than the mean value of triglycerides in the same group six months after delivery, while the median value calculated for the PE group was higher by 1.14 mmol/L (Z=-6.301, p=0.000). The mean HDL level was by 0.235 mg/dL higher in the PE group than the mean HDL level in the same group six months after delivery (1.638 mmol/L, t=3.834, p<0.0001). The mean LDL level in the PE group was by 0.815 mg/dL higher than the mean LDL level in the same group six months after delivery (3.422 mmol/L, t=3.834, p<0.0001), while the median value was higher by 1.000 mmol/L in the PE group (t=4.892, p<0.0001).

The mean value of CRP in the PE group was by 2.47 mg/L higher than the mean value of CRP in the control group, while the median value was higher by 0.5 mg/L in the PE group (Z=-1.726, p=0.084). The mean CRP level in the PE group six months after delivery was 4.793 mg/L (Z=-3.557, p<0.0001).

Exercise stress test suggested a possible coronary artery dysfunction in only two (3.64%) patients from the PE group six months after delivery. In seven (12.73%) patients, exercise test was not performed at full capacity or was contraindicated due to a current disease (elevated thyroid hormone, deep venous thrombosis, initial hypertension, tachycardia, hypertensive reactions during exercise), and was negative in a high percentage (83.64%) of patients.

Discussion

Preeclampsia is a pregnancy-induced syndrome characterized by tissue hypoperfusion as a result of arteriolar vasospasm and hypercoagulable state due to the activation of the coagulation cascade. Lipid levels, and particularly the total cholesterol level, as well as hypertriglyceridemia and HDL decrease in early pregnancy are significantly linearly associated with the risk of PE[14], but also with post-delivery development of atherosclerosis and subsequent cardiovascular morbidity[13,14]. CRP is a powerful marker of cardiovascular risk[15-18]. In addition to its presence in the state of systemic inflammation, it was found to have a direct effect on the endothelium in the process of atherogenesis. It binds to LDL, activates the complement system, interacts with monocytes/macrophages, and has a direct effect on the arterial wall, especially on the endothelial and smooth muscle cells of blood vessels[16-18]. CRP is proven to have a direct inhibitory effect on the smooth muscle cells of blood vessels in their production of nitric oxide (NO) mediated by cytokines, which results in vasoconstriction and increased endothelin production[19-21]. Furthermore, CRP has a pro-atherosclerotic action, stimulating the expression of angiotensin receptor 1[22]. Finally, together with other factors of inflammation (amyloid 1, interleukin-6, sICAM-1), it was found to be a significantly better predictor of cardiovascular risk than the model based only on determination of lipid levels[15].

Assessing the values of lipids and inflammatory parameters, in this study we found that HDL cholesterol was significantly lower in the PE group than the mean HDL values in the control group. Statistically significant differences in the mean values of triglycerides were also observed, with higher levels in the PE group. However, statistical analysis did not prove a difference between the mean values of LDL cholesterol and total cholesterol. The mean values of CRP were higher in the PE group compared with the control group, but the differences were not statistically significant. Differences in the CRP levels were statistically significant in the PE group both during pregnancy and six months after delivery.

The results indicated an inflammatory component of PE (among other mechanisms) and the possible consequential effects on the vascular system. Similar differences between the values of lipids were found by Girouard *et al.*[23] in a group of 168 patients with hypertensive disease in previous pregnancies, where the patients were followed up for 7.8 years after the first delivery. More obese women were found in the PE group than in the control group. In addition, lower values of HDL and higher apolipoprotein (apo) ApoB/ApoA, homocysteine, leptin, and insulin levels

were observed in the PE group compared to the mean values in the control group. The levels of inflammation markers such as IL-6 and CRP were higher in the PE group than in the control group. However, PAI values were similar in both groups. According to the study by Girouard *et al.*, lower HDL cholesterol and higher triglyceride values in the investigated women as compared to the control group were found to be statistically significant, while LDL values were increased in comparison to the control group, but not at the level of statistical significance. The same authors concluded that young women with previous hypertensive disease in pregnancy showed signs of insulin resistance within the first decade after delivery. In their opinion, these findings suggest that insulin resistance could be a link between hypertension in pregnancy and increased cardiovascular risk later in life[23].

The association of inflammatory parameters, primarily CRP, and the development of PE is interpreted differently in most recent studies. According to the study by Savvidou *et al.* from 2002, CRP concentrations between the 23rd and 25th weeks of pregnancy in women that would later develop PE did not differ significantly from CRP levels in normotensive pregnant women[24]. However, recent research found a positive correlation between inflammatory parameters and the development of PE[25-27]. It is assumed that elevated CRP levels may be an independent risk factor for the development of PE. However, further research is needed to determine the extent to which CRP and obesity before pregnancy, independently or together, may be included among the risk factors for PE development[27].

A large number of retrospective and prospective studies found an association of mild hyperhomocysteinemia with cardiovascular disease (CVD) and related mortality[7,28]. With respect to PE, in the American study performed by Powers *et al.*, the mean homocysteine levels were significantly elevated ($p<0.04$) in women with PE compared to the control group (9.7 *vs.* 7.0)[29]. The same was shown in the Finnish study by Laviouri *et al.* (6.7 *vs.* 3.8, $p<0.01$)[30]. Another study established a 4.57 times higher risk of PE development in women with higher levels of homocysteine[31], while Sorensen *et al.* in their study showed a 3.2 times higher risk (OR=3.2; CI 95%: 1.11-9.2)[32]. Both studies showed that the risk increased significantly in primiparas, compared with multiparous women with similar levels of homocysteine. Parity was not a significant risk factor in our study.

Scholten *et al.* demonstrated that 10%-20% of women with PE suffer from metabolic syndrome, thrombophilia, and hyperhomocysteinemia[4]. PE as a multiorgan disorder causes metabolic alterations which induce vascular lesions with subsequent vascular damage, particularly in the kidneys, liver, brain, and coronary arteries, which correlates with the values of sFlt-1 and PlGF reduction[1,14]. Recent studies corroborate the etiopathogenesis of ischemic-reperfusion placental injury due to inadequate trophoblast invasion as a several-month-long pathophysiological event, but on the maternal side these events cause long-term consequences associated with cardiovascular morbidity[13]. Biochemical markers can aid in the prediction of coronary heart disease, most recently along with carotid artery intima-media thickness and coronary artery calcium scoring, which will indicate the actual disease due to the long-term course of development of atherogenesis[2]. Planning delivery and completion of pregnancy depends on the severity of PE, antihypertensive treatment, gestational age, and parity[14,33]. The association between PE and the premature appearance of CVD has been demonstrated in many epidemiological, and especially retrospective studies[34,35].

Epidemiological studies have demonstrated an increase of 2.0-8.0 in the relative risk of developing hypertension at a later point, and an increase of 1.3 to 3.07 in cardiovascular morbidity and mortality compared to normotensive patients[36]. Pregnant women who had PE or maternal placental syndrome should reduce stress and make changes in their lifestyle and habits, including smoking cessation and dietary regimes[37].

In the Framingham study, Breetveld *et al.* demonstrated an increased risk of CVD in women with PE with 10- and 30-year risk scores for CVD[38]. A study performed by Lykke *et al.*[39] demonstrated an increased risk of thromboembolism after moderate and severe PE in patients with type 2 diabetes mellitus, as well as the severity and repetition of PE in subsequent pregnancies, which increased the risk of CVD.

In our study, the cholesterol and LDL levels in the PE group did not differ from those in the control group. Triglyceride levels in the PE group were higher than

the corresponding values in the women with normal pregnancies, while HDL levels in the PE group were significantly lower than those in the normal pregnancy group. The values of total cholesterol, LDL, HDL, and triglycerides in the PE group were higher compared to the values measured in the same group six months after delivery. The effect of PE as an inflammatory disease can be confirmed to a certain extent by elevated CRP levels. A very high percentage of negative exercise stress tests indicated a good cardiovascular response to the current PE in the otherwise healthy pregestational women.

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Sažetak

KARDIOVASKULARNI RIZIK KOD ŽENA S PREEKLAMPSIJOM

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U ovom članku prikazani su mogući biokemijski i funkcionalni kardiovaskularni pokazatelji kod žena s preeklampsijom. U ovu prospektivnu studiju uključeno je pedeset i pet trudnica s umjerenom (blagom) preeklampsijom (PE) te pedeset zdravih žena u kontrolnoj skupini inicijalno tijekom trudnoće te šest mjeseci nakon porođaja. Laboratorijska analiza je uključivala određivanje lipidograma, C-reaktivnog proteina (CRP) i razine homocisteina kao biohumoralnog pokazatelja aterogeneze, kao i test opterećenja na pokretnom sagu uz izdvajanje osnovnih poznatih kardiovaskularnih čimbenika rizika. U našoj studiji razina ukupnog kolesterola i LDL kolesterola u skupini s PE nije se razlikovala od onih u kontrolnoj skupini. Razine triglicerida u skupini s PE bile su više od odgovarajućih vrijednosti u normalnim trudnoćama, dok su razine HDL u skupini s PE bile značajno niže nego u kontrolnoj skupini ($p<0,001$). Vrijednosti ukupnog kolesterola, LDL-a, HDL-a i triglicerida u skupini s PE bile su značajno više u trudnoći u usporedbi s onima u istoj skupini šest mjeseci nakon porođaja ($p<0,001$). Učinak PE kao upalne bolesti može se u određenoj mjeri potvrditi povišenim razinama CRP-a ($p<0,001$). Vrlo visok postotak negativnih testova na testu opterećenja pokazao je dobru kardiovaskularnu funkcionalnu sposobnost naspram PE u inače pregestacijski zdravih žena. Može se zaključiti da je razvoj mogućih kardiovaskularnih supostojećih bolesti kod trudnica s PE dug proces, ali svakako zbog etiologije metaboličkih poremećaja kao što je dislipidemija, kao i povišenih upalnih pokazatelja i homocisteina, ujedno i rani prediktor kardiovaskularnih bolesti.

Ključne riječi: *Preeklampsija; Kardiovaskularni rizik; Aterogeneza*