

## Intima media thickness in women with preeclampsia

### *Debljina intima-medije kod žena s preklampsijom*

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#### Summary

**Aim:** To investigate the difference in intima-media thickness of common carotid artery in women 6 months after pregnancy and delivery complicated by preeclampsia as compared to the age-matched control.

**Material and methods:** The clinical study enrolled 55 women six months after pregnancy and delivery complicated by preeclampsia without actual hypertension, medication and comorbidity and control group of 50 healthy women six months after delivery without perinatal complications. Intima-media thickness was measured on the lower segment of both common carotid arteries on the exact site of 1 to 2 centimetres proximal to the bifurcation using optimal B-mode settings.

**Results:** The mean value of the intima-media thickness in patients who had preeclampsia 6 months prior to the measurement was  $0.419 \pm 0.29$  mm while in the control group the mean value was  $0.412 \pm 0.43$  mm. The difference in intima-media thickness was shown to be insignificant ( $p > 0.0001$ ).

**Conclusion:** It was not possible to detect early atherosclerotic changes by measuring intima-media thickness six months after pregnancy with preeclampsia. Due to the long atheropathogenesis process, long term follow-up is needed.

**Key words:** intima media thickness, common carotid artery, atherosclerosis, preeclampsia

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#### Sažetak

**Cilj istraživanja:** Procijeniti debljinu intima-medije, zajedničke karotidne arterije u žena šest mjeseci nakon trudnoće i porođaja kompliciranih s preklampsijom u komparaciji sa zdravim trudnicama.

**Materijal i metode:** Klinička studija uključila je 55 žena šest mjeseci nakon trudnoće i porođaja kompliciranih preklampsijom, bez aktualne hipertenzije, medikacije i komorbiditeta i kontrolnu skupinu od 50 zdravih žena, šest mjeseci nakon porođaja, bez perinatalnih komplikacija. Debljina intima-medije mjerena je u donjem segmentu zajedničke karotidne arterije na tipičnom mjestu 1-2 centimetra od bifurkacije uporebljujući B-mode.

**Rezultati:** Srednja vrijednost debljina intima-medije u bolesnica koje su imale preklampsiju iznosila je  $0,419 \pm 0,29$  mm, dok je u kontrolnoj skupini iznosila  $0,412 \pm 0,43$  mm, što je statistički neznačajno ( $p > 0,0001$ ).

**Zaključak:** Nisu pronađene rane aterosklerotske promjene, mjereći debljinu intima-medije šest mjeseci nakon trudnoće komplicirane preklampsijom, no zbog poznate dugotrajne ateropatogeneze, potrebne su dugoročnije studije, što je zaključak istraživanja.

**Ključne riječi:** intima-media debljina, zajednička karotidna arterija, ateroskleroza, preklampsija

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## Introduction

In 1945 Hertig described for the first time the injury of the uteroplacental vessels endothelium caused by the accumulation of lipid-laden macrophages in the process which was named as acute atherosclerosis.<sup>1</sup> This phenomenon was observed in placentas from pregnancies complicated by preeclampsia (PE) with pathological findings of endothelium disruption with underlying accumulation of the plasma proteins and macrophages filled by the fibrin and lipoprotein resulting in the decrease of the blood vessel caliber.<sup>1</sup>

The PE is a multiorgan heterogeneous disease with unclear etiology which can be partially described by uteroplacental and maternal vasculopathy. This disorder of pregnancy is associated with significant maternal and neonatal morbidity and mortality, mostly caused by dysfunction in cardiovascular and cerebrovascular system. Early atherosclerotic changes can be recognized by the thickening of the arterial wall which can be objectively assessed by the ultrasound measurement of the intima and media thickness (IMT). IMT can be considered as an early noninvasive marker of the subclinical changes of the arterial wall in the early stages of atherosclerosis but with potential vascular morbidity.<sup>2-4</sup>

There are few published clinical studies dealing with the assessment of IMT in patients with pregnancies complicated by preeclampsia.<sup>2-4</sup> The aim of this clinical study is to elucidate this problem within the first national clinical research focused in patients with pregnancies complicated by preeclampsia.

## Material and methods

The clinical study enrolled 55 women six months after pregnancy and delivery complicated by PE without actual hypertension, medication and comorbidity and control group of 50 healthy women six months after delivery without complications. PE was defined with hypertension (blood pressure measurements on at least two occasions at minimum 4-h interval  $\geq 140/90$  mm Hg), and with positive proteinuria ( $> 3$  g/L) after the 20th week of gestation). The study was approved by the Ethics Committee of Osijek University Hospital Center, a tertiary perinatal healthcare facility in Eastern Croatia. Prior to entering the study, all women were explained in detail the purpose and objectives of the study. The selected descriptive statistics parameters were determined for the Shapiro-Wilks, while t-test and Levene test were employed in cases where the hypothesis of normal distribution was confirmed. Data were processed by SPSS and Statistica software.

IMT was measured on the lower segment of both common carotid arteries on the exact site of 1 to 2 centimeters proximal to the bifurcation. IMT measurements were obtained for each near and far wall using angles of 90, 120, 150 and 180 degrees. Optimal B-mode settings of gain, depth, focal zone placement, and compression were individually adjusted for each vessel to enhance arterial wall structures and image quality using Philips Ultrasound HD 10 MHz probe. IMT was measured by manual technique using electronic calipers for 16 times and the average value was determined in millimeters with two decimals.<sup>5,6</sup>

## Results

The mean value of the IMT in patients who had preeclampsia 6 months prior to the measurement was  $0.419 \pm 0.29$  mm. No significant difference in outcome was observed when patients were divided according to the median IMT value since half of the women had IMT of 0.410 mm or less while in 50% of women the value of IMT was 0.410 mm and above. No significant difference in outcome was neither observed when patients were divided according to quartiles. The lower quartile showed that in 25% of women the IMT value was 0.390 and less, while the upper quartile revealed that in 25% of patients IMT measured 0.460 mm and above. According to that interquartile, the range of IMT in the preeclampsia group was 0.070 mm. In healthy uncomplicated pregnancies, the mean value of the IMT was  $0.412 \pm 0.43$  mm which is not significant as compared to the group with preeclampsia in the medical history and other statistical values ( $p > 0.0001$ ) (Table 1.).

## Discussion

Pathological changes of the arterial wall are associated with most of the cardiovascular proatherogenic risk factors such as arterial hypertension, smoking, hyperlipidemia, diabetes mellitus, psychosocial stress, plasma viscosity and hyperhomocysteinemia. These changes have also been shown to have correlation with the brain white tissue injury, left ventricle hypertrophy and microalbuminuria as well.<sup>7</sup> According to that increase, the carotid artery IMT can be associated with multiple different risk factors that impaired vessels throughout a certain period of time.<sup>7</sup> Although IMT is considered as a subclinical marker of atherosclerosis,<sup>8,9</sup> it is possible that in our case a period of 6 months is not long enough for atherosclerotic changes to be developed. Since the process of atherosclerosis probably needs several years for manifestation and ultrasound assessment, IMT could not be used as a useful predictor in these circumstances.<sup>10</sup>

Table 1 Intima media thickness (IMT) in women with and without preeclampsia 6 months after delivery  
 Tablica 1. Intima-media debljina (IMT) kod žena sa i bez preeklampsije 6 mjeseci nakon porođaja

Statistical data <i>Statistički podaci</i>	IMT (mm)	IMT (mm)
	Women with preeclampsia during pregnancy <i>Žene s preklampsijom za vrijeme trudnoće</i>	Women without preeclampsia during pregnancy <i>Žene bez preklampsije za vrijeme trudnoće</i>
Number of patients <i>Broj pacijenata</i>	55	50
Mean value <i>Prosječna vrijednost</i>	0.419	0.412
Median <i>Prosjek</i>	0.410	0.411
Lower quartile <i>Donji kvartil</i>	0.390	0.388
Upper quartile <i>Gornji kvartil</i>	0.460	0.461
Interquartile <i>Među kvartil</i>	0.070	0.068

In addition, Heilmann and de Moerloose have shown that placental vascular disorder and precocious cardiovascular disease might not be related by classical atherogenesis, but rather by the predisposition to acute thrombosis<sup>11,12</sup> or platelet hyperactivity.<sup>13,14</sup> In this way, carotid IMT in women after placental vascular disease could be normal despite their increased risk for cardiovascular events.<sup>10</sup>

Ray and coworkers underwent a retrospective cohort study in Ontario that enrolled 1.03 million of women who did not have cardiovascular disease by the time of their first delivery.<sup>15,16</sup> Within the study group 75380 (7%) women developed at least one form of the maternal placental syndrome that include PE, gestational hypertension, placental abruption and placental infarction. The incidence of cardiovascular disease was shown to be 500 on a million women in the placental syndrome group, while this number was 200 on a million women from the control group. The risk was even higher if placental pathology was associated with intrauterine growth restriction or intrauterine fetal demise. The authors concluded that the risk of precocious cardiovascular disease is increased after the maternal placental syndrome, especially with the association of fetal pathology. It has been stressed that these findings are not indicative for causal relation of maternal placental syndrome and future development of cardiovascular disease, but are more descriptive of the abnormal metabolic environment that precedes pregnancy and continue after delivery.<sup>15,16</sup> On the other hand, some recent

studies have revealed the possibility of long term development of atherosclerotic changes in women who had PE in their pregnancies. Blaauw and coworkers measured IMT of the femoral and carotid arteries after PE and have shown transient adaptive response of the arteries in preeclampsia women which is suggestive for the long term follow up of these patients.<sup>3</sup> The earlier study of the same group has revealed the increased value of the IMT which was measured 3 months after the delivery and 6 months following the termination of lactation in the group of women who had PE as compared to the healthy women.<sup>1</sup> In addition, Ciftci and coworkers found a decrease of the coronary flow reserve with IMT and C reactive protein elevation in a 5-year period in women who had PE in previous pregnancies,<sup>4</sup> while Sandvik and his group found an increase in IMT in women with elevated plasma levels of endothelial dysfunction markers.<sup>18</sup> Another study has shown that women who had PE have early structural and functional atherosclerotic changes 12 to 24 months after the affected pregnancy,<sup>19</sup> which was also confirmed by investigators with the finding of significant atherosclerotic plaques as independent risk factor for the development of atherosclerosis in women who had pregnancies complicated by PE.<sup>20</sup>

The results of our study revealed that in the time period of 6 months after preeclampsia in pregnancy there were no significant differences in the intima-media thickness as compared to the age-matched control. We assume that this time period is too short

for the pathological changes of the arterial wall to be visible by ultrasound, because the progression of IMT is 0.01 mm/year during life and depends on the comorbidity and life-style of patients. It is our intent to conduct a 5-year and 10-year follow-up which will hopefully be sufficient for the conclusion of the relation of PE with vascular disease as a multifactorial long time pathophysiological process including proatherogenic factors and life-style (hyperlipidemia, smoking, hyperhomocysteinemia, diabetes mellitus, obesity and age of patients).

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