

Raul Moreira Neto*, Jose Geraldo Lopes Ramos, Edin Medjedovic and Edin Begic

Increased of the carotid intima media thickness in preeclampsia

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Abstract

Objectives: The aim of the study was to determine carotid intima-media thickness (CIMT) values in patients who developed and did not develop preeclampsia (PE), and to determine whether CIMT values could be predictors of PE development.

Methods: The study included pregnant women who were examined by regular ultrasound examination at the Materno-Infantil Presidente Vargas Hospital (HMIPV) in Porto Alegre, Brazil, from April 2016 to September 2017. The examinations were performed every three months. Patients were divided into two groups. The first group included patients diagnosed with PE (n=21) and second group included patients who did not have PE (n=199). A high frequency ultrasound device (12 MHz) with a semi-automatic method was used to estimate CIMT.

Results: CIMT was significantly higher in pregnant women with PE than in women without PE (55 ± 0.11 vs. 0.44 ± 0.06 , respectively; $p<0.001$). Using a cut-off value of 0.51 mm, CIMT had a specificity of 77.9% and sensitivity of 81% in the diagnosis of PE. With CIMT ≥ 0.6 mm, the

probability of a patient developing PE was 44.4%; with CIMT >0.42 mm, the probability was only 4.2%.

Conclusions: An increase in CIMT was associated with the onset of PE. CIMT values were significantly higher in patients who develop PE.

Keywords: preeclampsia; pregnancy; screening.

Introduction

Atherosclerosis is the primary cause of cardiovascular diseases [1]. The complication of atherosclerosis is atherothrombosis which can have fatal consequences (cerebrovascular and cardiovascular incidents). Given the high percentage of potentially fatal complications of atherothrombosis (the process progresses through life, before finally manifesting as an acute ischemic event), a proper understanding of the pathogenesis of this disease is of great importance for determining the optimal modalities of prophylaxis and therapy [2, 3]. Atherosclerosis is a chronic inflammatory process in the arteria intima and is characterized by thinning of the blood vessel intima, with lipids and macrophage accumulation [2, 3]. Preeclampsia (PE) is a multisystemic disease, complicating 3–8% of pregnancies, and is one of the largest causes of maternal mortality [4, 5]. It is defined as new onset hypertension after 20 weeks of gestation with systolic blood pressure (BP) >140 mmHg or diastolic BP ≥ 90 mmHg and significant proteinuria 300 mg of protein in 24 h [6, 7]. Pathophysiological consequences are impaired placental perfusion and consequent involvement of the whole organism including renal, hematologic, hepatological and neurological complications and fetal growth retardation [6, 7]. Risk factors for atherosclerosis are also risk factors for PE [8, 9]. The first step in the process of atherosclerosis is increase in carotid intima-media thickness (CIMT) [2, 3]. CIMT is associated with the onset of incident hypertension in a population without already verified hypertension [10]. Endothelial dysfunction, the basis of the onset of atherothrombosis, is the process underlying the PE [11, 12]. Endothelial dysfunction contributes to the degree of PE [13]. Dysfunctional endothelium is characterized by reduced nitric oxide bioavailability and overproduction of endothelin one, which impairs vascular

*Corresponding author: Raul Moreira Neto, MD, Department of Gynecology and Obstetrics, School of Medicine, Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil. Phone: +55 51 99910 5500, E-mail: raul_m_neto@hotmail.com. <https://orcid.org/0000-0001-7308-376>

Jose Geraldo Lopes Ramos, Department of Gynecology and Obstetrics, School of Medicine, Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil. <https://orcid.org/0000-0002-3789-885X>

Edin Medjedovic, Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina; Department of Gynecology, School of Medicine, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina. <https://orcid.org/0000-0003-2357-9580>

Edin Begic, Department of Pharmacology, School of Medicine, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina; Department of Cardiology, General Hospital «Prim.dr. Abdulah Nakas», Sarajevo, Bosnia and Herzegovina. <https://orcid.org/0000-0001-6842-262X>

hemostasis; increased expression of adhesion molecules and increased blood thrombogenicity through excretion of locally active substances [2, 3]. Prediction of PE onset for optimal therapeutic modality and prevention of the effects of PE on the mother and fetus is a goal in the daily work of the clinician. The use of non-invasive, high-resolution ultrasound-based imaging has enabled the detection of atherosclerosis, and the question is whether CIMT can be a predictor of PE in an asymptomatic population. The aim of the study was to evaluate CIMT values in patients who developed and did not develop PE, and to determine whether CIMT values could be predictors of PE development.

Patients and methods

The research was prospective cohort study that included 220 pregnant women who undergone ultrasound examinations at the Materno-Infantil Presidente Vargas Hospital (HMIPV) in Porto Alegre, Brazil, from April 2016 to September 2017. Research compared a Gaussian continuous variable (CIMT) among pregnant women who developed PE and controls without PE, maintaining a ratio (m) of approximately 13 controls per event according to the expected rate of 7% of preeclampsia in Brazilian population [14]. A total of 325 pregnant women were screened for the study leading to the expectation of approximately 25(7.7%) PE and 300 controls, assuming $m=13$, statistical power of 90% ($\beta=0.10$), type I error of 5% ($\alpha=0.05$), standard deviation of 0.14 mm and effect size of 0.10 mm.

The examinations were performed every three months. Patients were divided into two groups. The first group included patients diagnosed with PE ($n=21$) and second group included patients who did not have PE ($n=199$). Each patient signed an informed consent and the study was approved by the National Ethics Committee, Brazilian Ministry of Health. All patients were monitored during pregnancy. The criterion for inclusion in the study was pregnant women who monitor their pregnancy in HMIPV. Exclusion criteria were as follows: multiple pregnancy, fetal abnormalities, previously verified hypertension, diabetes mellitus, thrombophilia, chronic renal disease, previous pregnancy with PE and molar pregnancy. Demographic and anamnestic data on each patient were processed.

The CIMT evaluation was performed in accordance with the statement From the American Society of Echocardiography CIMT Task Force as well as in accordance with the 2013 ESH / ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) [15, 16]. Ultrasound was performed while the patients were in a supine position. High-resolution B-mode images of the right and left common carotid arteries were collected using a Samsung HM70A, a device (Samsung, Seoul, South Korea), equipped with a linear, high-resolution transducer set to 12 MHz. CIMT was defined as mean distance between intima and media double-line pattern expressed in millimeters, measured on both sides of common carotid artery, considering mean values for analysis, as recommended in previous studies [15–17]. The detection was performed by semi-automated method, since it is less operator dependent, more reproducible, has lower inter-observer variation, and provides the average and maximum value of >100

points in a single evaluation compared to the manual method (Figure 1) [14, 18]. Patients were followed up until the end of their pregnancy to check whether they developed PE, as defined by the recommendations of the International Society for the Study of Hypertension in Pregnancy revised in 2014: i.e., onset and maintenance of hypertension after 20 weeks of gestation in association with significant proteinuria [19]. To consider the diagnosis of hypertension, the systolic BP must have been ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg. For proteinuria to be considered significant, it must have been ≥ 300 mg in 24 h urine sample [19]. Quantitative data were described by mean, standard deviation, minimum, and maximum values. When distributional assumptions were in doubt, results were presented in median and interquartile range. Comparisons between quantitative data were performed by Student's t-test or rank tests when needed. Comparisons between categorical data were performed by χ^2 -test or Fisher's exact test. The relationships between the variables were tested using the parametric Pearson or Spearman correlation. The results were presented by number of cases, percentage, arithmetic mean, standard deviation, median with interquartile range, area under the curve (AUC), while receiver operating characteristics (ROC) curve analysis was used to determine sensitivity and specificity. All tests were performed with an accuracy level of 95% ($p<0.05$). Data were analyzed using IBM-SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The mean age of pregnant women was 33.6 ± 14 years for patients with PE and 30.3 ± 9 years for those without PE. Patients with PE had, on average, more children than those without PE (2.38 vs. 1.84). No significant difference in age or number of pregnancies was found between those with PE or without PE ($p>0.001$). The general characteristics of the study population are given in Table 1. With regard to the evaluation period of the CIMT, more than half of the



Figure 1: Carotid intima media thickness measured by semi-automated method.

Table 1: Characteristics of the patients.

	Control group n=199	Group with preeclampsia n=21	p-Value
Age, years			0.012 ^a
Mean ± SD	30.3±5.9	33.6±4.6	
Minimum–maximum	16–43	25–42	
Number of pregnancies, n			0.059 ^b
Mean	1.84	2.38	
P50	2	2	
P25–P75	1–2	1–3	
Minimum–maximum	1–6	1–6	
Evaluation moment, n (%)			0.019 ^c
First trimester	50 (51.3)	11 (52.4)	
Second trimester	102 (25.1)	5 (23.8)	
Third trimester	47 (23.6)	5 (23.8)	

SD, standard deviation; p, statistical significance; p50, median; p25, 25th percentile; P75, 75th percentile. ^aStudent’s t-test. ^bMann–Whitney U-test. ^cFisher’s exact test.

pregnant women, both in the control group (51.3%) and PE group (52.4%), underwent CIMT measurement in the first trimester of pregnancy. No significant correlations were observed between CIMT and patient’s age ($r=0.22$; $p=0.01$), number of pregnancies ($r=0.08$; $p=0.23$), and gestational period in which the measurement was taken ($r=0.02$; $p=0.80$). Pregnant women with PE had higher CIMT than normotensive pregnant women (0.55 ± 0.07 vs. 0.45 ± 0.12 , respectively; $p<0.001$) (Figure 2). After verifying the significant difference in CIMT between patients with and without PE, a ROC curve was constructed to verify if this

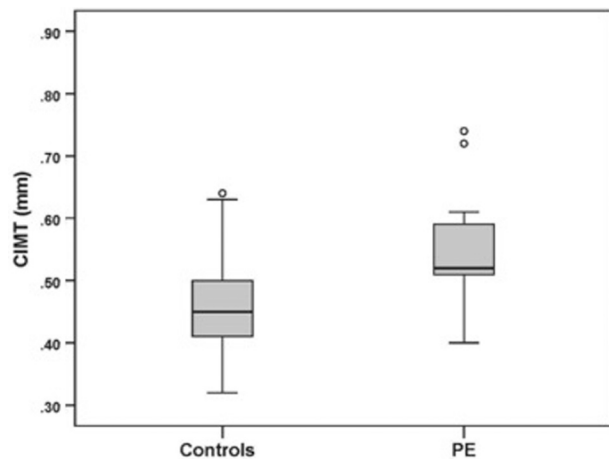


Figure 2: Distribution of carotid intima media thickness (CIMT) values between control (0.46 ± 0.07 mm) and preeclamptic patients (PE) (0.55 ± 0.12 mm).

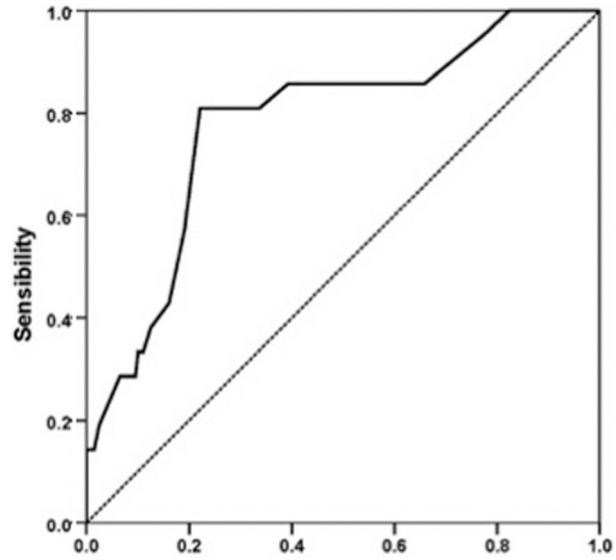


Figure 3: Receiver operating characteristics (ROC) curve illustrating CIMT diagnostic ability for preeclampsia detection.

test has good accuracy in the diagnosis of PE (Figure 3). The area under the ROC curves (AUC) was 0.78 and considered acceptable in the diagnosis of PE. With a CIMT cutoff point of 0.58 mm, the sensitivity of CIMT to diagnose PE is very low (28.6%), but the specificity is high (91%). However, if we choose a CIMT cutoff point of 0.51 mm, the sensitivity increases to 81%, and the specificity decreases at 77.9%. When CIMT value was ≥ 0.6 mm, the probability of the patient to develop PE was 44.4%; with CIMT < 0.5 mm, the probability was 6.1%, decreasing to 4.2% with CIMT < 0.42 mm (Figure 4).

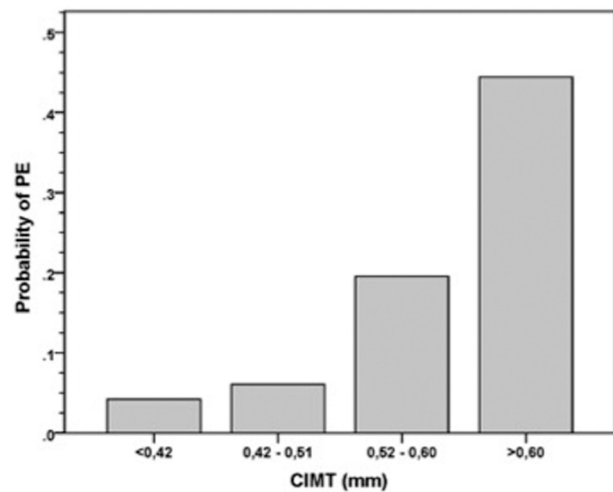


Figure 4: Bar graph representing the probability of the patient developing preeclampsia (PE) according to carotid intima media thickness (CIMT) values.

Discussion

Increased CIMT is an independent predictor of stroke and cardiovascular events [20–25]. Eikendal et al. have concluded in 3,067 adult patients younger than 45 years of age without symptomatic cardiovascular disease that CIMT may be a marker for cardiovascular risk [20]. Awad et al. in 89 patients between 20 and 80 years of age, 88% of patients with hypertension reported an increase in CIMT, 79.2% of those with diabetes mellitus and 75% of smokers [21]. Baldassarre et al. showed on sample of 4,482 patients that CIMT was associated with increased cardiovascular risk [22], which was also confirmed by Kokubo et al. in a study on 4,724 patients [24]. Utility of CIMT can predict vascular incident in asymptomatic patients [25]. In PE, the placental helix arteries fail to lose their musculoelastic layers, leading exclusively to decreased placental perfusion [26]. Milic et al. found that women who had PE had significantly higher CIMT than those who did not have PE, at the time of diagnosis and also in the first 10 years after giving birth [27]. The findings of our study showed that CIMT in pregnant women with PE was significantly higher than that in normotensive pregnant women, as has been similarly demonstrated in studies by other researchers [28–34]. Memari et al. were comparing 21 pregnant women with PE and 21 pregnant women without PE. They indicated that CIMT was significantly higher in carotid arteries [29]. Stergiotou et al. stated that early PE was characterized by increased carotid CIMT diameters, and arterial stiffness with no significant changes in inferior vena cava parameters as compared to normotensive pregnancies [30]. Late PE was characterized by significantly increased CIMT and lumen diameters as compared to controls while arterial stiffness, as expressed by distensibility, did not provide pronounced changes [30]. A significant decrease in inferior vena cava collapse index was also observed in late PE as compared to control [30]. Yuan et al. have concluded that changes in arterial internal diameter of carotids, wall thickness and arterial stiffening occur in PE, but this may reverse after giving birth [31]. Mori et al. have shown that pre-existing hypertension is a factor leading to an increase in CIMT, and concluded that endothelial dysfunction induced by enhanced oxidative stress is reversible in women with PE, and that vascular reactivity itself may be associated with earlier changes in hypertension [32]. In our study, sensitivity of PE predicting was 81% with a cutoff point of CIMT of 0.51 mm, while if CIMT ≥ 0.6 mm, the probability of patient develop preeclampsia is 44.4%. Magnusson et al. stated that estimated cardiovascular risk before pregnancy was associated with the onset of PE, and stated that already existing risk factors for cardiovascular disease may lead to the onset of PE

and cardiovascular disease [33]. This lead to the conclusion that optimal treatment of cardiovascular pathology was also of particular importance in women who plan their pregnancy [34]. Milic et al. concluded that atherosclerotic load is present in preeclamptic pregnancies and that it may be one of the mechanisms leading to this disease [34]. Radiologist should do CIMT measurements from the 20th week of pregnancy, because that is the moment when PE could appear. CIMT measurements should be considered as supportive method in addition to biochemical and ultrasound parameters, which could assist the gynecologist in screening and preventing PE. Our research limits the number of patients with PE enrolled, but nonetheless, the research offers useful information that CIMT could be a predictor of PE in a previously asymptomatic population, and indicates that atherosclerosis is also one of the etiologic factors for PE. Continued follow-up of these patients after delivery may be the basis for a new study in which the occurrence of PE could be associated with the onset of a cardiovascular incident.

Conclusions

An increase in CIMT was associated with the onset of PE. CIMT values were significantly higher in patients who develop PE. Early identification of high-risk patients in prevention of PE is imperative in the work of gynecologists and CIMT may be additional marker, which will be with other biochemical and ultrasound parameters a part of the mosaic that could predict the occurrence of PE.

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