https://doi.org/10.30702/ujcvs/22.30(03)/DK032-2934
UDC 618.3-005:618.173-008.1

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Intima-Media Thickness in Women with the History of Hypertensive Disorders of Pregnancy as a Risk Marker of the Occurrence of Cardiovascular Pathology in Advanced Reproductive and Perimenopausal Age

Abstract. Over the past twenty years, it has been proven that a history of preeclampsia entails a 4-fold risk of hypertension, coronary heart disease, stroke, type 2 diabetes, metabolic syndrome in the affected women at the age of 50-55 years. Evaluation of intima-media thickness (IMT) has diagnostic value for the assessment of remodeling and atherosclerotic vascular lesions and practical importance as a predictor of vascular accidents in patients with hypertension and atherosclerosis.

The aim. To evaluate the IMT as an integrative biomarker of the occurrence of cardiovascular pathology in women with hypertensive disorders of pregnancy in their advanced reproductive age and in perimenopausal age.

Materials and methods. We studied 51 women at the age of 48-55 years with the history of severe preeclampsia. The women were asked to fill out a questionnaire in which they indicated the presence of a diagnosis of hypertension, angina pectoris at the time of filling the questionnaire. The diagnosis of hypertension and angina attacks as well as other descriptions of the disease were taken away from the results of the women's questionnaire. The investigators were not given copies of medical records. The control group consisted of 20 women aged 48-55 who had no history of preeclampsia or any other hypertensive disorders of pregnancy. Ultrasound imaging of the carotid arteries was performed according to the recommendations of the American Society of Echocardiography 2020 in women of both groups using SonoAce-8000 Ex scanner (Medison, South Korea) with a linear sensor UST-5524 with a frequency of 7 MHz. IMT less than 0.7 mm was taken as a normal value for women.

Results. It was revealed that almost every fourth woman at the age of 48-55 with the history of preeclampsia had signs of early angina attacks, and 30% suffered from hypertension. A threatening fact is that almost 6% of women at the age of 48-55 had the history of vascular thrombosis which is a manifestation of early atherosclerotic vascular lesions in the group of women with gestational hypertensive disorders. It is noteworthy that 21 (41.2%) women with the history of severe preeclampsia felt healthy and did not have any complaints. Importantly, among the women surveyed who had no health complaints, 66.6% (14 of 21) had IMT 0.85±0.01 mm. This accounts for about one third (27.4%) among 51 patients. This category of women is at high risk of developing cardiovascular complications in the future and require further monitoring and detailed examination.

Thrombotic complications (dynamic bowel obstruction, mesenteric vascular thrombosis) were observed in 3 (5.9 %) women at the age of 48-55 with the history of severe preeclampsia.

C**onclusions**. Examinations of women with the history of preeclampsia revealed that women at the age of 48-55 had increased IMT. It should be noted that increased IMT was found both in women with cardiovascular pathology (hypertension, thrombosis, angina attacks) and in asymptomatic patients. Taking into account that increased IMT is one of the characteristics of target organ damage in patients with hypertension and the marker of cardiovascular events in asymptomatic patients, it is important to include this examination in follow-up for women with the history of severe preeclampsia in order to avoid the development of early severe cardiovascular pathologies.

Keywords: *preeclampsia, stroke, angina attacks, ultrasound examination, carotid artery, dynamic intestinal obstruction, mesenteric vascular thrombosis, anticoagulant therapy.*

Background. Today it is known that a significant number of people who develop serious cardiovascular diseases (CVD) and their complications did not have traditional risk factors [1, 2, 3]. Thus, an analysis of 136,905 hospitalized patients with coronary heart disease (CHD) in the United States found that 77% of them had low-density lipoprotein level not exceeding the target level of 130 mg/dL [4]. Such data indicate the need to find more effective indicators that can be used to stratify risk, quantify the severity of the pathology and predict further consequences. There are particular value markers of risk stratification in the general population, especially in patients who were initially considered healthy. It is considered that young age (<50 years) corresponds to the category of low risk.

A twofold or even threefold increase in mortality between the ages of 24 and 44 was mentioned due to the problem of "young heart attacks", which confirms the above assumption that the existing risk stratification scales "miss" many patients initially classified as low-risk. Well-known models for determining cardiovascular risk do not include a number of new non-traditional risk factors, including such an indicator as the intima-media thickness (IMT) of the carotid arteries (CA), and therefore the prognostic and diagnostic value of such models for more accurate risk stratification is reduced, which affects patient management tactics.

On the other hand, it is known that the history of preeclampsia in a woman causes a 4-fold risk of hypertension, CHD, stroke, type 2 diabetes, metabolic syndrome at the age of 48-55 [5, 6].

Ultrasound signs of thickening of arterial intima-media, determined by ultrasound examination of CA in B-mode, were included in European guidelines for the prevention, diagnosis and treatment of hypertension as one of the characteristics of target organ damages [5, 6, 7, 8]. The Mannheim IMT Consensus recommended IMT assessment for the initial detection of CVD risk in asymptomatic patients at intermediate risk, in the setting of two or more risk factors, in patients with metabolic syndrome, with a family history of premature CHD, or with a known coronary artery calcium score of zero [9]. The Mannheim definition of plaque was adopted by the 2021 ESC Guidelines on CVD prevention in clinical practice as possible cardiovascular risk modifier (Class II-b) [10]. A carotid IMT value above 0.7 mm in women, according to American Society of Echocardiography, should be considered abnormal [9].

According to the results of large studies (ARIC, Cardiovascular Health Study, Rotterdam Study [7, 8], etc.), an increase in IMT is associated with an increase in cardiovascular pathology, and this indicator itself is an independent risk factor for transient myocardial infarction, transient ischemic attacks. In epidemiological studies, increased IMT values in asymptomatic individuals indicate higher risk of stroke, myocardial infarction, or cardiovascular mortality [7]. The identification of carotid plaque even enhances this risk [7].

It is known that structural changes in the tunica media of the carotid artery, i.e. increase in IMT of the carotid arteries, are directly dependent on the level of increased endothelin in plasma of patients with hypertension, which confirms the role of endothelial dysfunction in the formation and progression of remodeling processes in blood stream and vessels [7, 8].

There is a close link between the increase in IMT and the risk of cardiac and cerebrovascular complications, especially in the presence of hypertension. Thus, according to the results of the Rotterdam study [7], IMT in the range of normal values (0.75-0.91 mm) is accompanied by a 4.8-fold increase in the relative risk of developing the first stroke. The ARIC study found a 4.3-fold increase in the incidence of CHD in men and a 19.5-fold increase in women with an increase in IMT in the range of 0.6-1 mm [7]. The study showed that there were 42 of 142 patients without signs of atherosclerotic disease, but with two risk factors, such as family history of CVD, hypertension, dyslipidemia, diabetes, overweight, smoking, low physical activity, increased IMT and atherosclerotic plaques were detected in 29.5% of cases. In other words, the high prognostic significance of the increase in IMT (often observed in asymptomatic patients) should determine the high need for CA ultrasound.

Measurement of carotid IMT with B-mode ultrasound is a noninvasive, sensitive and reproducible technique for identifying and quantifying subclinical vascular disease and for evaluating CVD risk. Evaluation of carotid IMT is useful for early diagnosis and prevention of possible disor-

ders, because people with carotid artery disease might not have any symptoms of the condition. Sometimes transient ischemic attack or stroke is the first sign that the person has carotid artery disease [4, 6, 7, 8, 9, 11].

Therefore, evaluation of IMT has diagnostic value for assessing the features of remodeling and atherosclerotic vascular lesions and its practical importance lies in prediction of vascular accidents in patients with hypertension and atherosclerosis.

At this stage of our study, we plan to find out the link between the presence of severe preeclampsia (hypertensive disorder in pregnancy with negative impact on the cardiovascular system in future), carotid IMT and the development of cardiovascular pathology at the age of 48-55 years (advanced reproductive and perimenopausal age).

The aim. To evaluate the carotid IMT as an integrative biomarker of the occurrence of cardiovascular pathology in women with a history of hypertensive disorders of pregnancy in their advanced reproductive and perimenopausal age.

Study design. We engaged 51 women at the age of 48-55 years with the history of severe preeclampsia. The women were asked to fill out a questionnaire in which they indicated the presence of a diagnosis of hypertension, angina attacks at the time of filling the questionnaire.

Questionnaire

1. How many pregnancies have you had?
2. Did you have preeclampsia during pregnancy? (Yes/No)
3. Preeclampsia was before 32 weeks? (Yes/No)
4. Preeclampsia was after 36 weeks? (Yes/No)
5. What stage of preeclampsia did you have? (Mild/Severe)
6. How quickly did your return to normal condition after delivery? (Immediately after delivery/After 2 days/After a week)
7. How quickly blood pressure returned to normal after delivery? (Immediately after delivery/After 2 days/After a week)
8. Do you currently suffer from hypertension? (Yes/No)
9. How long did you suffer from hypertension after delivery?
10. Do you currently suffer from angina attacks? (Yes/No)
11. When did your angina attacks started after delivery?
12. Have you ever had venous or arterial thrombosis after a complicated pregnancy? (if Yes, please specify)
13. What treatment are you currently receiving?

The diagnosis of hypertension and angina attacks, as well as other descriptions of the disease, were taken away from the results of the women's questionnaire. The study group members didn't give the investigators any medical records.

The control group included 20 healthy women aged 48-55 who had no history of preeclampsia.

CA ultrasound was performed in a supine position using SonoAce-8000 Ex scanner (Medison, South Korea) with a linear sensor UST-5524 with a frequency of 7 MHz. The study was performed according to standard methods in B-mode according the recommendations of the American Society of Echocardiography 2020 [9]. Common carotid artery, extracranial segments of internal carotid artery and external carotid artery were examined. IMT values less than 0.7 mm were taken as the norm [6, 9].

The research was carried out in accordance with the ethical norms of research with informed consent for every procedure.

Results and discussion. It was revealed that almost every fourth woman at the age of 48-55 with the history of preeclampsia had signs of early CHD, and 29.4% suffered from hypertension. The dangerous fact is that 5.9% of women at the age of 48-55 already had vascular thrombosis, which is a manifestation of early atherosclerotic vascular lesions in the group of women with gestational hypertensive disorders. The data obtained revealed that the history of preeclampsia is a risk factor for CVD at the age of 48-55 (Table 1).

It is worth noting that 21 (41.2%) women with the history of severe preeclampsia felt healthy and did not have any complaints.

Taking into account the above-mentioned facts, we determined the carotid IMT in 51 women at the age of 48-55 with the history of severe preeclampsia (Table 2).

Table 1

Data about cardiovascular diseases in women with the history of preeclampsia

Parameter	Number of women, abs. (%)
Presence of hypertension	15 (29.4)
Presence of angina attacks	12 (23.5)
History of thrombotic complications	3 (5.9)
Women without complaints	21 (41.2)

Table 2

Data of the IMT in examined women

Parameter	Number of women, abs. (%)	IMT, mm
Women with hypertension	15 (29.4)	0.89±0.01*
Women with angina attacks	12 (23.5)	0.91±0.01*
Women with the history of thrombosis	3 (5.9)	0.99±0.01*
Women without complaints	14 (27.4) 7 (13.7)	0.85±0.01* 0.69±0.01
Control group	20	0.64±0.03

* Significance of the difference with the control group.

All the examined women with the history of preeclampsia, who were diagnosed with cardiovascular disease (Table 2), had an intima-media thickening.

It must be emphasized that among women of preeclampsia group who had no health complaints, 66.6% (14 of 21) had intima-media thickening (0.85±0.01 mm).

Increased IMT was revealed in 27.4% of all the women of preeclampsia group, and these women were advised to undergo strict cardiac follow-up in order to prevent cardiovascular events in future. We revealed presence of hypertension and angina attacks totally in 50% in women from preeclampsia group: 12 (23.5%) women had angina attacks, 15 (29.4%) had hypertension.

Also, it should be noted that 1 woman (2%) from preeclampsia group suffered from dynamic intestinal obstruction at the age of 52 which was treated conservatively at a surgery clinic, and 2 (3.9%) women from this group suffered from mesenteric vascular thrombosis, which required bowel resection and long-term treatment with anticoagulants. Thus, 5.9% women of preeclampsia group had thrombotic complications, and all these women had the history of severe preeclampsia.

It is worth saying that no additional thrombosis triggers were revealed in these women (e.g. CVD, diabetes mellitus, autoimmune disease, such as antiphospholipid syndrome, systemic lupus erythematosus, systemic scleroderma). At the time of thrombosis manifestation they had no complaints induced by possible cardiovascular pathology. All of them took novel oral anticoagulants at the time of our study.

An important finding was that no atherosclerotic plaques were found among all the examined women at the stage of the examination.

Conclusions. Ultrasonic carotid IMT measurements may be considered as a marker for refining CVD risk assessment in asymptomatic patients. IMT measurement allows to detect precisely subclinical CVD and evaluate the group of patients with significant increased risk of CVD. Our study of women with the history of preeclampsia revealed that those women in advanced reproductive and early menopause age (48-55 years) had a carotid intima-media thickening, sometimes without any clinical presentation.

It should be noted that the increased carotid IMT was found in women with CVD (hypertension, thrombosis, angina attacks), and in 14 (66.6%) asymptomatic patients.

Importantly, women with clinical manifestations of mesenteric vascular disease had no complaints or any history of CVD, diabetes, or autoimmune disease at the time of thrombosis event manifestation.

Based on the results of our research we propose carotid IMT measurement as a component for the follow-up for women with the history of preeclampsia. The background for this recommendation is that IMT is one of the characteristics of target organ damage in patients with hypertension and the risk of cardiovascular complications in asymptomatic patients. We consider the continuation of the study in women with the history of hypertensive disorders of pregnancy, especially an early severe preeclampsia in order to prevent fatal or health threatening cardiovascular events in this cohort. This study would allow to determine timely and comprehensive measures in the follow-up for those women to choose the especially valuable markers, which could demonstrate the correlation between clinical presentation, stage, degree of cardiovascular pathology and IMT or other evidence-based biomarkers.

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Показник товщини інтими каротидних судин у жінок з гіпертензивними ускладненнями вагітності в анамнезі як маркер ризику виникнення серцево-судинної патології в пізньому репродуктивному та перименопаузальному віці

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Резюме

Вступ. Відомим є факт, що прееклампсія в анамнезі у жінки збільшує в 4 рази ризик виникнення гіпертонічної хвороби, ішемічної хвороби серця, інсульту, цукрового діабету 2-го типу, метаболічного синдрому у віці 48–55 років. Ультразвукові ознаки потовщення стінки артерій, що визначаються за допомогою ультразвукового дослідження каротидних артерій у В-режимі, увійшли в європейські рекомендації щодо профілактики, діагностики та лікування артеріальної гіпертензії як одна з характеристик ураження органів-мішеней.

Мета – оцінити товщину комплексу інтима-медіа судин як інтегративного біомаркера розвитку серцево-судинної патології в жінок з гіпертонічними розладами під час вагітності в пізньому репродуктивному та в перименопаузальному віці.

Матеріали та методи. Було обстежено 51 жінку віком 48–55 років, які в анамнезі мали важку прееклампсію. Жінкам було запропоновано заповнити анкету, в якій вони зазначили наявність діагнозу артеріальна гіпертензія, стенокардія, тромбозів в анамнезі. Ультразвукове дослідження сонних артерій виконували на апараті «SonoAce-8000 Ex» (Medison, Південна Корея) з лінійним датчиком UST-5524 з частотою 7 МГц згідно з рекомендаціями Американської асоціації лікарів ультразвукової діагностики 2020. За норму приймали значення товщини інтима-медіа менше ніж 0,7 мм.

Результати. Майже кожна четверта жінка у віці 48–55 років, з прееклампсією в анамнезі, відзначала напади стенокардії, а 30 % страждали на артеріальну гіпертензію. Загрозливим є той факт, що майже 6 % жінок віком 48–55 років вже мали тромбози судин, що є проявом раннього атеросклеротичного ураження судин у групі жінок з гестаційними гіпертензивними розладами. Усі обстежені жінки з прееклампсією в анамнезі, в яких було діагностовано серцево-судинну патологію, мали потовщення комплексу інтими-медіа. Важливо, що серед опитаних жінок, які не скаржилися на здоров'я, 66,6 % (14 жінок з 21), мали потовщення інтими-медіа (0,85 + 0,01 мм). Це становить майже 1/3 (27,4 %) серед усіх 51 обстежених. Серед обстежених нами жінок з важкою прееклампсією в анамнезі тромботичні ускладнення спостерігались у 3 (5,9 %) жінок віком 48–54 роки (а саме динамічна кишкова непрохідність і тромбоз мезентеріальних судин).

Висновки. Проведені дослідження жінок з прееклампсією в анамнезі довели, що жінки в пізньому репродуктивному віці та в період ранньої менопаузи (48–55 років) мали потовщення комплексу інтими-медіа.

Слід зауважити, що потовщення стінки каротидних артерій діагностували в жінок із серцево-судинною патологією (артеріальна гіпертензія, тромбози, стенокардія), а також у 14 (66,6 %) із 21 безсимптомних пацієнток.

Важливим є той факт, що жінки з клінічними проявами ураження мезентеріальних судин не мали жодних скарг або будь-якого серцево-судинного захворювання, цукрового діабету, аутоімунного захворювання в анамнезі.

На даному етапі дослідження серед обстежених жінок не було виявлено атеросклеротичних бляшок у каротидних судинах.

З огляду на те що ультразвукові ознаки потовщення стінки артерій є однією з характеристик ураження органів-мішеней у пацієнток з артеріальною гіпертензією та ризиком виникнення серцево-судинних ускладнень у безсимптомних пацієнток, важливим є проведення такого дослідження в жінок, які мали в анамнезі прееклампсію важкого ступеня з метою своєчасної діагностики патології серця і судин.

Подальші дослідження будуть спрямовані на виявлення корелятивної залежності між даними об'єктивного статусу пацієнтки, стадією та ступенем серцево-судинної патології та вираженістю товщини інтими-медіа.

***Ключові слова**: прееклампсія, інсульт, напади стенокардії, ультразвукове дослідження, каротидні артерії, динамічна непрохідність кишківника, тромбоз мезентеріальних судин, антикоагулянтна терапія.*

Стаття надійшла в редакцію / Received: 08.06.2022
Після доопрацювання / Revised: 09.09.2022
Прийнято до друку / Accepted: 23.09.2022