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Hypertension in women with pathologic menopause: definition and optimization of cardiovascular risk

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Objective — to determine the cardiovascular risk (CVR) in women with essential hypertension (EH) on the background of postsurgical or early physiological menopause and its possible correction due to hormone replacement therapy (HRT), that are prescribed to prevent postcastration menopausal symptoms.

Materials and methods. The study involved 112 women with essential hypertension (EH), II stage, grade 1—2, the average age (46.14 ± 1.60) years, formed 3 groups: 1 group with EH and postsurgical menopause which was not prescribed HRT; 2 group with EH and postsurgical menopause which prescribed lowest combined HRT; 3 group with EH and early physiological menopause. After a complex examination all patients underwent determine CVR using a SCORE (standard scale), SCOREHDL, SCOREBMI, SCORE with vascular ultrasound and scales PROCAM, FRAMINGHAM, DRS, IRIS.

Results and discussion. It is determined that calculation CVR by SCORE scale with using ultrasound of the carotid arteries improves detection of very high CVR to 83.8 % in 1 group, to 5.4 % in 2 group and to 13.1 % in 3 group. Determination of atherosclerotic plaques by ultrasound of carotid arteries in 5.4 % in 2 group forcing to cancel of HRT and the transition to the use of adaptive non-hormonal drugs. Calculation of the cardiometabolic risk by DRS and IRIS-II in all groups established high risk of developing and further progression type 2 diabetes with maximum in 1 group.

Conclusions. Hypertension in the background postsurgical and early physiological menopause without HRT is associated with a very high cardiovascular and cardiometabolic risk. Prescription of HRT can prevent as CVR and the development of diabetes.

Key words:
essential hypertension, postsurgical menopause, hormone replacement therapy, cardiovascular risk.

КОНТАКТНА ІНФОРМАЦІЯ

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Interest in the issue of gender differences in risk factors for cardiovascular disease (CVD) attracts the attention of the medical community. It is known that women of child-bearing period, in contrast to men have lower risk of cardiovascular events. However, after menopause the possibility of developing cardiovascular disease, including coronary artery disease significantly increased and sometimes exceeding subsequently such men [5, 6]. Significant increase in cardiovascular risk in postmenopausal women due to complex effects on the body of a number of external and internal risk factors. Some of these factors can not be modified (age, sex, heredity), while others can be modified in the primary prevention of CVD events [2]. Furthermore, menopause is considered as a risk factor, which is due to the progressive reduction of the estrogen effect on the cardiovascular system. This leads to redistribution of fat, and various metabolic, hemodynamic and inflammatory changes and direct effects of estrogen deficiency in the vessel wall. Risk factors of CVD has gender characteristics in a different periods

of life [1, 3, 7]. It is known that endogenous estrogens exercise pronounced antiatherogenic effects on blood lipid profile in premenopausal women, preventing the formation of atherosclerotic plaques.

However, after menopause, estrogen levels decline it is a triggering factor of many metabolic disorders (dyslipidemia, insulin resistance, visceral obesity, etc.), united by the term «menopausal metabolic syndrome». Woman's age when menopause begins, closely linked to the subsequent prognosis of CVD. There is evidence that early menopause and the surgical menopause increase the risk of coronary heart disease — in 3 and 7 times respectively [10]. Of surgical menopause in itself is an independent risk factor for cardiovascular disease and promotes more rapid manifestation of other risk factors [4]. At present, there are few studies that suggest a possible positive effect of hormone replacement therapy (HRT), which is intended to improve the flow of post surgical climacteric syndrome [8, 9, 12]. Categorical warning against the use of HRT in the treatment of cardiovascular disease in menopausal women, formed after the results of research WHI and HERS gradually wither away as soon, to be replaced on a balanced consideration of the positive effects of HRT in measures of primary prevention within the «therapeutic window», namely in women perimenopause at age 50—55 years [13, 15]. Recent results of the problem outlined in multidisciplinary document that is global consensus on hormone therapy in menopause (Global Consensus Statement on Menopausal Hormone Therapy, 2013) and practical guidance in respect of menopause (A Practitioner's Toolkit for Managing the Menopause, 2014), which is the position International Society for menopause and agreed with international societies and associations [11]. However, specific design regarding cardiac evaluation prospects of HRT in the primary prevention of cardiovascular risk in patients of reproductive age after hysterovarioectomy are isolated and sometimes controversial, which serve to the basis of the study.

The **aim** was to compare the cardiovascular risk calculated according to standard scales in women with GC on the background of physiological and postsurgical menopause and to assessment of its correction by hormone replacement therapy intended to prevent menopausal postcastration symtoms.

Materials and methods

In the Dyslipidaemia Department of National Scientific Center «M.D. Strazhesko Institute of Cardiology», had examined 112 women with essential arterial hypertension (EH), II stage, 1—2 degree, the average age was (46.14 ± 1.60) years, of which formed 3 groups test. The first group included 37 patients with EH II stage (average age (45.70 ± ± 1.45) years) and postsurgical menopause, formed after the operation in the reproductive age, patients are not prescribed HRT therapy in the postoperative period. The second group included 37 patients which had EH, II stage (average age (44.90 ± 1.82) years) and postsurgical menopause. To eliminate menopause symptoms they were intended lowest combined HRT containing estradiol 1 and 5 mg didrohesteron. The third group consisted of 38 patients with EH, II stage (average age (47.83 ± 1.70) years) and physiological menopause, HRT they were not intended. It should be noted that the third group of patients at the time of physiological menopause had the average age of the population age younger than the average age of menopause in Ukraine, which is 48.7 years, and because the classification of the European Congress on Menopause, 1999 this state has to be attributed to an early menopause (40—45 years), which was caused by the need comparability analyzed age groups. The duration of menopause in all groups was ranged from 2 to 5 years. History hypertension mainly coincides with the term of menopause. Exclusion criteria were the presence of subjective and objective data of coronary heart disease at the time of inclusion in the survey.

The study included determination of lipid content of total cholesterol, triglycerides (TG), high density lipoproteins (HDL) and low-density lipoprotein (LDL). Levels of total cholesterol, TG, HDL determined in venous blood serum enzymatic method on automatic analyzer firm «BioSystem», Spain, in mmol/l. Factions LDL cholesterol calculated by the Friedwald formula. All patients carried determining glycemic status (fasting glucose, fasting insulin level, determining insulin sensitivity by HOMA index, glycemic profile analysis). Insulin resistance diagnosed with HOMA index > 2.77.

All the patients to verify the diagnosis of coronary artery disease was suggested conducting stress test by standard protocol. The thickness of intima-media (TIM) common carotid artery (CCA) was calculated as the average of three measurements conducted at a distance of 1 cm from the bifurcation of the carotid artery on the back wall. TIM measured separately for the left and right CCA. According to Recommendations of the European Society of Hypertension (ESH, 2013) normal values considered the figure to 0.9 mm, and the value of 0.9 to 1.3 mm was evaluated as thickening TIM. Additional analysis of the presence of thickening TIM CCA examination held in groups according to gender and age norms by the American Society of Echocardiography Recommendations (2008). For gender and age limit was considered a thickness of TIM <

Table 1. The presence of atherosclerotic plaques in the carotid arteries in groups

Location of atherosclerotic plaques	The number of patients in groups (%)		
	Group 1 (n = 37)	Group 2 (n = 37)	Group 3 (n = 38)
The presence of plaque in left CA	27 (72.9)	2 (5.4)	2 (5.3)
The presence of plaque in the right CA	15 (40.5)	0 (0)	3 (7.9)
The presence of plaques in both CCA	11 (29.7)	0 (0)	0 (0)
Total patients with plaques in CA	31 (83.7)	2 (5.4)	5 (13.2)

< 0.77 mm for women aged 45—55 years. Plaque was diagnosed if TIM over 1.3 mm or if thickness of TIM was 50 % greater than the thickness of the surrounding areas. After a complex examination all patients underwent determine cardiovascular risk using a European scale: SCORE (standard scale), $SCORE_{HDL}$ (considering HDL cholesterol), $SCORE_{BMI}$ (including body mass index), PROCAM, FRAMINGHAM, DRS, IRIS II and at the scale of total cardiovascular risk as outlined in the Guidelines of the European Society of Hypertension (ESH, 2013) and the Association of Cardiologists of Ukraine (2012).

All scales SCORE calculated by a calculator on the website: http://www.heartscore.org/Pages/welcome.aspx; Scales PROCAM, FRAMINGHAM, DRS and IRIS II calculated on a calculator on the website: http://www.micardis.com/content/dam/internet/opu/micardis/com_EN/flash/CV_Risk_Calculator/riskcalculator.swf.

Statistical analysis of the results conducted by standard methods of variation statistics using a statistical software package Statistica 6.0. The results are shown as (M ± m), where M — the average rate, m — standard error. Statistical significance of differences between the indicators studied, determined using Student's t test.

Results and discussion

According to the results of definition SCORE in all three groups, the average risk level was within moderate in group 1 and in the border of moderate and low in 2 and 3 groups ($p < 0.01$). Similar patterns were observed after analysis $SCORE_{HDL}$ which also prevailed in 1 risk group, although it was within only moderate risk, is 1 % ≤ SCORE < < 5 % ($p < 0.01$). The exception only served calculating risk $SCORE_{BMI}$, which takes into account BMI patients and by definition is not found significant difference between group 1 and 3. However $SCORE_{BMI}$ 2 group was significantly lower ($p < 0.01$).

According to the definition of risk according to PROCAM scale of 1 group defined as low risk, and 2 and 3 groups of risk was defined as zero. According FRAMINGHAM scale in all groups identified as low risk (< 20 %), but found that the risk 1 group was significantly ($p < 0.01$) higher than the characteristics of 2 and 3 groups.

Unlike previous scales of overall cardiovascular risk according to the scale DRS in all patients identified at high risk (≥ 9 points) of type 2 diabetes in the next 10 years, which corresponds to the concept that menopause is a threat of manifest violations of carbohydrate metabolism . However, recorded that the parameters of 2 groups were significantly lower than in group 1 ($p < 0.01$), the possibility of developing diabetes against the backdrop of HRT was significantly lower. Given the presence of patients with type 2 diabetes in group 1 (11 patients) and group 2 (1 patient) were calculated risk of vascular complications of diabetes in the background using a scale IRIS-II. According to the results in 1 group risk is defined as high (≥ 70 points), while in group 2 it was low, indicating that despite the postsurgical menopause is not just the threat of type 2 diabetes, but and the conditions for the formation of its macrovascular and microvascular complications. The use of hormone replacement therapy in group 2 as actually reduced the risk of developing diabetes and its potential complications.

Thus, the analysis of risk scores indicated that the average cardiovascular risk in all groups was moderate and low in contrast to that the risk of type 2 diabetes was high, but 1 group also had a high risk of complications against the backdrop of manifest diabetes type 2 diabetes.

The next step in the analysis was the transfer of the distribution of patients according to the degree of cardiovascular risk in accordance with Recommendation of the European Society of Hypertension ESH (2013) and the Association of Cardiologists of Ukraine (2012). The results indicate, all patients were in the moderate range (all groups) and high risk only among the groups 1 and 2. Very high risk according to this analysis is not registered. Risk allocation testified that the maximum percentage of high-risk patients (29.7 %), which was formed by the detection of type 2 diabetes in 11 patients registered in 1 group; in group 2 it was only 2.7 %; in 3 group high-risk patients have not been identified. Moderate risk was detected in 70.3 % of 1 group and 97.3 % and 100 % in 2 and 3 groups respectively.

Table 2. The distribution of patients according to the degree of cardiovascular risk according to standard scales and SCORE with considering vascular ultrasound

Scale	Risk	The number of patients in groups (%)		
		Group 1 (n = 37)	Group 2 (n = 37)	Group 3 (n = 38)
SCORE	Low (SCORE < 1 %)	3 (8.1)	12 (32.4)	17 (44.7)
	Moderate (1 ≤ SCORE < 5 %)	34 (91.9)	25 (67.6)	21 (55.3)
	High (5 ≤ SCORE < 10 %)	0	0	0
	Very high (≥ 10 %)	0	0	0
SCOREHDL	Low (SCORE < 1 %)	2 (5.4)	8 (21.6)	11 (28.9)
	Moderate (1 ≤ SCORE < 5 %)	35 (94.6)	29 (78.4)	27 (71.1)
	High (5 ≤ SCORE < 10 %)	0	0	0
	Very high (≥ 10 %)	0	0	0
SCOREBMI	Low (SCORE < 1 %)	1 (2.7)	13 (35.1)	11 (28.9)
	Moderate (1 ≤ SCORE < 5 %)	33 (89.1)	24 (64.9)	25 (65.8)
	High (5 ≤ SCORE < 10 %)	3 (8.1)	0	2 (5.3)
	Very high (≥ 10 %)	0	0	0
SCORE + vascular ultrasound	Low (SCORE < 1 %)	0	13 (35.1)	15 (39.5)
	Moderate (1 ≤ SCORE < 5 %)	6 (16.2)	22 (59.5)	18 (47,4)
	High (5 ≤ SCORE < 10 %)	0	0	0
	Very high (≥ 10 %)	31 (83.8)	2 (5.4)	5 (13.1)

The final stage of evaluation of cardiovascular risk scales SCORE was his detailed distribution analysis given as an additional criterion adopted in the Guidelines ESC (2013) followed by atheromatous plaques determination to consider the results of the ultrasound of the carotid arteries. Given the data of 1 group in 31 patients (83.8 %) is defined as the risk is very high (table 1), as opposed to the much smaller number of similar patients in the last two groups, so at 2 group only in 2 patients (5.4 %) was very high risk and in 3 group with early physiological menopause — only in 5 patients (13.1 %). This demonstrates the significant prevalence of atherogenic potential of existing patients in 1 group with postsurgical menopause without HRT where rapid decrease estrogen levels in women of reproductive age was not timely compensated hormone replacement therapy. It should be noted that two of the patients 2 group which were taking HRT and in which the ultrasound revealed atheromatous plaque — hormone therapy was discontinued immediately under the supervision of a gynecologist, and the transition to non-hormonal drugs to eliminate postcastration symptoms.

Thus, analyzing the results of calculating cardiovascular risk according to standard scales, we can conclude that women with hypertension in the background as early physiological and postsurgical menopause increase risk of both cardiovascular and fatal cardiovascular vascular events. For optimal its calculation along with the standard scale SCORE and scale according Recommendations of arterial hypertension of the European Society of Hypertension ESH (2013) and the Association of Cardiologists of Ukraine (2012) should use the scale on $SCORE_{IMT}$ and, especially considering the scale SCORE with atheromatous plaques registration by ultrasound carotid vessels, since for the last two scales may predict the maximum cohort of high and very high risk of fatal cardiovascular events (table 2).

As a result of calculation cardiometabolic risk scales DRS and IRIS-II in women with hypertension in the background as early physiological and postsurgical menopause all patients with established high risk of developing type 2 diabetes, which confirms the current view of the fact that menopause is natural model of insulin resistance and always connected at high risk for serious violations of carbohydrate metabolism. However, the maximum risk profile were characterized patients of 1 group patients with hypertension on the background postsurgical menopause without HRT, the appropriate parameters 2 groups of patients who took HRT were significantly ($p < 0.01$) lower and more optimal state answered in carbohydrate metabolism, antidiabetic effects caused by estrogen treated patients of this group. Confirmation of the opinions received from the analysis further calculation cardiometabolic risk scale IRIS-II: in all 11 patients with diagnosed type 2 diabetes with EH without HRT in 1 group revealed a high risk of macro- and microvascular complications, while in group 2 a similar calculation testified to the presence of low-risk vascular complications of type 2 diabetes, that predicted a more favorable course of the disease.

Summarizing the above, we can conclude that the timely appointment of hormone replacement therapy to prevent postcastration symptoms in patients with EH and postsurgical menopause was associated with optimization of prognosis and should be

considered in measures of primary prevention. Determination of atherosclerotic plaques by ultrasound of carotid arteries should be an indicator of the need to discontinuation of HRT and the transition to the use of adaptive non-hormonal drugs.

Conclusions

1. Revealed increase risk of cardiovascular disease and fatal cardiovascular events in women with hypertension on the background of physiological and postsurgical early menopause. For optimal its calculation along with the standard scale SCORE and scale of risk for patients with hypertension according Recommendations of the European Society of Hypertension ESH (2013) and the Association of Cardiologists of Ukraine (2012) should use the scale on the basis of body mass index SCOREIMT and, especially considering the scale SCORE with atheromatous plaques registration by ultrasound carotid vessels to optimize the allocation of a cohort of very high risk.

2. It was determined that the results of the calculation cardiometabolic scales DRS risk in women with hypertension in the background as early physiological and postsurgical menopause recorded in all patients at high risk for type 2 diabetes, and it was highest in patients not taking HRT. In the same group 1 patients with manifest type 2 diabetes on a scale IRIS-II is a very high risk of macro- and microvascular complications, while in group 2 patients taking HRT, a similar calculation testified to the presence of low risk, that is predicted more favorable disease course.

3. It is established that the timely appointment of hormone replacement therapy to prevent postcastration symptoms in patients with essential hypertension and postsurgical menopause was associated with optimization of prognosis and should be considered in measures of primary prevention. Determination of atherosclerotic plaques by ultrasound of carotid arteries should be an indicator of the need to discontinuation of HRT and the transition to the use of adaptive non-hormonal drugs.

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Гіпертонія у жінок з патологічною менопаузою: визначення та оптимізація серцево-судинного ризику

Мета роботи — визначити серцево-судинний ризик (ССР) у жінок з гіпертонічною хворобою (ГХ) на тлі постхірургічної або ранньої фізіологічної менопаузи та його можливу корекцію гормональною замісною терапією (ГЗТ), яка призначалась для запобігання посткастраційних симптомів.

Матеріали та методи. У дослідженні взяли участь 112 жінок з ГХ II стадії, 1—2 ступеня, середнім віком (46,14 ± 1,60) року, які були розподілені за трьома групами: перша група з ГХ і постхірургічною менопаузою, яким не призначали ГЗТ; друга група з ГХ і постхірургічною менопаузою, яким призначали низькодозову комбіновану ГЗТ; третя група з ГХ і ранньою фізіологічною менопаузою. Після комплексного обстеження у всіх пацієнтів визначено ССР з використанням шкал SCORE (стандартна шкала), SCOREHDL, SCOREBMI, SCORE з урахуванням даних ультразвукового дослідження судин, а також шкал PROCAM, FRAMINGHAM, DRS, IRIS.

Результати та обговорення. Встановлено, що розрахунок ССР за шкалою SCORE з урахуванням даних ультразвукового дослідження судин поліпшує виявлення дуже високого ССР до 83,8 % у першій групі, 5,4 % у другій і до 13,1 % у третій. Визначення атеросклеротичних бляшок у сонних артеріях у 5,4 % у другій групі змусило відмінити ГЗТ і перейти до використання адаптивних негормональних препаратів. Розрахунок кардіометаболічного ризику за DRS і IRISII у всіх групах виявив високий ризик розвитку та подальшого прогресування цукрового діабету 2 типу з максимумом у першій групі.

Висновки. Гіпертонічна хвороба на тлі постхірургічної й ранньої фізіологічної менопаузи без ГЗТ пов'язана з виникненням дуже високого серцево-судинного і кардіометаболічного ризику. Призначення ГЗТ може запобігти як розвитку ССР, так і цукрового діабету.

Ключові слова: гіпертонічна хвороба, постхірургічна менопауза, гормональна замісна терапія, серцево-судинний ризик.

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Гипертония у женщин с патологической менопаузой: определение и оптимизация сердечно-сосудистого риска

Цель работы — определить сердечно-сосудистый риск (ССР) у женщин с гипертонической болезнью (ГБ) на фоне постхирургической или ранней физиологической менопаузы и его возможную коррекцию гормональной заместительной терапией (ГЗТ), которая предназначалась для предотвращения посткастрационных симптомов.

Материалы и методы. В исследовании приняли участие 112 женщин с гипертонической болезнью (ГБ) II стадии, 1—2 степени, средним возрастом (46,14 ± 1,60) года, которые были распределены на три группы: первая группа с ГБ и постхирургической менопаузой, которым не назначали ГЗТ; вторая группа с ГБ и постхирургической менопаузой, которым назначали низкодозовую комбинированную ГЗТ; третья группа с ГБ и ранней физиологической менопаузой. После комплексного обследования у всех пациентов определен ССР с использованием шкал SCORE (стандартная шкала), SCOREHDL, SCOREBMI, SCORE с учетом данных ультразвукового исследования сосудов, а также шкал PROCAM, FRAMINGHAM, DRS, IRIS.

Результаты и обсуждение. Установлено, что расчет ССР по шкале SCORE с учетом данных ультразвукового исследования сосудов улучшает выявление очень высокого ССР до 83,8 % в первой группе, 5,4 % во второй и до 13,1 % в третьей. Определение атеросклеротических бляшек в сонных артериях в 5,4 % во второй группе заставило отменить ГЗТ и перейти к использованию адаптивных негормональных препаратов. Расчет кардиометаболического риска по DRS и IRISII во всех группах выявил высокий риск развития и дальнейшего прогрессирования СД 2 типа с максимумом в первой группе.

Выводы. Гипертоническая болезнь на фоне постхирургической и ранней физиологической менопаузы без ГЗТ связана с возникновением очень высокого сердечно-сосудистого и кардиометаболического риска. Назначение ГЗТ может предотвратить развитие как ССР, так и сахарного диабета.

Ключевые слова: гипертоническая болезнь, постхирургическая менопауза, гормональная заместительная терапия, сердечно-сосудистый риск.