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Risk factors of complicated course of non-st elevation acute coronary syndrome in women

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Abstract
Introduction. Given the high morbidity and growth in recent decades of lethality from acute forms of CAD, especially among women, there are questions about the impact of risk factors on the adverse and complicated course of non-ST elevation ACS, among which one of the most important is the development of estrogen deficiency due to the onset of menopause.
Aim. Conduct a comparative analysis of the risk factors of the occurrence of an unfavorable course of non-ST elevation ACS in women, depending on the hormonal status.
Materials and methods. The study involved 112 women with non-ST elevation ACS aged 39 to 72 years (mean age 58.52 ± 0.99 years). They were divided into two groups: group A – 64 patients with estradiol level <80 pmol/L and LH / FSH index <1; group B – 48 patients with estradiol level >80 pmol/L and LH / FSH> 1. The features of the course were determined by comparing the basic clinical characteristics and anamnestic data at the time of hospitalization.
Results. In women with estrogen deficiency (A) in 1.3-1.5 times there is a higher prevalence of hypertension (82.81 ± 4.72%) and angina (79.69 ± 5.02%). In persons with a preserved hormonal balance (B) – diabetes (31.25 ± 5.15%), smoking (54.16 ± 7.19%) and professional hazards (89.58 ± 4.41%), a larger proportion of persons with atypical pain syndrome (47.92 ± 7.21%) and late hospitalization (58.33 ± 7.11%). Their course was more frequent with rhythm and conduction disorders (68.75 ± 6.69%), with recurrence of pain syndrome (35.42 ± 2.43%) and longer treatment. In group A, pulmonary edema was more common (68.75 ± 5.79%), 48.43 ± 6.24% of them were at high risk of in-hospital mortality (GRACE risk score), at three-fold higher risk of recurrent MI, at 5.7 higher risk of HF and twice higher – the chance of death.
Conclusions. In the group of women with estrogen deficiency with non-ST elevation ACS develops on the background of greater prevalence and duration of hypertension and angina, accompanied by a heavier and more unfavorable prognosis. In women with relatively preserved hormonal status, non-ST elevation ACS occurs on the background of a greater prevalence of smoking and the impact of professionally harmful labor, diabetes, which promote predominantly atypical symptoms and their late hospitalization, and more frequent development of life-threatening arrhythmias, recurrence of pain syndrome and prolongation of treatment.

Keywords: acute coronary syndrome, women, estrogen deficiency, clinical course, cardiovascular risk

1. Introduction

Over the past decades, the paradigm of the views on the risk of cardiovascular accidents in women has changed. It has been established that, in particular, myocardial infarction (MI) in females may occur on the average, and even at younger ages. This is due to an increase in the frequency and expressiveness of the most important risk factors among them: hypertension, smoking, dyslipidemia (DLP), obesity, etc., which adversely affect both the systemic arterial bed and the branched arterial net of ovaries. Until recently, the gender characteristics of coronary artery disease (CAD) remained underestimated. Therefore, current knowledge of the course and principles of treatment of various forms of CAD is mainly based on research results, in which the majorities (up to 70-85%) were men. The data, obtained in them, cannot always be extrapolated to patients with CAD due to features of its occurrence, clinical picture, prognosis, and necessary methods of intervention in women.

According to the Framingham Study, as the first manifestation of CAD, 65.0% of women reported angina pectoris, compared with 35.0% in men. At the same time, MI, as the first manifestation, predominantly occurs in men (correspondingly, 29.0% vs. 43.0%) [1]. In women, more often than in men, acute forms of CAD are presented by non-ST elevation acute coronary syndrome (non-ST elevation ACS) [2], which occurs much more often on the basis of non-occlusive coronary sclerosis (MINOCA) [2].

According to the GRACE registry, chest pain, which is the main symptom for most patients with MI, is much less common in women than atypical symptoms such as jaw pain, nausea [3]. Such features in women make some difficulties in timely diagnosis of this disease and increase the frequency of complications. In particular, the prognosis for females with CAD is worse than for males. In our time, the average hospital mortality rate for MI is 19.0% for women and 12.0% for men. The part of fatal cases during the first year after MI in the female population is 36.0%, which is 10.0% more than in males [4]. R.D. Keele and M. Driscoll (2010) found that among women the basic conditions for the occurrence of 10-year mortality from coronary heart disease are age 51-65 years, elevated blood pressure (125 - 151 mm Hg), inadequate control over the state of health and the key risk factors [5].

Despite the advent of a calendar menopause, women may have relatively preserved estrogen background, although, as a rule, estrogen deficiency is recorded. Therefore, there are modern hormonal criteria for the onset of menopause: lowering estradiol levels below 80 pmol/L = 21.79 pg/ml (hypoestrogenemia); a sharp increase in the level of follicle-stimulating hormone, with a decrease in the LH / FSH index <1; decrease in the index of estradiol / estrogen <1; relative hyperandrogenemia; low levels of inhibin B in ovaries; antimyler hormone and testosterone-estradiol binding globulin [6].

Aim

Conduct a comparative analysis of the risk factors of occurrence, features of the clinical course of non-ST elevation ACS in women of the peri- and post-menopausal period, depending on the hormonal status.

Materials and methods

The study included 112 women with non-ST elevation ACS aged 39 to 72 years (mean age 58.52 ± 0.99 years) who were hospitalized in an infarct department of the municipal city clinical hospital for emergency medical care in Lviv. The diagnosis was established on the basis of clinical and anamnestic data, laboratory and instrumental studies (ECG, coronary angiography (CAG)) according to the recommendations of the ESC working group for the management of non-ST elevation ACS [7], national recommendations – the Unified clinical protocol for medical care "non-ST elevation ACS (emergency, primary, secondary (specialized) medical aid) ", 2015, and the order of the Ministry of Healthcare of Ukraine dated 03.03.2016 № 164 "About approval and implementation of medical-technological documents of the standardization of medical care of non-ST elevation ACS"[8]. The following criteria for the selection of women with non-ST elevation ACS were the following signs of peri- and postmenopause: delayed, absent or disturbed menstrual cycle; disturbance of the balance of female sex hormones: LH / FSH <1, estradiol <21.79 pg/ml; neurovegetative manifestations of perimenopause (vasomotor, metabolic and psychoemotional) verified according to the Kupperman menopause index in the modification of E.V. Uvarova (MMI) – more than 12 points [6]. The levels of sex hormones in serum (estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) were determined by immunoassay. Modern endocrine criteria for climacteria are: low level of estradiol (<80 pmol/L = <21.79 pg/ml); high concentration of FSH and the ratio of LH to FSH <1 [6]. Depending on the hormonal status of all female patients, they were divided into groups A and B. Group A consisted of 64 women with non-ST elevation ACS aged 39-72 years (mean age 60.77 ± 1.16) with hormonal signs of postmenopause: estradiol level <80 pmol/L (21.79 pg/ml) and LH / FSH index <1. Group B included 48 female patients with non-ST elevation ACS aged 35 to 65 years (mean age 52.29 ± 1.63) with estradiol levels> 80 pmol/L (21.79 pg/ml) and a LH / FSH index >1.

To find out the features of the course, the main clinical characteristics and anamnestic data of patients at the time of hospitalization were analyzed: age, time from the beginning of symptoms to hospitalization, anamnestic data about the disease, and basic hemodynamic parameters at the time of hospitalization, class of acute heart failure proposed by Killip. Risk of mortality was stratified by calculating the GRACE index using a standard calculator, taking into account all the necessary factors.

The study did not include women of the fertile age and the elderly; patients with severe heart failure; carried over in the past aortic coronary artery bypass graft surgery or endovascular coronary intervention.

The statistical processing of the results was conducted using the program package for statistical analysis - STATISTICA (version 10.0). In the case of a normal distribution, the data is presented in the form of an average value and standard deviation (M ± m). The reliability of the differences between groups on a quantitative basis was estimated using the t-criterion of Student (in the case of normal distribution) and the Wilcoxon-Mann-Whitney test (in the case of distributions other than normal). Differences were considered reliable at a level of significance >95% (p <0.05) [9].

Results and discussion

The average age of women with relatively preserved hormonal background (group B) was 52.29 ± 1.63 years, which was 8.48 years less than among women with estrogen deficiency (group A). These data are consistent with the results of AACE (2011), according to which the average age of menopause in North America is approximately 51 years [10].

Table 1: Middle age and levels of sex hormones in Women with non-ST elevation ACS, depending on hormonal status.

Indexes	Group A (n=64)	Group B (n=48)
Mean age, years old	60.77±1.16*	52.29±1.63
Estradiol, pg/ml	17.24±1.29*	30.69±2.77
LH / FSH, units	0.65±0.03*	1.64±0.10

Note: * - p <0.05 - the difference between the indicators of groups A and B

The levels of estradiol in patients of group A were significantly lower in comparison with those in group B (17.24 ± 1.29 pg/ml (A) vs. 30.69 ± 2.77 pg/ml (B), p <0.01), which indicated the status of relative estrogen deficiency of persons in group A (Table 1). The average index of LH / FSH ratio was also significantly lower in patients of group A (0.65 ± 0.03 units (A) vs. 1.64 ± 0.10 units (B), p <0.01), which shows more pronounced dyshormonal changes in patients with estrogen deficiency (Table 1).

The prevalence of concomitant pathology and comorbid conditions were analyzed from anamnesis in patients of both groups. It turned out that in women with a preserved estrogen background (B) the prevalence of diabetes was reliably higher (31.25 ± 5.15% (B) vs. 18.75 ± 4.88% (A), p <0.05). These

patients also had reliably more professionally harmful working conditions (89.58 ± 4.41% (B) vs. 53.13 ± 6.24% (A), p <0.01) (Table 2). In the group of patients with preserved hormonal balance (B) more than half had a bad habit – smoking, which was almost 1.5 times more frequent than in patients with estrogen deficiency (group A) (54.16 ± 7.19% (B) vs. 37.50 ± 6.05% (A), p <0.05) (Table 2). Before the development of non-ST elevation ACS, 82.81 ± 4.72% of women with loss sexual function (A) had hypertension, which was significantly higher than in patients who had a practically preserved hormonal balance (62.50 ± 6.99%), p <0.05 (Table 2). These patients also had prolonged course of hypertension (13.15 ± 1.09 years (A)) compared with individuals in group B (10.24 ± 1.12 years), (p <0.05) (Table 3). Angina pectoris was recorded in anamnesis in three out of four (79.69 ± 5.02%) women with estrogen deficiency (A), which is 1.5 times reliably more than in women with relatively preserved background of sex hormones (B) (54.17 ± 7.19%).

Table 2: The prevalence of comorbidity and main risk factors in women with non-ST elevation ACS, depending on the type of hormonal status (%).

Indexes	Group A (n=64)	Group B (n=48)
MI in anamnesis	21.88±5.17	27.08±6.41
Obesity	29.68±5.71	29.17±6.56
Diabetes	18.75±4.88*	31.25±5.15
Hypertension	82.81±4.72*	62.50±6.99
Angina pectoris in anamnesis	79.69±5.02*	54.17±7.19
Heredity	46.87±6.23	41.67±7.12
Professional harm	53.13±6.24*	89.58±4.41
Smoking	37.50±6.05*	54.16±7.19

Note: * - p <0.05 - the difference between the indicators of groups A and B

Table 3: Average values of the main indicators of the clinical course of non-ST elevation ACS in women, depending on the hormonal status.

Factors	Group A (n=64)	Group B (n=48)
Hospitalization from the beginning of symtoms, hours	35.28±9.27*	69.36±7.44
Hypertension in anamnesis, years	13.15±1.09*	10.24±1.12
Angina pectoris in anamnesis, years	6.68±0.57	6.11±0.91
GRACE, points	136.13±5.00*	124.64±5.14
Risk of mortality	3.95±0.89	2.3±0.52
Annual mortality risk	9.38±1.39*	6.11±0.90
Duration of inpatient treatment, days	14.64 ± 0.60	16.00 ± 1.02

Note: * - p <0.05 - the difference between the indicators of groups A and B

An analysis of the time of hospitalization from the beginning of symptoms showed that patients with non-ST elevation ACS and relatively preserved estrogen background (group B) reliably later applied for help compared with women who had estrogen deficiency (A) (69.36 ± 7.44 hours (B) vs. 35.28 ± 9.27 hours (A), p <0.05) (Table 3). Delayed hospitalization in a profile hospital (> 24 hours) was more common among women with preserved hormonal balance (58.33 ± 7.11%) compared with women with loss hormonal background (39.06 ± 6.09%), apparently due to a significantly higher frequency of atypical pain in younger women (47.92 ± 7.21% (B) vs. 35.93 ± 6.93% (A), p <0.05) (Table 4). Our data agrees with the results of other researchers, which record the higher frequency of the atypical clinic, especially in young women [11]. This leads to difficulties in timely diagnosis, which is a cause of greater delay in the initiation of specialized treatment in connection with their late appeals to doctors [12].

Table 4: The prevalence of the main indicators of the clinical course of non-ST elevation ACS in women, depending on the type of hormonal status (%).

Indicators	Group A (n=64)	Group B (n=48)
Hospitalization >24 hours	39.06±6.09*	58.33±7.11
Atypical pain syndrome	35.93±6.93*	47.92±7.21
GRACE>140 points	48.43±6.24	37.50±6.98
Killip IV	4.68±2.64	4.16±2.88
Killip II-III	68.75±5.79*	50.00±7.21
Rhythm disorders	48.43±6.24*	68.75±6.69
Recurrences of pain syndrome	18.75±3.28*	35.42±2.43

Note: * - p <0.05 - the difference between the indicators of groups A and B

The course of non-ST elevation ACS in 68.75 ± 5.79% of patients with estrogen deficiency (A) was accompanied by signs of subclinical pulmonary edema or cardiac asthma (Killip II-III), which is 1.3 times reliably more than in patients with preserved endocrine function of female sex hormones (B) (Table 4). At the same time, women of group B were reliably 1.4 times more often reported about disorders of rhythm and conduction, as well as more frequent recurrences of angina pectoris (35.42 ± 2.43% vs. 18.75 ± 3.28%), which was probably the result of higher sympathetic disturbances on the basis of estrogen imbalance, which led to prolonged inpatient treatment (16.00 ± 1.02 days vs. 14.64 ± 0.60 days) (Table 3, 4).

We also conducted a comparative assessment of the risk of annual mortality of patients with non-ST elevation ACS using the GRACE scale in comparable groups. It turned out that the average values of this index were reliably higher in the group A (136.13 ± 5.00 points (A) vs. 124.64 ± 5.14 points (B), p

<0.05) (Table 3). Almost half of the patients in this group (48.43 ± 6.24%) had a high GRACE index (> 140 points). The average risk of hospital mortality without a significant difference predominated in patients of group A (3.95 ± 0.89% (A) vs. 2.3 ± 0.52% (B), p >0.05). At the same time, the estimated risk of annual mortality of these women reliably exceeded in 53% in women of group B (9.38 ± 1.39% (A) vs. 6.11 ± 0.90% (B), p <0.05) (Table 3).

We have conducted a comparative analysis of the chances of developing of non-ST elevation ACS and its unfavorable course in comparable groups. It turned out that the absence of the preserved hormonal background of female sex hormones in women of group A compared with patients in group B was accompanied by a higher risk of CV complications during the course of non-ST elevation ACS and unfavorable prognosis during the term of hospitalization, and after 6 months (Table 5). In particular, compared to patients in group B, patients in group A have a three-fold higher risk of developing a recurrent MI (OR = 3.00 ± 0.11, CI = 1.73-4.21), 5.7-fold higher risk of HF progression (OR = 5.74 ± 0.12, CI = 4.27-7.11), twice higher chances to die after 6 months (OR = 2.03 ± 0.21, CI = 0.69-3.32).

Table 5: Value of risk chances of developmetn of non-ST elevation ACS and its unfavorable course in women, depending on the hormonal status.

Indexes	Group A n=64		Group B n=48	
	OR±m	95% CI	OR±m	95% CI
Professional harm	0.14±0.56	0.01-0.26	7.37±0.25	3.93-10.81
Smoking	0.73±0.28	0.01-1.58	1.36±0.23	0.22-2.51
Hypertension	0.69±0.73	0.04-1.34	1.45±0.65	-0.02-2.91
Recurrent MI	3.00±0.11	1.73-4.21	0.34±0.14	-0.43-1.10
Progression of HF	5.74±0.12	4.27-7.11	0.18±0.115	-0.47-0.82
Death after 6 months	2.03±0.21,	0.69-3.32	0.50±0.26	-0.21-1.21

Instead, in women with a preserved hormonal balance, professional harmful work in 7.3 times (OR = 7.37 ± 0.33, CI = 3.93-10.81), smoking in 1.4 times (OR = 1.36 ± 0.23, CI = 0.22-2.51), hypertension in 1.5 times (OR = 1.45 ± 0.65, CI = 0.2-2.91) increase the risk of development of non-ST elevation ACS and its unfavorable course. The findings are consistent with the results of the WISE study, which proved that an unfavorable CV prognosis is also associated with elevated levels of systolic and diastolic blood pressure in women [13].

Conclusions

1. In women with estrogen deficiency (group A), the prevalence of hypertension (82.81 ± 4.72%) and angina pectoris (79.69 ± 5.02%) is 1.3-1.5 times higher before the development of non-ST elevation ACS. The duration of the course of hypertension is significantly higher (13.15 ± 1.09 years (A) vs. 10.24 ± 1.12 years (B), p <0.05).
2. Compared with women with a deficiency of sex hormones (group A), in women with a preserved hormonal balance (group B), non-ST elevation ACS develope on the background of significantly higher prevalence of diabetes (31.25 ± 5.15%), smoking (54.16 ± 7.19 %) and professionally harmful work (89.58 ± 4.41%), which is probably the reason for a significantly greater proportion of people with atypical pain syndrome during the period of the manifestation of non-ST elevation ACS (47.92 ± 7.21% (B) vs. 35.93 ± 6.93% (A), p <0.05) and, accordingly, their late (> 24 hours) hospitalization in a profile hospital (58.33 ± 7.11% (B) vs. 39.06 ± 6.09% (A)), p <0.05), more frequent recurrences of the pain syndrome (35.42 ± 2.43% vs. 18.75 ± 3.28%), which were probably the result of higher sympathetic disturbances on the basis of estrogen imbalance, which led to prolonged inpatient treatment (16.00 ± 1.02 days versus 14.64 ± 0.60 days). Professional harmful work in 7.3 times (OR = 7.37 ± 0.33, CI = 3.93-10.81), smoking - 1.4 times (OR = 1.36 ± 0.23, CI = 0.22-2.51), hypertension in 1,5 times (OR = 1.45 ± 0.65, CI = 0.2-2.91) increase the risk of the development of non-ST elevation ACS and its unfavorable course in women with relatively preserved hormonal background (group B).
3. Compared with women with relatively preserved endocrine function of female sex hormones and non-ST elevation ACS (Group B), in women with an estrogen deficiency (group A) lung edema or cardiac asthma is in 1.3 times significantly more common (Killip II-III, 68.75 ± 5.79%); the high risk of hospitalized mortality (the GRACE scale > 140 points, 48.43 ± 6.24%) is recorded in almost one-half of the cases, and the estimated risk of annual mortality is reliably higher (9.38 ± 1.39% (A) vs. 6.11 ± 0.90% (B), p <0.05). They have a three-fold higher risk of developing a recurrent MI (OR = 3.00 ± 0.11, CI = 1.73-4.21), in 5.7-fold higher risk of progression of HF (OR = 5.74 ± 0.12, CI = 4.27-7.11) and twice higher chances of death after 6 months (OR = 2.03 ± 0.21, CI = 0.69-3.32).

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