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RISK FACTORS FOR CORONARY HEART DISEASE IN MENOPAUSAL WOMEN ANNOTATION

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Abstract:

According to the literature review, it was revealed that after the onset of menopause, 70% of women develop cardiovascular diseases, and 30% develop osteoporosis. In postmenopausal women, a complex of symptoms of adverse changes with an increased risk of cardiovascular events is manifested. However, it remains unclear whether the presence of menopausal symptoms can actually predict the clinical events of cardiovascular disease (CVD) or is primarily due to associated risk factors for cardiovascular events. To date, no consensus has been reached on this issue. There are many proposed mechanisms that explain the role of endogenous estrogen as a protector of CVD. Consequently, cardiovascular diseases remain the main cause of morbidity and mortality in women in many countries, among people in the postmenopausal period, and it is quite possible that with an increase in the number of older people, they will remain the main risk factor for the development of cardiovascular diseases and mortality.

Keywords: *cardiovascular diseases, estrogens, cardioprotection, postmenopausal period, risk factors.*

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CASE REPORT:

The main cause of morbidity and mortality in the population worldwide is cardiovascular disease (CVD). In the structure of cardiovascular diseases, the most significant share is ischemic heart disease (IHD), which occupies one of the leading places among the causes of mortality in the adult population [1, 10]. According to the estimates of the World Health Organization (WHO), more than 17 million people die from CVD annually in the world, of which more than 7 million people die from IHD [1, 8].

Coronary heart disease (CHD) is the world's leading cause of death for men and women. According to the American Heart Association, over 15 million people have some form of the disease. CHD is a pathological process with the formation of atherosclerotic plaque in the blood vessels that supply the heart with oxygen and nutrients. In this case, the process can be both obstructive and non-obstructive. The complex process of atherosclerosis begins at an early age and is believed to begin with dysfunction of the endothelial cells that line the coronary arteries, which are no longer able to adequately regulate vascular tone using the signal of nitric oxide [4, 19]. Progressive infiltration of the vessel wall with cholesterol-bearing lipoprotein particles promotes the spread of the inflammatory response through cholesterol-laden macrophages "foam cells". Smooth muscle cells beneath the vessel wall proliferate and lead to vessel remodeling, which can ultimately lead to a narrowing of the vessel, obstructing blood flow. Myocardial infarction usually occurs when a blood clot is triggered by a rupture at the surface of the plaque - this deprives the heart muscle downstream of adequate blood flow and leads to cell death.

There are many factors that affect this condition. One of them is menopause, which is characterized by a change in the woman's life and the last menstrual period. Studies have shown that after the onset of menopause, 70% of women develop cardiovascular diseases, and 30% develop osteoporosis [22].

A number of researchers believe that middle age is not just a period when women experience hot flashes and other symptoms of menopause, but also when the risk of their cardiovascular complications increases, as changes in numerous clinical manifestations of their physical health occur [30]. Menopause signals the end of her reproductive life. This usually happens between 49 and 52 years old. By the age of 58, nearly 97% have menopause. Although this is a natural phenomenon, however, the physical and psychological changes that accompany menopause can be depressing for many women.

With the onset of menopause, there is a decline in the function of the ovaries, which produce less female sex hormones, namely estrogen and progesterone. Estrogen levels gradually decline over the years after menopause. Hormonal imbalance and concomitant menopause are responsible for many of its features [15, 26].

After the onset of menopause, the incidence of cardiovascular disease (CVD) increases dramatically [3, 13, 31, 41].

The prevalence of hot flushes and other menopausal symptoms, which reaches 80% in menopausal women, are influenced by various factors such as age, ethnicity, education, smoking, and mood [6, 33, 37]. More and more data indicate that menopausal symptoms are associated with risk factors for the development of ischemic heart disease of cardiovascular complications [5, 21, 42].

Women with menopausal symptoms show adverse changes with an increased risk of CVD [18]. However, it remains unclear whether the presence of menopausal symptoms can actually predict clinical CVD events or is primarily due to associated risk factors for cardiovascular events. To date, no consensus has been reached on this issue [34].

The presence of high blood levels of the male hormone (testosterone) and a high ratio of male to female type (estrogen) hormones are associated with a higher risk of developing cardiovascular diseases later in life. The risk of developing cardiovascular diseases in women is significantly lower than in men until women reach the age of 50, then the risk increases sharply after menopause. Researchers from the American College of Cardiology assessed the association of sex hormone levels with cardiovascular disease, coronary artery disease, and heart failure over a 12-year follow-up of 2834 postmenopausal women who were cardiovascular-free at baseline [17].

Considering that cardiovascular diseases remain the main cause of morbidity and mortality among women in many countries, among people over 50, and it is quite possible that with an increase in the number of older people, they will remain the main cause of morbidity and mortality [20, 27]. In this age group, there are more deaths of women from cardiovascular diseases (41.3%) than from the following seven causes

of death combined. The latest data from the American Heart Association (AHA) shows that only 46% of women are aware of this fact. Studies show that postmenopausal women have an increased risk of CHD with estrogen and progestogen therapy, while others warn that this risk is no longer present when women start hormone replacement therapy immediately after menopause [14, 35].

A high testosterone to estradiol ratio has been associated with an increased risk of CHD. High total testosterone was associated with an increased risk of cardiovascular complications such as coronary artery disease plus stroke events, while higher estradiol levels were associated with a lower risk of coronary heart disease. In addition, the risk of developing cardiovascular disease and coronary heart disease was approximately linear in the range of total testosterone, testosterone to estradiol, and estradiol levels, but there was a U-shaped relationship between testosterone to estradiol and a higher risk of heart failure. A number of researchers note that while sex hormone levels may be associated with future cardiovascular events, it is unclear which best intervention is to change sex hormone levels to reduce the risk. However, a sex hormone profile with higher levels of male hormones may identify a woman with a higher risk of cardiovascular disease, who may benefit from other risk reduction strategies [24].

In Brazil, the female population is more numerous and has a high life expectancy. Of the total of 195.2 million, 100.5 million (51.5%) are women. Females are not only more expressive, but they also belong to older age groups. Among the population over 30, women predominate, in contrast to men, who stand out among the younger strata of the population [14]. The increased risk of CHD in women over 50 years of age appears to be associated with menopause due to subsequent estrogen deprivation, as the cardioprotective benefits offered by estrogens gradually disappear during menopause [32]. However, the relationship between menopause and a risk factor for coronary heart disease is still unclear. The high prevalence of arterial hypertension, hyperglycemia, and endothelial dysfunction in postmenopausal women may be associated with obesity, not just menopause [9].

Hospital mortality from CHD is higher in women, since they have narrower coronary artery lumens and less collateral circulation than men, which can lead to increased ischemia, especially when activities require effort or stress [23]. Such data have generated great interest around the world, more and more studies are repeating this reality and trying to get closer to how men and women experience and feel their illness, with the search for ways to increase efficiency in the fight against diseases, and especially with coronary heart disease [23]. As a result of age-related cessation of follicular development or surgical removal of the ovaries, a sharp decrease in circulating estrogens, especially estradiol, follows. Depending on the individual characteristics of a woman, a decrease in the level of circulating estrogens is accompanied by numerous signs and symptoms of estrogen deficiency: vasomotor episodes, sleep disturbances, depression, metabolic imbalance, a decrease in bone mineral mass and a decrease in skin turgor [11]. The results of hormone replacement therapy have shown that it is an effective pharmacological approach to postmenopausal health [28]. However, most researchers are controversial about whether the cardioprotective value of estrogen administration in menopausal women is possible, the results obtained when testing this additional positive effect better defined prevention as a lifelong approach to women's health. But this does not apply to treatment for established heart conditions, such as heart failure.

Although the available evidence supports the cardioprotective effect of timely estrogen administration in postmenopausal women, definitive prospective evidence for a reduction in cardiac events remains to be seen. Without such definitive evidence, the inclusion of cardioprevention as a justification is not warranted. Rather, it is advisable to develop an approach to the management of postmenopausal women, based on patient education, lifestyle changes and treatment, in order to provide the possible additional value of cardioprotection without adding additional burden of unwanted side effects [2].

The first suggestions that estrogen is considered cardioprotective arose due to gender differences in the clinical picture of symptoms and cardiovascular events: angina pectoris and myocardial infarction appear about a decade earlier in men than in women [39]. Since cardiac events in women are usually accompanied by cessation of ovarian function (natural or induced menopause), it has been suggested that estrogen loss was causal and that the 10-year hiatus reflects the effects on the cardiovascular system due to loss of estrogen-secreting ovarian follicles [32]. Epidemiological studies have confirmed this idea [34].

There are many proposed mechanisms that explain the role of endogenous estrogen as a protector of cardiovascular disease (CVD). One of the proposed mechanisms is that the introduction of estrogens has a

known positive effect on the plasma lipid profile, anti-platelet and antioxidant effects [36]. Previous studies have shown that postmenopausal women have persistent hypertension, more vascular aging than premenopausal women [41], and estrogen improves endothelium-dependent vasodilation [20].

Estrogen and aromatase receptors are present in the endothelium of the human coronary artery [30]. Estrogen receptors have profound effects on muscle and insulin, both of which are required for vascular maintenance [16]. With abnormalities of the alpha estrogen receptor, cardiorespiratory diseases are more common. Aromatase abnormalities are less common, probably due to the need for aromatase during fertilization, and have been associated with early atherogenesis [20, 24]. It was shown that estradiol also inhibits the adhesion of monocytes to the vascular endothelium, which is a well-known stage in the development of atheroma and atherosclerosis [26]. It has now been proven that this process is mediated by sexual steroid-induced inhibition (more specifically, sialylation) of nerve cell adhesion molecules (nCAMs), which are one of the early mechanisms of leukocyte uptake in areas of inflammation; sexual steroid-induced sialylation of nCAM molecules prevents the attachment of monocytes to endothelial cells [39, 40]. Similar studies have been published on the uptake of leukocytes by hormonal molecules, but not directly related to cardioprotection [30]. It is believed that the cardioprotective effect on premenopausal women is due to the adequacy of the level of endogenous estrogens produced during the menstrual cycle. This may be a possible reason for a decrease in the incidence of coronary artery disease in fertile women than in men [38]. However, by the end of reproductive life, the ovaries do not produce significant amounts of estrogen, which provoke postmenopausal women more prone to diseases associated with estrogen deficiency, such as heart disease, osteoporosis and dyslipidemia [36]. Postmenopausal hormonal changes, such as low plasma estrogen and elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, have a significant effect on plasma lipid and lipoprotein metabolism, leading to terminal cardiovascular disorders.

Estrogen has a cardioprotective effect by maintaining high LDL cholesterol levels and low HDL cholesterol and triglyceride (TG) levels. Mass clearance of LDL-C from blood plasma is probably due to accelerated conversion of hepatic cholesterol to bile acids and increased expression of LDL receptors on the cell surface. An increase in the production of apolipoprotein A-I and a decrease in the activity of hepatic lipase contribute to an increase in the level of HDL cholesterol. Estrogen causes hepatic expression of the apoprotein gene, therefore, affects lipid and lipoprotein metabolism [36].

This cardioprotective effect is lost after menopause, which puts postmenopausal women at high risk of developing debilitating and often fatal complications of cardiovascular disease [40]. Estrogen regulates cellular levels by directly producing mRNA for a specific protein including proteins for the metabolism of lipoprotein lipase (LPL) and hormone sensitive (HSL) lipase to adipose tissue. Estrogen also has an indirect effect on adipose tissue by stimulating the release of other hormones such as growth hormone (GH), catecholamine, and glucagon, which increase HSL activity. 17-beta-estradiol (the main circulating form of estrogen) regulates the rate of synthesis of structural apolipoproteins for VLDL and HDL in the liver. It reduces the rate of apob-100 synthesis, thereby decreasing the concentration of VLDL, which is a risk factor for atherosclerosis. On the contrary, it increases the rate of synthesis of apoa-I and apoa-II, thereby increasing the concentration of HDL, which is atheroprotective. HDL containing apoa-I and apoa-II promote the degradation of cholesterol from VLDL and chylomicron by reverse transport of cholesterol from peripheral tissues to the liver [3].

TC and TAG are major contributors to the circulation of lipids in our body, while chylomicron, VLDL, IDL, LDL and HDL are lipoproteins that function as a vehicle for transporting cholesterol. The cholesterol content of VLDL, IDL, LDL and HDL determines total plasma cholesterol. LDL transports endogenous cholesterol from the liver to peripheral tissues. Under certain circumstances, LDL cholesterol is deposited in the intimal layer of the arteries, thereby initiating the atherosclerotic process. HDL functions as an atheroprotective agent because it has a reverse cholesterol transport activity, thereby removing excess cholesterol from cells, including cholesterol absorbed by macrophages in atherosclerotic lesions, and transporting it to the liver for hepatic excretion via bile acid. The emergence, progression and complications of atherosclerotic plaque are determined by the balance between these two lipoproteins [36]. A fatty band of lesions is formed with the accumulation of cholesterol esters in the intimate layer of the arteries, which indicates the initiation of atherosclerosis. A fatty streak can progress to an atherosclerotic plaque if the process continues for a long time. If plaque continues to grow, it can block a vessel or form thrombosis and lead to further complications of

coronary artery disease such as ischemic stroke, coronary artery disease, or peripheral arterial disease [29].

Dyslipidemia, especially hypercholesterolemia, is a major risk factor for CVD and the most vulnerable public health problem, prevailing in every corner of the world, including Nepal. In Nepal, women make up over 50% of the population, with the majority of the population over 50 years of age. In particular, this group of the population lacks physical activity due to their retirement life; in addition, the consumption of unhealthy foods makes them more prone to suffering from atherogenic effects. This is the average age for menopause, suggesting that more Nepalese women are likely to be at risk of developing complications associated with cardiovascular disease, which is a matter of concern [7, 44].

Since estrogens play a crucial role in the metabolism of lipids and lipoproteins, it is necessary to control the lipid profile in postmenopausal women, who tend to decrease estrogen levels [13].

It seems that female sex hormones may play a preventive role, since other risk factors for this disease are the same in both sexes. This is further supported by the fact that early menopause leads to the premature development of coronary artery disease [18, 44]. Estrogen has a beneficial effect on metabolic risk factors for coronary heart disease, lowers total cholesterol, and maintains the effect of treatment for a long time [42]. All this leads mainly to a decrease in the level of cholesterol, low density lipoprotein (LDL). Small, dense LDL particles are more readily released via scavenger mechanisms rather than apoB 100 receptors, and are more likely to be incorporated into the subendothelial space. Although hormone replacement therapy can increase the level of small, dense LDL particles, it also increases their clearance from circulation. This can reduce the likelihood of their being retained in the arterial wall. Small dense LDL particles may be more prone to oxidative damage, leading to the formation of "foam cells" and ultimately to atheroma, but estrogens can protect LDL from oxidative damage [9]. Estrogen also increases high-density lipoprotein (HDL) cholesterol levels, in particular HDL-2 subfractions. It inhibits the activity of hepatic lipase and increases hepatic synthesis of apolipoprotein AI, the main protein component of HDL and HDL2.

While the level of LDL cholesterol is not affected by the addition of progestogen, the increase in HDL cholesterol is reversed or significantly reduced by the addition of androgenic progestogens due to an increase in hepatic lipase activity [33]. The effects of hormone replacement therapy are clearly related to dose and route of administration, which determine its effect on triglycerides. Progesterone increases triglycerides, and vice versa, transdermal estradiol reduces triglyceride levels, which should reduce the risk of coronary heart disease [31].

Estrogen has a beneficial effect on glucose and insulin metabolism, which leads to a decrease in insulin resistance [16].

The accumulation of central body fat is an important risk factor for CVD. It is a common misconception that hormone replacement therapy leads to weight gain and has little overall effect on body weight. In fact, just as many women lose weight with hormone replacement therapy, they gain weight. Central fat distribution is associated with insulin resistance and metabolic syndrome and therefore poses an increased risk of coronary heart disease. Menopause increases central fat distribution [37], but hormone replacement therapy reverses changes in body fat distribution associated with menopause. This leads to a decrease in central fat storage [24]. Oral estrogen use is associated with increased activation of blood clotting and a transient increase in venous thromboembolism (VTE). This occurs even though oral estrogen lowers levels of certain clotting factors (such as fibrinogen and factor VII) and decreases plasminogen activator inhibitor-1 (PAI-1). This adverse effect can be avoided by using transdermal estrogen or low doses of oral estrogen [26]. Estrogens have a broad effect on the entire vascular system, including endothelial function [22].

Estrogen increases endothelial nitric oxide synthase (eNOS) levels and subsequently increases nitric oxide (NO) production. This powerful vasodilator regulates blood pressure and platelet function, and inhibits vascular smooth muscle proliferation and adhesion molecule expression. Estrogen also reduces the release of endothelin-1, a potent vasoconstrictor [44]. Oral and transdermal estrogens simultaneously reduce the level of cell adhesion molecules, which indicates an anti-inflammatory effect on blood vessels [25]. Estrogen inhibits calcium channels [28] and activates BKCa channels, increasing vasodilation and improving arterial function. Estrogen also reduces the activity of the angiotensin-converting enzyme (ACE), which has a beneficial effect on the state of the cardiovascular system [12].

Abnormal deposition and remodeling of the vascular extracellular matrix are important processes involved

in the pathogenesis and progression of atheroma. Normalization of these processes can inhibit atherogenesis. Matrix metalloproteinases (MMPs) and their tissue inhibitors play a central role in vascular remodeling and may contribute to the development of cardiovascular disease. Research has shown that estradiol increases the release of MMPs in a dose-dependent manner [20]. Thus, the increase in MMP induced by low doses of estrogens can normalize vascular remodeling, while high doses of estrogens can lead to a significant increase in MMP and cause excessive remodeling.

Thus, the dose of estrogen at the start of therapy is of vital importance in terms of beneficial or harmful effects on vascular remodeling. Estrogen plays a role in the renin-angiotensin-aldosterone system (RAAS). Oral and transdermal HRT both reduce ACE activity, which reduces the risk of CVD. Progestogendrospirenone has an anti-mineralocorticoid effect, and also affects the RAAS, blocking the effects of aldosterone.

Consequently, cardiovascular diseases remain the main cause of morbidity and mortality in women in many countries, among people in the postmenopausal period, and it is quite possible that with an increase in the number of older people, they will remain the main risk factor for the development of cardiovascular diseases and mortality.

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