

Effects of Hormone Replacement Therapy and Tibolone on Cardiovascular System

HORMON REPLASMAN TEDAVİSİ VE TİBOLONUN KARDİYOVASKÜLER SİSTEM ÜZERİNE ETKİLERİ

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Summary

Coronary heart disease (CHD) is the leading cause of death in women, with a significantly increased risk after the loss of ovarian function. The putative benefits of estrogen replacement therapy (ERT) for the prevention of CHD among menopausal women have been documented by most observational studies leading to widespread use of ERT in menopause.

However, recent randomized clinical studies evaluating the effects of combined estrogen replacement therapy on endothelial function demonstrated no improvement over placebo, even detrimental effects that are not of cardiovascular benefit in postmenopausal women.

Due to these discrepant results, the investigators continue to search for the ideal alternatives. In this review we will try to outline the effects of hormone replacement therapy (HRT) on cardiovascular system and the effects of tibolone on some risk determinants of cardiovascular disease briefly.

Key Words: Hormone replacement therapy, Tibolone, Cardiovascular system, Menopause

T Klin J Gynecol Obst 2004, 14:239-242

Özet

Koroner arter hastalığı, kadında ölümün en sık sebebidir. Over fonksiyonunun da kaybolması ile belirgin bir risk artışı gösterir. Menapoz dönemindeki kadında, koroner arter hastalığının önlenmesinde östrojen replasman tedavisinin sayısız yararlarını bildiren birçok çalışma, östrojen replasman tedavisinin (ERT) menopozda yaygın bir şekilde kullanılmasına yol açmıştır.

Fakat yapılan son randomize klinik çalışmalar, kombine östrojen replasman tedavisinin endotel fonksiyonu üzerinde plaseboya göre etkisinin olmadığını, hatta kardiyovasküler açıdan yararlı olmayabileceğini göstermiştir.

Bu birbirinden farklı sonuçlar sebebiyle, araştırmacılar ideal alternatifleri aramaya devam etmektedir. Bu derlemede, hormon replasman tedavisi (HRT) kardiyovasküler sistem üzerine etkilerini ve tibolonun bazı kardiyovasküler risk belirleyicileri üzerine etkilerini ana hatları ile gözden geçirmeye çalışacağız.

Anahtar Kelimeler: Hormon replasman tedavisi, Tibolon, Kardiyovasküler sistem, Menopoz

T Klin Jinekoloj Obst 2004, 14:239-242

Coronary heart disease (CHD) is the leading cause of death in women, with a significantly increased risk after the loss of ovarian function whether naturally or surgically induced (1). The relative risk of CHD which is two-to fourfold lower in premenopausal women compared to postmenopausal women, increases exponentially after the menopause and equals that of men between the sixth and seventh decade (2). Estrogen replacement therapy (ERT) is considered as a justifiable component of preventive health care for postmenopausal women. Observational studies seem to support the primary protective role of ERT with an average risk reduction of 50% for CHD (3). In the Nurse's Health Study, CHD mortality was

significantly reduced among current users compared to the young women with surgical menopause without ERT (4). Furthermore, estrogen (E) seems to be more effective in women with a greater cardiovascular risk (5).

Nevertheless, the mechanisms by which ERT reduces the risk of CHD are not yet fully understood (6). Until recently this protection was mostly attributed to the favorable effects of estrogen on lipoproteins, but now an increasing line of evidence supports that gonadal hormones have generalized impact on cardiovascular system (CVS) with direct beneficial effect on endothelial function, prostaglandins and coagulation system (7).

Moreover, the non-lipid effects include a variety of beneficial changes in metabolic factors such as insulin resistance and hyperinsulinaemia that may be pivotal disturbances in CHD risk (8). Furthermore, direct arterial and cardiac effects can not be overlooked.

The incidence of CHD differs significantly between men and women, because of differences in risk factors and gonadal hormones (9). The incidence of CHD is low in premenopausal women, rises in postmenopausal women and reduced to premenopausal levels with ERT (10). These putative benefits of ERT for the prevention of CHD among menopausal women have been documented by most observational studies leading widespread use of ERT in menopause (3,11).

As the favorable changes on lipid metabolism are not adequate to explain the full primary cardioprotection, further studies have focused on the non-lipid effects of estrogens particularly to the vascular system. Estrogen induced lipid changes account for only 25% of the observed cardioprotective benefits. Recent data suggest that direct vascular effects of estrogen contribute substantially to this cardioprotective effects as observed in most studies (7,12). The vasculature, like the reproductive tissues is now recognized as an important target of estrogen action (13,14). Estrogen increases vasodilatation and inhibits the response of blood vessels to injury and the development of atherosclerosis through their direct or genomic-dependent activities that may potentiate cardiac diastolic and left ventricular function (15-19).

However, its role in secondary prevention in postmenopausal women with established CHD is questionable based on the results of the Heart and Estrogen/Progestin Replacement Study (HERS) (20). In the HERS, no significant effect was observed of 4.1 years of treatment with conjugated estrogens plus medroxyprogesterone acetate (MPA) on the risk of coronary atherosclerosis. The Women Health Initiative (WHI) study results indicated higher rates of thrombosis and coronary heart disease among women receiving estrogen-progestin therapy (EPT) compared to those receiving placebo (21). The Estrogen Replacement and

Atherosclerosis (ERA) trial reported that the use of estrogen alone or estrogen plus MPA for 3.2 years had no effect on the progression of coronary atherosclerosis assessed by coronary angiography, in women with established CHD (22). In another long-term study evaluating the effects of combined ERT on endothelial function demonstrated no improvement over placebo suggesting that HRT may not be of cardiovascular benefit in postmenopausal women (23).

There are several possible explanations, both methodological and biological (24). Some discrepancies may be the result of methodologic differences between the study designs; the observational data could be influenced by confounding bias, compliance bias and in particular have a restriction to detect short-term effects. Other explanations may be related to differences in the treatment regimens and in the subjects. Experiments have indicated that the beneficial effect of estrogen on atherosclerosis may be attenuated by the addition of medroxyprogesterone acetate (MPA), but not by addition of progesterone (25-27).

A synthetic 19-nortestosterone derivative; tibolone has attracted considerable attention since its estrogenic, gestagenic and androgenic metabolites reduce climacteric complaints and prevent osteoporosis without causing postmenopausal bleeding (28). These characteristics increase the compliance of postmenopausal women and allow the treatment of elder postmenopausal women without prior hormone replacement therapy. Tibolone shares many biological effects with HRT on the cardiovascular system and has a few notable differential effects. Tibolone decreases some cardiovascular disease (CVD) risk factors, such as Lipoprotein-a, fibrinogen, plasminogen activator, inhibitor-1, triglyceride and improves glucose tolerance, insulin sensitivity and endothelial function but lowers HDL cholesterol by more than 20% (29). Other lipids that are favorably altered by tibolone and ERT include apolipoprotein B, and apolipoprotein A1 (29). HRT has a beneficial effect on raising high-density lipoprotein (HDL) cholesterol, whereas tibolone, lowers HDL cholesterol, most likely due to its androgenic metabolite, yet animal

studies showed no adverse cardiovascular consequences (30).

Endothelial dysfunction may be an early indicator of atherosclerosis and both estrogen and tibolone have been shown to improve endothelial-dependent vasodilatation by stimulating the release of nitric oxide (NO) by increasing endothelial NO synthase activity (31). Inflammatory mediators contribute to endothelial dysfunction by increasing the expression of vascular adhesion molecules, such as E selectin and intracellular adhesion molecule 1 (ICAM-1), which are reduced by both HRT and tibolone (32). Another marker of vascular activation, vascular cell adhesion molecule (VCAM)-1 is reduced by both HRT and tibolone (32). The expression of matrix metalloproteinases (MMP), a feature of vascular inflammation, is increased both with ERT and tibolone (33). C reactive protein(CRP) is one of the most widely studied inflammatory markers, and elevations in CRP levels are correlated with increased risk of cardiovascular events in women (34). Tibolone has been shown to decrease CRP (33).

HRT and tibolone, have been shown to decrease fibrinogen levels, yet both have been shown to increase risk of venous thromboembolic events (34). It is not known if factors that increase the risk of venous events are also correlated with an increase in risk of arterial events (35). The Osteoporosis Prevention and Arterial effects of tibolone (OPAL) study is a recently designed large randomized study to assess the effects of tibolone and EPT in healthy postmenopausal women using carotid intima-media thickness (CIMT) as a primary endpoint (36).

There are still much to learn about women's health and hormone use. Given the current evidence from these studies, we can conclude that EPT should not be initiated or continued for the purpose of preventing cardiovascular disease or recommended long-term(five years or more) for women of any age for the prevention of chronic disease. Likewise for ERT, more definitive answers regarding long-term effects of tibolone and selective estrogen receptor modulators(SERM) on

CVD should await the results of ongoing trials and further studies.

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Geliş Tarihi: 19.02.2004

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