Hormone-Dependent Aging Problems in Women

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One of the major social issues nowadays is the aging society. Korea is already an aging society, and 63 cities and districts are ultra-aged societies where the rate of people older than 65 yr exceeds 20%. Among them, more than 67% are women. These statistics reveal the importance of healthcare for older women. Disease and disability of older women are very closely related to the loss of female sex hormones after menopause. Major hormone-dependent aging problems in women such as osteoporosis, Alzheimer's disease (AD), urinary incontinence, and coronary atherosclerosis were surveyed in this review, and the key role of hormones in those diseases and hormone replacement therapy (HRT) were summarized. We expect that this review would provide some understanding of factors that must be considered to give optimal care to older women for healthy lives.

Key Words: Aging, sex hormone, menopause

INTRODUCTION

According to the report of National Statistics Office of Korea in 2007, life expectancy of Korean women is anticipated to extend to an average age of 81 yr. Women's lives are very closely related to female sex hormones. Hormonal changes proceed gradually in men but women encounter fast hormonal change (menopause). Menopause, the permanent loss of menstruation after amenorrhea lasting more than 1 yr due to the loss of estrogen production by the ovaries, is a major aging process of women and most women encounter this hormonal change between 40 and 55 yr of age.[1] Therefore, many women spend almost 1/3 of their lives in menopause. As women age, they are more likely to experience disease and disability.[2]

The effects of ovarian steroids are very diverse. Although sexual dysfunction is the most well-known disability of women after menopause, there are many effects of female sex hormones on other vaginal functions. They may play a role in the pathophysiology of senescence. Whereas only subtle changes occur in pituitary dynamic, adrenal gland physiology, and thyroid function, changes in glucose homeostasis, reproductive function, and calcium metabolism are more apparent.[3] There are significant alterations in metabolism of skin and hair, body composition, and subcutaneous fat distribution throughout life.[4] Therefore, women have many diseases and disabilities requiring intervention and treatment after menopause.[5] However, HRT has not been used in 2/3 of Korean postmenopausal women with higher rates in older population.[6] When used, it tends to be used for treatment of menopausal symptoms.

This review explored major significant diseases in older women that are hormone-dependent including osteoporosis, AD, urinary incontinence, and coronary atherosclerosis, and we would like to provide some understanding of factors that must be considered in order to provide optimal care for these patients.

OSTEOPOROSIS

Osteoporosis is a worldwide problem and the most prevalent metabolic bone disease in developed countries including the United States.[7]

Women are generally disproportionably affected by osteoporosis in developed countries, and fracture rates among women are approximately twice as high as men.[8] The cause of osteoporosis is very complex but it is clear that hormonal changes after menopause increase the rate of bone resorption, leading to greater risk of osteoporosis.[9] HRT with estrogen only or estrogen and progesterone has been used for treatment of osteoporosis in women. HRT has been reported to be associated with a significant decrease in osteoporosis-related fracture.[10] In the Women's Health Initiative (WHI) study, the short-term administration of a continuous combined estrogen and progestin regimen or standard dose of conjugated estrogens confirmed fracture reduction efficacy.[11,12] However, HRT has decreased after the report came out that the overall health risks exceed the benefits from use of estrogen and progestin for an average 5.2 yr of follow up among healthy postmenopausal US women.[13] Another choice to treat osteoporosis are selective estrogen receptor modulators (SERMs). SERMs are a class of medications that act on the estrogen receptor.[14] A characteristic that distinguishes these substances from pure receptor agonists and antagonists is that their action is different in various tissues, thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues. Raloxifen is the only SERM currently marketed for management of osteoporosis.[15] It has been known to have agonistic effects on bone and lipoprotein production but antagonistic effects on breasts.[11] A new type of SERM, lasofoxifene, is in Phase III development for the prevention and treatment of osteoporosis in postmenopausal women. It has remarkably improved oral bioavailability and selectively binds to both estrogen receptor subtypes (estrogen receptor-alpha or -beta) with high affinity.[16,17] It also shows favorable safety profile, and it could be used to treat osteoporosis in the clinical field.

ALZHEIMER'S DISEASE

AD is a major health issue for women. Women comprise 72% of the population over the age of 85 yr, and roughly half of this group has AD.[18]

Not only do women constitute a grated population of this older population but AD is expressed earlier in women than men.[19,20] This may be related to estrogen loss that occurs with menopause.

The brain is a target for estrogen and other gonadal steroids. Subsets of neurons possess intranuclear receptors for estrogen.[21] Estrogen receptors (α and β) act as ligand-activated transcription factors. The complex of estrogen and its receptor translocates into the cell nucleus where it regulates transcription of target genes. Through interactions with membrane receptors, estrogen also influences neuronal functions.[22]

Estrogen has been reported to have beneficial effects on the nervous system. It is neuroprotective against oxidative stress, excitatory neurotoxicity, and ischemia.[23,24] It can also promote the growth of nerve processes and modulate synaptic plasticity.[25,26]

Other beneficial effects of estrogen include augmentation of cerebral blood flow, enhancing glucose transport into the brain, and reducing in β-amyloid formation.[27-29]

In spite of its beneficial roles on the neurological system, estrogen replacement therapy (ERD) to treat AD remains discrepant. Many researchers reported the preventive effect of estrogen on AD in epidemiological studies,[30-35] and early observational studies implied that women with AD receiving HRT had milder symptoms of dementia than women with AD not receiving HRT.[36,37]

However, the results from Women's Health Initiative Memory Study (WHIMS) show that HRT did not reduce dementia risk. Instead, overall rates of dementia were increased by HRT and HRT did not improve global cognitive test score.[38]

The highly consistent and apparent effect on verbal memory in the acute period of ERT, particularly in the early postmenopausal period, indicates that ERT during this period may be especially beneficial. However, long-term use of ERT is not a replacement for healthy lifestyle, and it is likely that women should be able to attain the same benefits by improving their health habits.[39]

URINARY INCONTINENCE

Urogenital problems in the elderly female

population are experienced by 1/3 of women from the age of 50 yr and onward.[40]

Urinary incontinence is 1 of the most significant urinary symptoms. Depending on pathophysiologic processes, it is further categorized into stress urinary incontinence (SUI), urge incontinence (sensory and motor), mixed incontinence, reflex incontinence, overflow incontinence, anatomic incontinence (e.g., ectopic ureter, vesicovaginal fistula), and behavioral incontinence (e.g., immobilization).[41] The prevalence of SUI has been reported to increase at menopause and at postmenopausal age, and is more common in women than men, implicating menopause.[42] The tissues originating from the urogenital sinus were shown to be estrogen sensitive in as early as 1931.[43] The female lower urinary tract is though to be a target organ for the action of the sex steroid hormones estrogen and progesterone since estrogen receptors are found in the urethra and lower urinary tract.[44,45] Changes in urethral cytology are observed during the menstrual cycle and after administration of estrogen.[46-48] Therefore, it is reasonable to postulate that hypoestrogenism is a factor in the development of SUI. The therapeutic effect of estrogen on SUI remains controversial.[49,50] The combination therapy of estrogen and phenylpropanolamine raises intraurethral pressure and significantly reduces urinary loss by 35% in a standardized physical strain test.[51] Rud et al. also suggested that estrogen increases urethral closure pressure and improves pressure transmission to the proximal urethra actions that promote continence.[52]

However, a large placebo controlled randomized clinical trial with 109 patients did not uncover any benefits from estrogen therapy in women with subjectively documented SUI.[53] Urinary concentrations of endogenous steroid metabolite including estrogen in postmenopausal patients with SUI were not significantly different from normal patients,[54,55] thus more precise and controlled studies should be carried out to find out the role of steroid hormones in the genesis and development of SUI.

CORONARY ATHEROSCLEROSIS

The incidence of coronary heart disease (CHD) is extremely rare in premenopausal women, even in a high-risk population, and much lower in premenopausal women than in men of similar age.[56,57] However, the incidence rapidly increases in women after menopause and loss of ovarian function.[58] Some results show that women who experienced early menopause have increased risk of heart disease. Gordon et al. reported that women experiencing natural menopause between 45 to 49 yr or a surgical menopause between 40 to 44 yr are more likely to develop CHD than premenopausal women of the same age.[59] Another cohort study of postmenopausal women, age 50 - 65 yr at enrollment and followed up to 10 yr, showed that the risk of cardiovascular mortality was higher for women with early menopause than those with late menopause.[60] Recently, a significant inverse relationship has been reported between the age at menopause and both the prevalence and extent of atherosclerosis assessed by ultrasound in 2588 postmenopausal women.[61] Thus, it could be suggested that endogenous estrogen in premenopausal women provides protection against cardiovascular disease.[62]

Decreased risk of cardiovascular disease has been known for a long time as the main expected benefit of HRT, and conjugated estrogen was 1 of the most frequently prescribed medications in the US.[63,64] Several studies support this expectation. Observation studies initially suggested a protective function of postmenopausal HRT against heart disease with risk reduction of about 35 - 50%.[65] Adams et al. provided direct evidence for the beneficial effects of ERT on progression of coronary artery atherosclerosis using ovarectomized monkeys with 30 mo of 17β-estradiol treatment.[66] In this study, an approximate 50% reduction in coronary artery atherosclerosis was observed compared to the control animals. The Women's International Study of Long-duration Oestrogen after Menopause (WISDOM) also showed 29% reduction of cardiovascular disease in the HRT treated group compared with the placebo group.[67] On the other hand, controlled clinical endpoint studies, such as Heart and Estrogen/Progestin Replacement Study (HERS) and the recently completed WHI trial, reported no protective function of HRT that consisted of conjugated equine estrogen and medroxy progesterone-acetate

for the primary or secondary prevention of coronary artery disease.[68] Similar results were also observed in the treatment with conjugated equine.[69] The study on the effect of postmenopausal HRT on the progression of existing coronary artery atherosclerosis as assessed by angiography showed no differences in disease progression in all treatment groups.[70]

The risk of cardiovascular event rather increased in women treated with HRT for many years after menopause.[71] However, Rossouw and colleagues suggested that the effect of HRT would be different depending on the starting point of treatment since they observed that women who initiated HRT close to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause.[72] In spite of those controversial studies, there is an interesting report about the long-term study of HRT: 2763 women who were older than 65 yr of age and had pre-existing CHD were treated with estrogen/progestin replacement therapy with a combination of conjugated equine estrogen and medroxyprogesterone acetate for 4.1 yr. During the first yr of the trial, there was an increase in relative risk, mostly seen in the first 4 mo. After 2 yr of treatment, there was a tendency toward risk reduction, and strongest reduction of risk in the fourth yr.[73] Therefore, the effect of HRT on CHD seems to depend on the duration and initiation time.[74]

Despite disappointing outcomes from trials to evaluate estrogen treatment on postmenopausal cardiovascular disease, some considerable evidences support the beneficial effects of estrogens in atherosclerosis in postmenopausal women. Lack of compliance with HRT such as increased risk of breast cancer still remains, however, future regimens may overcome this problem.[62]

OTHERS

Skin aging has been reported to be affected by the reduction of female hormones after menopause.[75] Carbohydrate metabolism and adipose tissue distribution are also regulated by female sex hormones, and metabolic change leads to obesity.[76,77]

ADMINISTRATION ROUTE FOR HORMONE REPLACEMENT THERAPY

HRT has been mentioned in the several hormone-dependent women aging problems in this review. Regardless of many controversial studies, HRT may play a role in the prevention of these problems. However, adverse effects such as increased risk of cardiovascular and breast cancer still remain. Therefore, non-oral HRT (low-dose transdermal HRT) has been tried to reduce the incidence of side effects.

Transdermal HRT appears as effective as oral HRT in preventing postmenopausal osteoporosis,[78,79] and has been shown to have beneficial effects on vascular function and coronary heart disease risk marker.[80] It has also been reported that cardio-vascular and invasive breast cancer risk is lower with transdermal estradiol than with oral estrogen.[81]

However, transdermal HRT also has side effects. It may also cause more irregular and breakthrough bleeding with sequential and continuous therapies than its oral counterparts.[82] Therefore, careful adjustment to individual patients and continuous monitoring are needed to receive the benefits from HRT.

CONCLUSION

Over their life span, women have experienced disease and disability that are closely related to the loss of female sex hormones. Most diseases in older age such as adult diseases (diabetes, obesity, and CHD), osteoporosis, urinary incontinence, and AD are affected by female sex hormones, suggesting hormone control or HRT in treatment of postmenopausal women. This review is expected to offer a wide range of healthcare options for women who experience perimenopause and menopause.

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