Current Considerations of the Menopause

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ABSTRACT

Menopause occurs in approximately 50 percent of women by the time they reach the age of 50. Increased lifespan owing to modern medical achievement allows women to spend more than one-third of their life time in menopausal period. Although mechanism of ovarian aging is not fully understood, menopause associated clinical problems can be controlled and improved. Estrogen replacement therapy in conjunction with a progestin regimen not only controls hot flashes, osteoporosis, dyspareunia, and other estrogen-deficiency symptoms, but also prevents the potential risk of estrogen treatment such as endometrial and/or breast carcinoma and cardiovascular disorders. In addition to hormonal therapy, nutritional supplements such as calcium and vitamin D, and physical exercise are essential to the well-being of women in the post-menopausal period.

Introduction

Aging of gonadal function, known as the climacteric, occurs in both sexes. Significant clinical symptoms of gonadal aging, however, only occur in women. Menopause is clinically defined as amenorrhea for more than one year after age 40, and a highly elevated plasma follicle stimulating hormone (FSH) level (>40 mIU per ml). Approximately 50 percent of the female population become menopausal by the age of 50.\textsuperscript{22} In spite of decreasing age of menarche in the last century, the age of menopause has not changed;\textsuperscript{1} furthermore, modern medical technology extends the average human lifespan to the seventh and eighth decade. Therefore, women will spend more than one third of their lifespan in the menopausal period (figure 1). This trend may continue to increase, and the duration of post-menopausal years will increase in the future. Significant numbers of women in the menopause will suffer from clinical symptoms which can drastically influence their life style and well-being. Therefore, medical attention of menopausal women deserves to be emphasized especially as the symptoms are treatable and preventable.

Aging

It is generally agreed that the process of aging is genetically controlled. Although the mechanism and etiology of aging are not fully understood, it has
been suggested that aging is a continual developmental process in which organs involute at a certain specific time table. For example, the placenta involutes at the 40th week of gestation, while the decidual teeth and thymus involute during childhood, and the ovaries at menopause. Hayflick and Moorehead found that normal human fibroblasts will continue to grow in the most favorable environment for approximately 50 population doublings, and at that point the death of cultured fibroblast will occur regardless of the environment. Therefore, in the normal cell there is limit to cell division potential which leads to eventual mortality. This process can be disrupted when a cancer cell develops under the influence of endogenous or exogenous factor(s), thereby rendering the cell relatively immortal.

Aging is also explained by the degeneration of collagen and the loss of its reducibility owing to development of cross links. Collagen is generally classified as interstitial collagen and basement membrane-pericellular collagen. The former collagen is predominant in skin, fascia, hyaline cartilage, blood vessels, and synovium. The latter collagen, the basement membrane and pericellular collagen, constitutes the renal glomerulus and cell surface collagen. As aging proceeds, the collagen degenerates and loses its flexibility as fibrillar cross links develop. Cross links are responsible for the rigidity of collagen and gradually replace the more stable linkage. Therefore, aging of organs might be explained by the gradual accumulation of both intracellular and extracellular complex molecules that undergo cross linkage, preventing the normal cellular function and subsequently leading to the death of organs.

The “time clock”, the neuroendocrine system theory, is the third attractive hypothesis to explain the aging. This theory is most relevant to the phenomenon of menopause. In spite of prolongation of human lifespan in the last century, the age of menopause stays relatively constant. This suggests that perhaps the female reproductive system has some kind of self destructive mechanism which is initiated at a certain time of life. The dopaminergic system in the hypothalamus has been implicated in the estrogen positive feedback to the GnRH and LH release. Progressive failure of dopaminergic system in aging has been noted in the central nervous system. Therefore, gonadal failure, at least in the rat species, is controlled by the neuroendocrine system which may also influence the timing of menopause in the human female. The pre-programmed impairment of the immune system has also been implicated as an explanation of the aging phenomenon. The decline in the immune responsiveness following thymus involu- tion suggests that a weakened surveillance by thymus-dependent cells leads to the development of an immune disorder which may subsequently pre-determine lifespan.

**Endocrinology**

Endocrine changes during aging are not as drastic as some other metabolic function, except for the senescence of female reproductive function. The pituitary gland remains active during aging.
A slight decrease in growth hormone and a decreased thyroid stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) stimulation are noted in older men. The adrenocorticotropic hormone (ACTH) reserve and its response are relatively intact as well as prolactin release. However, a drastic increase in the synthesis and the release of gonadotropins (both FSH and luteinizing hormone [LH]) occurs in older women. This is likely secondary to the hypoestrogenic state subsequent to ovarian failure. Primary ovarian failure is the most significant endocrine change in aging women and causes menopause. Germ cell multiplication in the ovaries reaches its maximum at the sixth month of gestation and, thereafter, the numbers of germ cell or follicle in the ovaries continue to decline throughout life until their complete disappearance at the time of menopause. Approximately six to seven million germ cells are developed in the ovaries by the sixth month of gestation and decline progressively in number to approximately one million at the time of birth. The number of ovarian primordial follicles is reduced to less than one half-million at the time of menarche, and it will continue to decline to zero by the time of menopause; of these, approximately 400 follicles are fully matured and ovulated during reproductive life.

In some pathologic states, the degeneration of germ cells in the ovaries is drastically accelerated because of either genetic or environmental reasons, thus causing loss of all follicles at a young age, such as at birth (Turner's syndrome) or during the early reproductive age (premature ovarian failure or premature menopause) depending on the severity of loss. The menopausal ovaries secrete little estrogen but do secrete significant amount of androgens (both androstenedione and testosterone). Low estradiol output owing to failing ovaries subsequently leads to elevated FSH and LH secretion from the pituitary. Lack of inhibin secreted by the follicles during the menopause may further elevate FSH level. Therefore, a highly elevated FSH (more than 40 mIU per ml) before the age of 40 is a hallmark of ovarian failure and of menopause in a woman over 40 years of age.

Adrenal function also declines during aging and is especially reflected in the drop in levels of adrenal androgens such as dehydroepiandosterone (DHA) and DHA-Sulfate. Androstenedione and testosterone secretion also decline gradually as age advances. The adrenal corticosteroid secretion, however, is not affected during aging. A significant increase in the peripheral conversion of androgen to estrogen occurs in aging women, namely androstenedione to estrone. Estrone in the menopausal woman is primarily derived from androstenedione by an increased conversion rate in fat tissue or some other peripheral tissues. Thyroid function only minimally changes during aging. There is depressed TSH response to the TRH stimulation in elder man, but this is not observed in elder women. Aging pancreas decreases its insulin response to glucose or carbohydrate loading.
fore, the glucose tolerance test in the elder person should be interpreted with caution. The increased incidence of diabetes in elder persons may also be explained by this reduced glucose tolerance.

**Metabolism**

Metabolic or structural changes during aging are similar in both sexes, thus they may not be related to the menopause itself. Generally, the basal metabolic rate decreases in the elder person as well as the cell count, brain cell number, and cell water content. Mineral content of bone, especially in trabecular bone, continues to decline as age advances. This phenomenon is drastically accelerated during the menopause which is most likely related to the declining estradiol level owing to the ovarian failure. Pulmonary and renal function are also decreased during aging as well as the immune defense system. The surveillance of the thymus-dependent immune system may be exhausted during aging and lose its surveillance capacity to prevent autoimmune diseases or neoplastic changes of normal cells. Some of the neurological and psychiatric changes during aging are well-known, yet their relationship to the menopause is not well-documented.

**Symptomatology**

**Onset of Symptoms**

Menopausal symptoms can be divided into those that are definitely related to estrogen deficiency and those that are questionably related to estrogen deficiency. The first group includes hot flashes, osteoporosis, and dyspareunia from atrophic vaginitis. These symptoms usually occur at an earlier stage of menopause and are not only quite responsive to estrogen replacement therapy but can also be prevented by early estrogen treatment.

The symptoms which are not particularly related to estrogen deficiency are cardiovascular disorders, psychiatric problems, urinary incontinence, insomnia, headaches, and so on. These can occur anytime during the peri- and post-menopausal period and may relate to aging rather than estrogen deficiency.

**Symptoms of Estrogen Deficiency**

*Hot flashes* are related to estrogen deficiency. They will not occur in those patients with hypothalamic pituitary failure (i.e., hypogonadotrophic hypogonadism) in spite of their extremely low estradiol. Therefore, it was thought that hot flashes or vasomotor flashes in the menopausal woman may be directly induced by the high level of gonadotropins, as the episodes of hot flashes were found to coincide with the pulsatile LH peaks in menopausal women (figure 3). However, in a recent study, it was shown that norepinephrine pulses precede LH peaks in the blood of menopausal women. Therefore, catecholamines such as norepinephrine, instead of gonadotropins, are likely the primary initiators of hot flashes. This catecholamine pulsatile release could probably be secondary to the lack of estrogen negative feedback at the hypothalamic level. Hot flashes occur quite frequently in the early stage of menopause but its frequency gradually decreases as the age advances. Estrogen replacement therapy is specific and effective in controlling hot flashes.

*Osteoporosis* is the result of significant mineral loss in bone during menopause. The mineral content of bone gradually decreases throughout reproductive age...
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by the increased activity of the osteoblast which is positively promoted by mechanical stress (such as exercise), calcitonin, vitamin D, growth hormone, and calcium ion, but is negated by the parathyroid hormone. On the other hand, bone destruction is carried out by the osteoclast and its function is activated by parathyroid hormone and thyroxine.

Osteoporosis itself also enhances osteoclast activity. Estrogen, androgen, and calcitonin in contrast, will suppress osteoclast activity thus preventing bone destruction or resorption. Therefore, in order to prevent osteoporosis in menopausal women, it is not only necessary to use estrogen replacement therapy but it is also important to supplement with vitamin D, calcium, and exercise as well as to assure the normal function of other endocrine glands. The dyspareunia developed during menopause is directly related to atrophic vaginitis secondary to estrogen deficiency. Fortunately, this can be eliminated easily by estrogen replace-

and its process drastically accelerates during menopause (figure 4). Women in reproductive age who have had an oophorectomies also tend to have an acceleration of the osteoporotic process. Therefore, it is clear that the acceleration of osteoporosis during menopause is closely related to estrogen deficiency. Estrogen replacement therapy can slow down osteoporosis, but it will not reestablish the bone formation in these patients. Bone formation is accomplished

![Figure 3. Pattern of pulsatile lutineizing hormone (LH) release and associated menopausal flush episodes. Arrows indicate flush onset. Each part illustrates a separate eight to ten hour study in which blood samples were obtained at 15-minute intervals. Note that each flush is synchronized with an LH pulse. Reprinted with permission from Casper, R. F., Yen, S. S. C., and Wilkes, M. M.: Science 205:823, 1979.](image)

![Figure 4. Bone mineral mass of the radius, determined by photosensitivity, in 305 normal men (●) and 308 normal women (○). Bars indicate the S.E. of the mean. Reprinted with permission from Meema, S. and Meema, H. E.: Israel J. Med. Sci. 12:601, 1976.](image)
ment therapy, either systemically or topically.

**Symptoms of Questionable Estrogen Deficiency**

**Cardiovascular disorder.** The risk and the benefit of estrogen in cardiovascular disorders has been a controversial issue. Based on demographic and epidemiologic studies, estrogen seems beneficial in preventing the incidence of myocardial infarction as well as reducing the mortality rate of ischemic heart disease. The lower incidence and mortality rate of myocardial infarction in the younger woman compared to the younger man has been attributed to the effect of estrogen on the cardiovascular system. However, a critical evaluation of the incidence and mortality rate of myocardial disorder in women showed a gradual increase of both rates throughout the peri- and post-menopausal period, whereas the rates in men tend to flatten out after age 50 (figure 5). Therefore, it is not certain that estrogen is responsible for the lower incidence and mortality rate of systemic heart disease in young women.

Laboratory data indirectly suggest that estrogen could decrease the risk of coronary heart disease by increasing high-density lipoprotein (HDL) and lowering low-density lipoprotein (LDL) in blood. Progestins, in contrast, could increase the risk by lowering the high density lipoprotein level. High blood pressure and high triglycerides, however, were frequently observed in the estrogen user; thus, it could increase the risk of cardiovascular disorder. Although estrogen seems to be beneficial in preventing cardiovascular disorder, its real benefit or risk cannot be concluded without further investigation.

**Urinary incontinence** is a quite common problem associated with menopause. The urinary bladder has long been considered partially estrogen sensitive. Therefore, a lack of estrogen during the menopause may weaken the urethral sphincter leading to uncontrollable urinary leakage. However, weakening of the bladder owing to aging process can also contribute to its occurrence. Estrogen replacement therapy may improve or control urinary incontinence in some menopausal women, but it may not do so consistently.

**Psychiatric or emotional problems** associated with the menopause have been frequently referred to as estrogen deficiency symptoms. However, because of the complexity of social life and emotional status in addition to the physical changes of aging, it seems difficult to associate estrogen deficiency directly to all these problems. Although some improvement has been observed during estrogen therapy, these symptoms are not consistently controlled without psychiatric or psychological support.
Associated Medical Problems

**Osteoporosis and hip fracture:** Bone resorption is a continuous phenomenon in both sexes after the age of 30. The rate of bone resorption drastically increases following menopause, and this is probably secondary to the estrogen deficiency. The first three years of menopause are considered to be the most significant bone-resorption period, especially in those patients without adequate estrogen therapy. These women tend to develop osteoporosis which subsequently leads to bone fractures. Immobility and mortality subsequent to fractures from osteoporosis are more serious problems than endometrial cancer in menopausal women, as they tend to affect much larger numbers of women. Therefore, estrogen replacement therapy is currently emphasized. Nevertheless, the potential risk of estrogen therapy can not be underestimated and has been the main concern of estrogen therapy in the menopausal women. The current approach of combining progestin with estrogen as replacement therapy has significantly decreased the risk of *endometrial carcinoma* in menopausal women. Therefore, estrogen replacement therapy should be considered without hesitation, especially if progestin is added in the second half of the cycle.

**Breast cancer** was also considered to be a potential risk associated with estrogen therapy. However, the incidence of breast cancer is actually decreased in a long-term contraceptive user. Furthermore, there is evidence to suggest that estrogen and progestin sequential therapy given to the post-menopausal women can prevent benign fibrocystic breast disease as well as breast carcinoma. Therefore, estrogen replacement therapy supplemented with progestin seems beneficial rather than harmful in preventing benign and/or neoplastic breast lesions.

Management

The management of post-menopausal syndrome can be divided into three areas: (1) specific hormone therapy, (2) other non-specific therapy, and (3) psychiatric care.

**Estrogen Therapy**

Low dose estrogen replacement therapy has been used effectively to treat menopausal symptoms. Prolonged estrogen therapy, however, tends to increase endometrial hyperplasia and even induce endometrial carcinoma, and its value has been debated in the past. The potential risk of endometrial hyperplasia and/or carcinoma, however, has been negated or prevented when progestin is added to low-dose estrogen therapy in cyclic fashion. Estrogen-progestin sequential therapy has become the treatment of choice for patients with post-menopausal symptoms. The role of estrogen replacement therapy has been questioned in those patients without symptoms; however, it is justified in order to prevent osteoporosis even in the asymptomatic menopausal women. One of the drawbacks of estrogen-progestin sequential therapy is the frequently induced withdrawal bleeding which occurs in significant numbers of menopausal women undergoing therapy. This can be a nuisance and deterrent to treatment; however, with careful explanation and reassurance, some women may accept the cyclic withdrawal bleeding.

The route of medication can significantly affect the dose-effectiveness. Estrogen oral medication usually requires higher doses in order to reach biologically effective levels in the blood. This is due to the large portion of estrogen going through liver metabolism and conjugation. Estrogen effect on liver function and its subsequent metabolic changes are also considered harmful;
therefore, alternate routes of administration have been explored. Vaginal route of estrogen administration seems to elevate estrogen to a sufficient level with minimal doses (figure 6).\textsuperscript{25} The estrogen remains as a non-conjugated form in blood when it is administered by vaginal route.\textsuperscript{19} This is mainly because of direct absorption into the systemic circulation without going through the portal vein system and subsequent liver metabolism. In spite of this advantage, vaginal medication has not been popular because of its cumbersome and unpopular way of administration.

Subcutaneous implantation of estrogen pellets has also been considered as an alternative.\textsuperscript{30} It is effective but is not quite as acceptable because of the surgical procedure required for pellet implantation. Percutaneous administration has also been tried by using estrogen ointment or cream.\textsuperscript{18} Although significant amounts of estrogen can be absorbed through the skin to reach the systemic circulation, the amount of estrogen required is relatively large, and its practicality is not quite established. Therefore, it is still in the experimental stage.

**Non-Specific Therapy**

Clonidine (\(\alpha\)-adrenergic agent) has been used effectively to control vasomotor flashes.\textsuperscript{7} Tranquilizers have also been used to improve symptoms of postmenopausal women. Vitamin D and calcium in conjunction with estrogen therapy are highly recommended in menopausal women to prevent osteoporosis. Physical exercise to strengthen muscle and bone are also highly recommended, not only to strengthen bone structure but also to improve general well-being through physical fitness.

**Psychiatric Care**

Those postmenopausal women with significant psychiatric symptoms such as depression, anxiety, nervousness, etc., deserve psychiatric attention. The social and emotional difficulties encountered during this period of life require professional support in some women.

**Summary**

In summary, the menopause is a biological phenomenon in the process of ovarian aging which occurs around the age of 50 in 50 percent of women. Since the lifespan of women continues to increase, most women will spend more than one-third of their life time in the post-menopausal period. Therefore, emphasis should be given to the management of menopause-related medical problems to fulfill the best potential of women's life. Etiology of aging is not cer-
tain in spite of several attractive theories. Nevertheless, the improvement of life style in the older woman is currently attainable and should be accomplished through medical and social support. Estrogen replacement therapy in conjunction with supportive management should be considered in almost all menopausal women. Estrogen in low doses plus progestin given in sequential fashion seems to be the best choice of treatment for post-menopausal symptoms as well as osteoporosis. The potential problems of endometrial and breast cancer during estrogen therapy seem to be eliminated by additional progestin regimen. In addition, vitamin D and calcium replacement are highly recommended to improve the bone structure, while physical fitness is also considered to be an important part of therapy, not only to strengthen the bone structure but also to improve the general well-being. In spite of the many benefits of estrogen replacement therapy in the menopausal woman, caution should still be exercised as significant side effects still exist during long-term estrogen administration.

References


