Evolution of Management for Postmenopausal Women

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Menopause originated from two Greek terms, menos (month) and pause (stop). Menopause is defined as the time when a woman has her final menstrual period. The diagnosis of menopause is retrospective and uses only clinical information, i.e. the absence of a period for one year.[1] Menopause is not a disease but a physiological aging process caused by the cessation of ovarian function; accordingly postmenopausal women are eventually in a hypoestrogenic stage. The hypoestrogenic state in middle-aged women, although it is considered a normal change, it can cause health problems in some. Menopausal symptoms are problems during the early phase of the hypoestrogenic state, while urogenital atrophy and osteoporosis are later problems. In addition to these hypoestrogen related problems, the middle-aged and senior women also encounter with other aging related health problems such as musculoskeletal diseases, cardiovascular diseases, diabetes mellitus, and cancers. Current management for menopause is based on the principle of preventive medicine, which includes health promotion, prevention and early detection of diseases, treatment, and rehabilitation. The management has the ultimate goal to maintain and/or improve quality of life rather than to eradicate all of the health problems.

Approximately two centuries ago, almost all women never had experience of menopause because they died before reaching the age of menopause. Only a minority of women could live long enough to be menopause. Their menopause related problems were neglected since it was thought that these problems did not really exist. In the past, some women with menopausal symptoms were diagnosed as 'involutional melancholia', a psychiatric disorder of gradual onset occurring during late middle age, with symptoms of marked anxiety, agitation, restlessness, somatic concerns, hypochondriasis, occasional somatic or nihilistic delusions, insomnia, anorexia and weight loss. This term was presented in the Diagnostic and Statistical Manual of Mental Disorders, second edition (DSM-II, 1968). By that time, there was a concept that hormonal change during the middle age was linked to this psychiatric disorder. After careful consideration, this concept was no longer accepted because there was not enough evidence to show that menopausal depressed patients have a depressive disorder that could be separated as a distinct subtype[2] since qualified studies[3,4] failed to confirm the increased risk for depression during menopause. Consequently the term involutional melancholia was listed under major depression in the DSM-III (1980), and was later excluded from the DSM-IV (1994).

During the past two centuries more and more women could live long enough to reach menopause. The improvement in the health care system was responsible for the prolongation of life expectancy. However, such improvement has little effect on the age at menopause;[5] the age of which is determined by genetic potential rather than other factors. In 1995, the life expectancy at birth of Thai women was 74.9 years old.[6] The mean age at menopause of Thai women varied from 49.5 to 51.2 years.[7,8] The life expectancy of Thai women is shorter than that of many countries, especially those in North America and Europe, despite the age at menopause is similar. Currently almost all women worldwide live approximately 20-30 years, or 1 in 3 of their lives, in the postmenopausal period.[5] Therefore menopause has become the issue of public interest since the middle of the 20th century. However, the evolution of management for menopausal problems can be traced back up to the early 18th century. The following review is derived from the reviews by Samsioe G (1955)[9], Speroff L and Fritz MA (2005)[10], and Stefanick ML (2005)[11].

Management in the 18th century

The evidence of problems related to menopause was documented in a German thesis published in 1710 by Simon David Titius, a student of Georg Ernst Stahl. The thesis described the negative effects of the cessation of menstruation on female health. In this century there was the first account of increased life expectancy, as the upper class 20-year-old English women could live up to 65 years old. By that time there was a concept that menstruation was a cleansing process for women; therefore cessation of menstruation would retain toxin in their body, which consequently caused ailments. The remedies for the ailments in that era were achieved by the means of '*ancient or traditional medicine*' including blood-letting, enema, cleansing- and sweat-baths, and cupping.

Management in the 19th century

The biomedical aspect of menopause was considered in this century. It was hypothesized that ovarian failure caused menopause. The terms 'menopausie or menopause'

were first introduced by de Gardanne, a French physician in 1812. The first evidence of hormonal replacement therapy (HRT) was documented in 1889 when Brown-Sequard, an English physician, reported that he was rejuvenated by self-injection with testicular extracts, and he suggested that a similar result would be obtained by injection with ovarian extracts. The era of '**early HRT**' began by the end of the 19th century. Hormone from crude extracts of bovine ovaries was used to relieve menopausal symptoms.

Management in the 20th century

The knowledge of ovarian function and menopausal problems was well-established in this century. In 1906 it was known that ovaries produce two substances, responsible for menstruation and implantation. Thereafter there was rapid increase in knowledge of ovarian hormones, beginning with estrogen, then progesterone. Estrogen was found in ovary (1923); it could be extracted from human pregnant urine (1929), then from pregnant mare urine (1930); and estradiol (E2) could be purified (1936). Shortly thereafter, progesterone was found in corpus luteum (1934); it could be extracted from Mexican yam (1939-49); 19-nortestosterone progestogens were synthesized and used in contraceptive pills (1951).

The era of '*commercial HRT*' started in the early 20th century. Since 1930s menopausal syndrome had been treated with products derived from estrogen-containing biological agents, such as cow ovaries, human amniotic fluid, and urine of pregnant women. Not until 1940s when Ayerst Laboratories could extract a considerable amount of estrogen from pregnant mare urine, i.e. conjugated equine estrogen (CEE), did the '*HRT Surge*' begin. The marketing of CEE in the trade name of Premarin®, was accelerated by the book '*Feminine Forever*' which was published in 1966 by Robert Wilson, M.D.[12] under the financial support of the Ayerst Laboratories. By 1960s, 12% of postmenopausal women in the USA used Premarin® (1.25, 2.5 mg). Shortly thereafter the side effect of HRT emerged; the association of unopposed estrogen and endometrial cancer was published in 1975. The HRT market had been dull until 1980 when progestogen, which was shown to protect the endometrium, was added to estrogen.

From the last quarter of the 20th century, medical practice has been based on '*evidence based medicine*' (EBM). Afterward various landmark clinical studies in menopause have been developed. In 1976, the Nurses' Health Study (NHS, a large cohort study) was initiated to evaluate the effects of menopausal estrogen use on cardiovascular disease, cancers, mortality and other disease processes. A number of reports have been published from this study demonstrating various beneficial effects of HRT. In 1980s, Premarin® 0.625 mg was proposed to be the standard dose of HRT and used with indications to improve quality of life, relieve menopausal symptoms, reduce cardiovascular disease and fracture risk. However, it had the potential to increase breast cancer and deep vein thrombosis. In 1993, the Postmenopause Estrogen/Progestin Intervention (PEPI) trial, a randomized controlled trial (RCT), demonstrated the benefit of various HRT regimens on cardiovascular risk. These further supported HRT as a panacea, or a miracle drug that can heal all ailments.

Just before the end of the 20th century, the ecstatic period of HRT began to drop after the result of Heart and Estrogen/progestin Replacement therapy Study (HERS, an RCT) was published in 1998. It showed that HRT has no benefit for cardiovascular disease. The status of HRT was further deteriorated by the publications of the Women's Health Initiative (WHI, an RCT) Study in 2002, and Million Women Study (MWS, a cohort study) in 2003 which confirm the increased breast cancer risk in HRT users. Such bad news turned the era of '*HRT surge*' to the era of '*HRT phobia*'.

Management in the 20th century

The recommendation for HRT[13] after WHI study limits the indications of HRT to the treatments of menopausal symptoms and urogenital atrophy, and prevention and treatment of osteoporosis. Since it is used for the treatment, not for replacement, the term HRT is changed to hormonal therapy (HT). HT should be individualized and used at the lowest dose with the shortest duration that the treatment is still effective for the patient's condition.

In 2007, the concept of '*window of opportunity*' was proposed,[14] as there is evidence that HT may be cardioprotective if started around the time of menopause and continued long-term. Subgroup analysis of the WHI study and NHS[15] showed a potential benefit of HT on cardiovascular disease when a low dose HT was initiated within 10 years after menopause. HT is the most effective treatment for menopausal symptoms which are common in perimenopausal and early postmenopausal periods. HT is usually initiated in the window of opportunity period; therefore when low dose HT (e.g. CEE 0.3 mg/day or estradiol 0.5-1 mg/day) is prescribed, it is possible to be used long-term.

HT is not the only treatment for menopause related problems. There are various problem specific medications such as non-HT medication for hot flushes (e.g. alpha sympathomimetic drug, selective serotonin/norepinephrine receptor inhibitors), for dyslipidemia (e.g. statins), for osteoporosis (e.g. bisphosphonates, strontium, parathyroid hormone fragment, selective estrogen receptor modulator). In addition, complementary alternative medicine (CAM) is used for menopausal symptoms. However, none of the treatments is perfect. The hot flushes medications are not as effective as HT; the bone and lipid medications are more effective but not as cost-effective; the majority of CAM measures cannot prove their efficacy. Therefore HT still has its future despite bad news during the past decade. HT has been traveling a long journey in the management for menopause. During the journey, HT has been tested and proved for its efficacy and side effects. As a result, HT dosages and regimens have been modified to balance risk and benefit.

The evolution of management for postmenopausal women began in the period of ancient or traditional medicine, then passed through the period of HRT surge and HRT phobia, and is now in the period of developing more rational use of HT. The treatment needs individualization and multimodalities, not only the HT. In fact, the treatment is only a small part of management which is based on the principle of preventive medicine, with holistic approach and considering all aspects of biopsychosocial medicine.

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