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Impact of menopausal hormone therapy on cardiovascular diseases

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Menopausal transition is recognized as a time of significant changes in the vascular system, body fat distribution, blood pressure, and blood lipid profiles, all of which contribute to increase the risk of CVD. Although the risk of cardiovascular disease (CVD) in women before menopause is relatively low, the risk increases markedly after menopause. Whether the loss of cardio protection is entirely attributable to the dramatic decline in estradiol levels after menopause remains unclear. These observations have subsequently led to concern in understanding how the timing of menopause impacts CVD. Women with premature and early menopause have a shorter total duration of estrogen exposure than women with later menopause and are hypothesized to have an elevated risk of CVD. This relationship has been observed for coronary heart disease, ischemic stroke, total CVD, and even heart failure.

The risks and benefits of menopausal hormonal therapy (MHT) have been evaluated extensively over the past three decades. The efficacy of MHT for management of menopausal symptoms, including vasomotor symptoms and vaginal dryness is well established. However, its relationship to CVD is complex. Previous evidence from systematic reviews of observational studies suggests that MHT may have beneficial effects in reducing the incidence of CVD in postmenopausal women, however the results of randomized controlled trials have had mixed results. A 2015 Cochrane review was conducted to assess the effects of MHT for the prevention of CVD in postmenopausal women, and whether there are differential effects between use in primary or secondary prevention. MHT in both primary and secondary prevention had no protective effects for all-cause mortality, cardiovascular death, non-fatal myocardial infarction, angina, or revascularization. However, there was an increased risk of stroke and venous thromboembolic events.

The timing hypothesis proposes that the cardiovascular effects of MHT depend on the timing of initiation of MHT in relation to menopause. The timing hypothesis provides a framework to

explain discrepancies in results between multiple observation studies and 2002 WHI trial. Newer observational data and reanalysis of older studies by age or time since menopause, including the WHI, suggest that for healthy, recently menopausal women, the benefits of MHT (estrogen alone or with a progestogen) outweigh its risks, with fewer CVD events in younger versus older women. Sub analysis of the WHI results by age group, and more recent randomized control studies, including the Kronos Early Estrogen and Prevention Study (KEEPS) and Early Versus Late Intervention Trial (ELITE), demonstrate that the risk of adverse CVD for MHT are low for women < 60 years of age or within 10 years from menopause. Women who initiate MHT when aged older than 60 years and/or who are more than 10 years, and clearly by 20 years, from menopause onset are at higher absolute risks of CHD, VTE, and stroke than women initiating MHT in early menopause. Personal and familial risk of CVD, stroke, and VTE should be considered when initiating MHT.

Although current data does not support using MHT for primary prevention of CVD, it does suggest that MHT can be safely used to treat symptoms in appropriately selected women close to menopause. It is important to weigh the benefits against the risks, including the rare risk of breast cancer, venous thromboembolism, and stroke. Understanding the safety profile of MHT will lead to physicians provide better individualized treatment for premature menopausal, perimenopausal and postmenopausal women.

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Menopause and Diabetes

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Diabetes is the fifth leading cause of death in Taiwan and the prevalence and incidence of diabetes mellitus increased with age, especially after those aged ≧ 50 years. Regarding to the effects of aging on glucose metabolism, it is generally recognized that age is an important factor for the incidence of diabetes. However, during the transition to menopause, an abrupt decrease in endogenous estradiol results in phenotypical, metabolic and biochemical changes. Besides aging itself, whether these changes in perimenopausal and menopausal women are associated with increase the risk of diabetes should be considered. In addition, the role of menopausal hormone therapy (MHT) in women with and without diabetes should be also concerned.

The aim of this presentation is to discuss the following issues:

1. Does Menopause Increase Diabetes Risk?
2. Impact of MHT on the risk of T2DM.
3. Effect of DM on Age at Menopause.
4. MHT in Women with DM.
5. Strategies for Diabetes Risk Reduction during the Perimenopause & Postmenopause.

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Global consensus position statement on the use of testosterone therapy for women

There are no clearly established indications for testosterone therapy for women; thus, a global consensus Position Statement on testosterone therapy for women was posted in 2019 by experts on behave of the international menopause society. This Position Statement has also been endorsed by The Endocrine Society, The EMAS, The NAMS, The International Society for Sexual Medicine, The International Society of Endocrinology, etc. This global consensus points 14 items of recommendations regarding the measurement of testosterone, the definition of female sexual dysfunction, the associations of androgen and female sexual function, the systemic testosterone therapy for postmenopausal women, the effects of testosterone on the psychological wellbeing and the musculoskeletal system in postmenopausal women, the possible androgenic side-effects of testosterone therapy on cardiovascular health and breast health and other serious adverse events, the assessment of female sexual dysfunction before testosterone therapy, current testosterone therapy and other androgenic preparations. The global consensus Position Statement reiterates the only evidence-based indication for testosterone therapy for women is for the treatment of HSDD in postmenopausal women but not for the treatment of any other symptom or clinical condition, or for disease prevention. To date, this consensus is the most authoritative report on comprehensive review of testosterone therapy in postmenopausal women.

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Hormone therapy in women with breast and gynecological disorder

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The incidence of gynecological and breast cancer increased and they affect both premenopausal and peri-menopausal women. The surgical and adjuvant treatments for cancer often cause the abrupt onset of menopause in younger women and, as treatments improve, women are living longer and quality of life is a critical concern. It is important to consider whether there are additional cancer-related risks in survivors of gynecological cancer, such as an increased rate of recurrence or decreased survival, which would preclude the use of hormone replacement therapy(HRT) when it may otherwise be indicated.

Available studies do not show an increase in recurrence or decrease in survival among women with endometrial, ovarian or cervical cancer who use HRT. Data regarding the risks of systemic HRT in survivors of breast cancer are varied, and an increase in breast cancer recurrence with the use of systemic HRT has been demonstrated in randomized controlled trial. Limited data exist regarding the use of vaginal estrogen, however, no effect on recurrence.

The decision regarding the use of HRT in women with cancer must be individualized and should take into account issue regarding quality of life.

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Individualized osteoporosis treatment in postmenopausal women

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Osteoporosis is characterized by skeletal fragility and microarchitectural deterioration. The conceptual definition of osteoporosis links the high risk of postmenopausal fractures to low BMD and qualitative changes in microarchitecture. The prevalence of osteoporosis varies depending on whether it is defined by fracture incidence or by low BMD (a T score of − 2.5 or less). It is estimated that postmenopausal woman has a 15 to 20% lifetime risk of hip fracture and a 50% risk of any osteoporotic fracture. Hip fractures can result in poor quality of life, a dependent living situation, and an increased risk of death. Spine fractures are also associated with an increased risk of death, are strong predictors of future fractures, and may result in chronic pain, kyphosis, and a loss of self-esteem needs.

Menopausal hormone therapy can effectively prevent bone loss, osteoporosis and fractures in postmenopausal women, including: estrogen, combined with estrogen-progestin, and CEE combined with bazedoxifene (conjugated estrogen)、Tibolone. Women's Health Initiative (WHI) confirms that hormonal supplementation therapy is meaningful to reduce bone fractures, including hip, spine and all non-vertebral fractures, but the bone protection effect quickly disappears after hormonal supplementation is interrupted. However, no increased risk of fracture rebound was found.

Without hormone contraindications, hormone replacement therapy may be the most appropriate method for the prevention and treatment of osteoporosis in women younger than 60 years old who have vasomotor symptoms or within 10 years after menopause; Women with early-onset menopause (less than 45 years of age) with bone loss are best treated with menopause hormones, at least until the average age of menopause (50 years).

When alternative osteoporosis treatment is not suitable or causes adverse reactions, long-term use of menopause hormone therapy is the choice of women at high risk for osteoporosis fractures; whether to stop menopause hormone therapy depends on the benefits and risks of non-skeletal factors.

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Progesterone vs Progestins: Clinical Dilemma and Concerns

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The main reason, which causes clinicians' dilemma and concerns on progesterone vs progestins for MHT, is the risk of breast cancer (BC). The others are risks of cardiovascular diseases (CVDs) and venous thromboembolism (VTE). These risks were published by WHI study and were overly reported by the media in 2002. However, researchers realize that those risks may be different between the use of different progestogens, namely, natural progesterone or synthetic progestins for MHT.

Micronized progesterone (MP) is a bioidentical hormone with a molecular structure identical to that of endogenous progesterone produced by the ovary. Synthetic progestins are structurally related to progesterone (e.g., medroxyprogesterone acetate (MPA), dydrogesterone) or to testosterone (e.g., levonorgestrel, drospirenone) and may mimic some of the effects of progesterone but may have different actions on progesterone receptors.

WHI studies evaluated the use of CEE+MPA and CEE alone and found that there was increased risks of BC and CVD by E+P but not by E-alone. These have brought enormous impacts on the use of MHT and caused considerable concerns and dilemma among HRT users and prescribers worldwide including Taiwan. However, studies have been conducted for evaluation of the related risks of progesterone and other progestins used in MHT. One of the most eminent studies should be count for the French E3N-EPIC cohort study (Breast Cancer Res Treat 2008; 107:103), which evaluated breast cancer risk in relation to different types of HRT. The study showed that the risk was significantly greater with MHT containing synthetic progestins than with MHT containing micronized progesterone. Other studies by Finland (Obst Gyn 2009;113:65– 1173) and UK (Climacteric 2009;12:514– 524) also showed the similar results. In addition, the UK-based General Practice Research Data showed no increase of CV risk with the use of estradiol and dydrogesterone.

Apparently, progesterone is different from synthetic progestins in its chemical structure, pharmacokinetics, metabolism, and importantly in the affinity to receptors. These differences may cause significantly lower risks of BC and CVD by the use of progesterone than synthetic progestins for MHT. Nevertheless, since not all progestins are created equal, dydrogesterone, which has similar characteristics of progesterone, when used with estrogen for MHT could have lower risks of BC and CV compare to other progestins.

Based on the above evidences and knowledge, IMS and NAMS both recommend transdermal estrogen combined with either micronized progesterone or dydrogesterone for MHT in women with intact uterus. By understanding all the differences, clinicians could be relieved from dilemma and concerns on the use of progesterone vs progestins for MHT.

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Menopause Hormone Therapy update at 2019

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Timing

Recent evidence suggests that women in early menopause who are in good cardiovascular health are at low risk of adverse cardiovascular outcomes and should be considered candidates for the use of estrogen therapy or conjugated equine estrogen plus a progestin for relief of menopausal symptoms. There is some evidence that lends support to the "timing hypothesis", which posits that cardiovascular benefit may be derived when estrogen therapy or hormone therapy is used close to the onset of menopause.

Route

The transdermal administration is preferred because this administration route bypasses the first-pass effect seen with the oral route of administration of estrogens. Recent studies suggest that orally administered estrogen may exert a prothrombotic effect, whereas transdermally administered estrogen has little or no effect in elevating prothrombotic substances and may have beneficial effects on proinflammatory markers.

Breast Safety

There is no increased risk of breast cancer with Estrogen-only therapy (ET). For estrogen– progestogen therapy (EPT), the choice of the progestagen component in combined HRT is of importance regarding breast cancer risk. There are unequal risks for breast cancer associated with different hormone replacement therapies. Micronized progesterone or dydrogesterone used in association with oral or percutaneous estradiol may be associated with a better risk profile for breast cancer than other progestogens for at least 5 years.

Endometrial safety

The progestogen dosages necessary for secretory transformation during sequential -combined use as well for achieving and/or maintaining endometrial atrophy during continuous combined use are dependent on the dosage of estrogen. Recent data suggest that, whereas micronized progesterone is apparently safer for the breast, it could be less efficient than synthetic progestin on the endometrium. Formulation of EPT containing natural progesterone was not associated with increased risk of breast cancer but may poorly protect against endometrial cancer. 5 mg daily dydrogesterone appears to be the lowest effective dose to ensure endometrial safety in a continuous combined regimen with 1 or 2 mg 17 β -oestradiol.

Duration

The benefits of MHT outweigh its risks in healthy menopausal women who initiate MHT during the 'window of opportunity' in the 10 years after the menopause or before age of 60 years. Because some women aged 65 years and older may continue to need systemic hormone therapy for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years

Conclusion

Regular follow up and check your HRT prescription! Start the estrogen with low doses and, if not effective, adapt the dose of your regimen according to body mass index. Check your patient' s compliance on hormone replacement therapy (HRT). The age of 52 is said to be a threshold for administering sequential EPT. Later, in postmenopausal cases, a switch to combined continuous EPT is recommended.

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Responds to Lancet Article on Timing of HT and Breast Cancer Risk

About Collaborative Group on Hormonal Factors in Breast Cancer * An article published in Lancet 2019.8.29 on " **Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence** " It's worth caring.

Most of the information on breast cancer and MHT in this paper is not new, although the results of studies related to Estrogen-only therapy are different from those reported in randomized trials of WHI. It is important to note that when collecting data in this paper, most of the MHT schemes are different from the currently recommended ones. This paper provides an important public health message about obesity and breast cancer risk. The impact of MHT on women with early menopause (before 45 years of age) must be judged by the condition of "normal (non-menopausal)" women of this age. In addition to the analysis of potential breast cancer risk, the use of MHT must also include the severity of symptoms and potential benefits to bone and cardiovascular. It is important to note that this paper does not mention the impact of the currently recommended MHT prescriptions on breast cancer risk.

The Taiwanese Menopause Society gathered expert opinions and formulated guidelines for health management and drug recommendations for menopausal women in Taiwan in 2019. Estrogen provides many important and effective treatments for women, but it can also cause health incompatibility. Although 60% of women think that hormone therapy is beneficial, they have doubts about its side effects, especially breast cancer. The society also continues to be rooted in empirical data. Physicians and medical staff must understand the indications for hormonal therapy, contraindications that are likely to be produced, and maintain good relationships and communication with menopausal women to maintain women's health and improve women's quality of life.