Editorial

Emerging Trends Of Menopausal Hormonal Therapy " Time Makes A Difference"

Menopausal hormonal therapy (MHT) was universal panacea for women problems from midlife onward, between 1980-1990. Promotion of concept was feminine forever. This concept was challenged by women's health initiative (WHI) and million women study (MWS) ,prescription of HT declined dramatically. Since publication provider became more concerned about risk of HT rather than benefits. Breast cancer risk with use of HT was identified as major concern for public & practitioner. WHI trial also revealed that women assigned HT had an increase in coronary heart disease events.

In past few years there has been renewed interest in risks of menopausal HT especially that of breast cancer and coronary events. Since original publication of WHI results in 2002, large no of subsequent studies have looked at these concepts on detail. Analysis of effect of age, proximity to menopause at time of intitation therapy, duration of treatment, dose, route of administration, and persistence of risks & benefits after stopping therapy have been recently described " Timing Hypothesis" .

Coronary heart disease; " Timing Hypothesis"

WHI showed increase risk of CHD events, hazard ration (HR) 1.20 in estrogen (E) + progesterone (p) therapy but women randomized to oestrogen alone have same risk as placebo. Absolute excess risk per 10000 women years attributed to E + P were 7 more CHD events.

Obserational studies suggested beneficial cardiovascular effect of HT. Here treatment initiated for vasomotor symptoms at time of menopause. In contrast in WHI, treatment was initiated more than a decade. It led to development of "timing hypothesis" . WHI trend towards lower rate of CHD events was noted in women who were given HT within 10 years of onset of menopause, HR of 0.89 in E +P whereas 1.7 in >20 years. In E alone HR was only 0.5 which increased to 1.0 at 20 years (p value 0.02). This supports timing hypothesis. It is obvious that HT can only be protective before development of advanced atherosclerotic changes.

"HT closer to onset of menopause-safer for CHD"

Breast cancer: " Gap Time Hypothesis"

Effect of MHT on breast cancer has caused concern. WHI confirmed the effect of MHT on breast cancer but showed no significant increased risk of breast cancer among E (CEE) along for an average 7 yrs. In contrast to effect on CVS, starting estrogen> 5 yrs from onset of menopause was associated with significant reduction in breast cancer (RR 0.58). This effect so called " gap time" within 2 yrs after MHT risk for breast cancer was 1.5 when untreated within 3 yrs from onset of menopause but not elevated if after 3 yrs (1.0)

Paradoxical Response in Breast Cancer

In post menopausal women, breast tumour that express estrogen receptors respond to high dose estrogen therapy. However similar tumour in premenopausal don't respond to estrogen. Decline in estrogen level associated with menopause may sensitize breast cancer cells to proapoptitic effects of estrogens. Estrogen deprivation using aromatose inhibitor also sensitized hormone receptor positive breast cancer to later treatments with estrogen. Recent trials have shown that high doses of estrogen therapy can be used to treat postmenopausal breast cancer. This paradoxical response to additional or loss of

oestrogen may explain both the short term decrease in breast cancer reported after stopping estrogen.

"HT later to onset of menopause is safer to the breast cancer"

Future Development

Breast cancer seems significantly effected by use of progestrone, which is used to oppose estrogen action on intact uterus which may lead to bad effect on the uterus and development of endometrial cancer. so we need to develop such therapy where both complications can be obviated.

Combination of low dose CEE with selective estrogen receptor modulator provides a new entity called tissue selective estrogen complex (TSEC). Which may be effective in reducing menopausal symptoms, increasing bone density providing favourable lipids effects while not increasing breast cancer risk and proving endometrial protection with progestin.

We look forward for such satisfactory menopausal hormonal therapy which can keep " feminine forever ".

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