DRUG REVIEW

Hormone Replacement Therapy : Impact of WHI Study

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Introduction

Menopause is defined as no menstrual period for 12 consecutive months. "Perimenopause" and "menopause transition" is the time approaching menopause, when pattern of menstrual periods starts changing. In the perimenopausal period, ovaries begin to shrink, levels of oestrogen and progesterone fluctuate as the ovaries try to compensate the hormone production. The symptoms of menopause vary greatly, the most common symptoms are hot flashes/flushes, night sweats and disturbances in the sleep pattern. Others are vaginal dryness, mood swings, osteoporosis, heart disease and memory disturbances(1). The therapeutic application of the postmenopausal hormone replacement therapy (HRT) is to counteract the symptoms of menopause which present due to the falling oestrogen levels during this period.

Oestrogen production from the ovaries falls at the time of menopause or following removal/damage to the ovaries. But continuous extragonadal production of oestrogen occurs in fatty tissues and the adrenal glands. As the ovarian oestrogen fluctuates and declines during menopause, the body goes through a period of readjustment. Menopause, rather than being a time of deficiency could provide biological protection. As the oestrogen promotes development of breast cancer; so a natural reduction in oestrogen levels in the body is beneficial for the prevention of breast cancer. Progesterone is another hormone which helps to bring about menstrual periods, prepares the uterus to receive a fertilised egg, maintain pregnancy and affects the development of breasts in pregnancy. It is added to HRT to prevent uterine cancer. Earlier studies seemed to support hormone therapy's ability to protect women against the diseases that tend to occur after menopause.

Therapeutic Intervention in Menopause

The crucial difference between HRT and other hormonal treatment is that HRT counteracts this natural reduction in the level of oestrogen which occurs at menopause. In other cases, such as an underactive thyroid, hormonal treatment is given because the gland functioning is improper and a deficiency state could be hazardous if not treated. HRT had been the standard therapy for treatment of menopausal symptoms. Not only did HRT relieve discomforts as hot flushes and vaginal dryness but also it provides protection against several postmenopausal conditions such as osteoporosis and heart diseases(2).

In July 2002, the Women's Health Initiative (WHI) – a large, multicentric clinical trial by the National Heart, Lung and Blood Institute (NHLBI) and other units of National Institute of Health (NIH) – reported that HRT actually posed more health risks than benefits. This was the turning point in HRT, as the number of health hazards attributed to HRT grew, practitioners discontinued routine prescriptions for this once a time very popular and rampant treatment modality and HRT use substantially decreased in the general population(3-5).

WHI study included two arms

(I) Women who took oestrogen progesterone combination therapy

With 5.2 years of follow up, for every 10,000 women each year, on oestrogen plus progesterone (combination therapy) when compared with a placebo, resulted in risk(s) and benefit(s) reported here as under.

Increased Risks

Breast cancer (26%), Stroke (41%), Coronary heart disease (29%), Venous thromboembolism (42%).

Increased benefits

Colorectal cancer (37%) and fractures (37%).

(II) Women who took only oestrogen therapy

With 6.8 years of follow up, for every 10,000 women each year, on only oestrogen therapy when compared with a placebo, resulted in risk(s) and benefit(s) as reported below.

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Increased risk

Stroke (39%) and venous thromboembolism (47%).

Increase benefit

Bone fractures (39%).

No difference in risk (neither increased nor decreased risk)

Coronary heart disease, colorectal/total cancer, deaths with uncertain effects in breast cancer

The two WHI studies cannot be compared directly because women on only oestrogen therapy began the trial with a higher risk of cardiovascular disease (like hypertension, hyperlipidemia, diabetes and obesity) than those, on combination therapy. Both studies were to be continued till 2005, but were stopped early. The oestrogen plus progesterone study was abruptly halted in July 2002 and only oestrogen study at the end of February 2004 but the follow up lasted till 2007.

WHI study also reported the effects of HRT on

(1) Mental functions

The women on combination therapy in the age group of 65 years and above had twice the rate of dementia, including Alzheimer's disease as compared to those on placebo. The only oestrogen therapy marginally increased the risk of mild cognitive impairment plus dementia.

(2) Urinary incontinence

WHI study has shown that both the therpaies increased the risk of development of urinary incontinence and worsened the symptoms of incontinent women.

(3) Quality of life

WHI study did not find any improvement with combination therapy on quality of life

Among younger WHI participants (age 50-54 years), there was a slight improvement in sleep pattern. Relief of hot flushes, night sweats occurred in the majority of women on combination therapy.

U.S Food and Drug Administration (FDA) suggested the following recommendations for HRT:

(1) For the treatment of hot flushes, night sweats, vaginal dryness and prevention of osteoporosis associated with menopause but carried serious risks. Therefore HRT is to be taken only when benefits outweigh the risks.

(2) For vaginal symptoms topical application (gel or cream applied locally) should be considered. If HRT is used for osteoporosis, the risk of osteoporosis must outweigh the risk of HRT, the practitioners should consider other treatment modalities before prescribing HRT for osteoporosis.

(3) HRT is not approved for the prevention of cognitive disorders such as Alzheimers' disease on memory loss.

(4) HRT should be used at the lowest doses for the shortest duration to reach the treatment goals.

Findings from the WHI study have concluded that HRT should not be used:

(1) To prevent coronary heart disease.

(2) In women with underlying heart disease(6).

The media reaction to the WHI data resulted in two–thirds of the users of HRT to terminate the therapy even without medical consultation(7). Various professional and non-professional bodies also quickly issued edicts, based on the WHI report, advocating the use of HRT in minimal dose and for shortest possible duration(8). Recent analysis of the WHI data and other randomized controlled trails have now unified much of the data on HRT and greatly changed the risk-benefit ratio for most women who commence HRT for symptomatic control around menopause. It has been observed that when HRT is initiated near menopause for control of menopausal symptoms, there may be additional benefits (reduced fractures and cardiovascular risks) that outweigh the risks (which are not significantly raised in women in perimenopausal period(9).

Risks Vs Benefits In Perimenopausal/Menopausal Group

Cardiovascular disease

There is a strong data to support the "critical therapeutic window" hypothesis that oestrogen is cardioprotective if initiated around menopause when there are still vascular oestrogen receptors responsive to exogenous HRT(10-12). HRT administered near menopause appears to reduce the progression of atherosclerotic plaque, but if administered many years after menopause is not beneficial and may sometimes disrupt established plaques with adverse consequences. A meta-analysis of randomized trials – has shown a statistically and clinically significant 39% reduction in cardiac events in the treatment groups, compared with the placebo control groups, when HRT is initiated in women under 60 years of age, but this cardioprotective effect was not seen in women starting HRT after 60 years(13). All cause mortality in younger HRT users compared with placebo was significantly reduced(14). Currently data from trials in women in perimenopausal period suggest that only oestrogen regimen may offer

greater cardioprotection than combined HRT, but more research is needed on the timing and type of progesterone therapy in combined regimen(13,15). The WHI study enrolled women who were on an average 13-14 years post-menopause (with an average age 63-64 years). Hence the outcome of this study is more relevant for women of older age group. The population in WHI study was unrepresentative of symptomatic women who start HRT near menopause. Data from the WHI study which included 8832 women under the age of 60 years in the two HRT trial arms now suggest a cardioprotective effect in women who start with HRT in perimenopausal period especially when only oestrogen therapy is given(10-15).

Breast Cancer

When increased relative risk (RR) of breast cancer found in the WHI study (RR=1.26) was compared to the other common risks of breast cancer, this relative risk was found to be similar to the breast cancer risk in a women with late menopause (RR=1.22) or in a nulliparous woman (RR=1.67)(16). Subsequent analysis of the WHI data showed that there was no significant increase in breast cancer among those who initiated combined HRT for the first time during the 7 years of the WHI study(17). Further data from the WHI study analysed that the women who had hysterectomy and were on only oestrogen therapy showed a significant reduction in the breast carcinoma(18). These results although are not in conformity with the relationship of oestrogen and breast carcinoma, but may incriminate use of systemic progesterone but the observational data reported that the incidence of breast carcinoma may increase with only oestrogen therapy when used for more that 20 years(19).

Thromboembolism

The risk of thromboembolism in women taking oral HRT is highest in the initial two years and in women with thrombophillia or obesity. The risk increases with age at the initiation of HRT(20). Hence parenteral routes of oestrogen delivery with micronised progesterone in women with intact uterus is not associated with thromboembolic risk(21).

Fractures

One-third reduction in fractures was seen by the WHI study. HRT remains a cost-efficient and relatively safe option for the prevention of fractures. When initiated before 60 years of age in women with osteoporosis, who also often have menopausal symptoms(22,23). This indication for HRT needs to be reevaluated as now the risks of HRT (especially low dose only oestrogen therapy) have been recalculated.

Cognitive Function and Dementia.

The effect of HRT on the cognitive function is likely to remain controversial because a long term trial from the time of menopause is probably impossible. Observational studies support critical therapeutic window hypothesis in which HRT use from perimenopausal period shows greater benefit for cognitive function than HRT taken many years after menopause(24).

Stroke

The prevalence of stroke is age-dependent and the numbers under age 60 years were small (in the WHI study) so as to test the critical window hypothesis for stroke.

Ovarian Cancer

Data from the WHI study showed a non-significant increase in ovarian cancer after 5 years of combined HRT but a significant increase after 5 years of unopposed only oestrogen therapy(25,26).

Menopausal symptom control and quality of life

Symptom control and perceived improved quality of life are the main reasons for commencement of HRT and for the high continuation rates. Review studies have shown that HRT efficiently controls vasomotor symptoms and urogenital symptoms(27,28).

Conclusion

The latest data on HRT do not warrant the fear and ultra-conservative edicts issued in 2002. The incidence of potential toxicity and hazards of HRT that may be decreased by gradually tailoring the therapy as per the individual needs. Adverse effects may be reduced by: a) Bare minimal HRT dosage, b) Using intrauterine progesterone delivery system to minimise or eliminate systemic progesterone adverse effects, c) Using parenteral routes, d) Starting HRT in symptomatic women in perimenopausal period for symptomatic control and for additional benefits (like reduced fractures and cardiovascular risks), e) Beyond the perimenopausal period women can terminate HRT if their quality of life is maintained without therapy, f) Older women with menopausal symptoms should not be denied HRT, if the risk-benefit ratio is assessed on an individual basis and each patient is educated so as to be aware of the risks.

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