REVIEW ARTICLE

Latest Evidence on Using Hormone Replacement Therapy in the Menopause

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Summary:

Hormone replacement therapy (HRT) is the most effective therapy of menopausal symptoms for perimenopausal and menopausal women. When HRT is individually tailored women gain maximum advantages and the risk are minimized. There are different types of hormones with different doses and different routes of delivery exist. . The use of HRT is an individual decision which women can only make once she has been given correct information and advice from healthcare professionals. HRT should be recommended in women with premature ovarian insufficiency with advice to continue until the average age of menopause at 51.4 years. This review item promotes confidence in prescribing HRT in most symptomatic women. Prescribing HRT in women with relative contraindication where evidence is limited. Quality of life is priority. Multidisciplinary approach may be necessary and informed written consent documented.

Key words: Hormone replacement therapy (HRT), Menopause, Quality of life.

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Methodology:

It is a literature review item. It reflects the need of HRT in perimenopausal and menopausal women. It also notices the adverse effect of HRT. It reviews in Bangladesh medical journal (BMJ) , the topic on menopause and hormone therapy. This review is supported by information from the latest evidence on HRT in gynecology, It also collected from different journals e.g. TOG, Evidence based assessment of the impact of HRT. Information also collected from different web side like FIGO, American menopausal society recommendation of hormone replacement therapy and systemic review of Cochrane database study.

Introduction:

Permanent cessation of menstruation for at least 1 year in a normally menstruating woman is called menopause[1]. The mean age of menopause is different in different region of the world. In European country mean age is 51.4 years. Common menopausal symptoms are vasomotor symptoms, mood changes, loss of concentration, dryness of vagina, atrophy of secondary sexual characteristics, loss of libido, musculoskeletal pain, osteopenia, osteoporoses etc.[2] Frequency of vasomotor symptom varies on different geographical region. Distressing symptoms last for 2-3 yrs in the premenopausal period. It is predominant in premature ovarian failure and iatrogenic menopause. Vasomotor symptom responds effectively to replace estrogen. HRT in which the estrogen is similar to natural ovarian production should not be confused with the potent ethinyl estradiol used in combined oral contraception regimens. The addition of a progestogen or micronized progesterone is essential of women still has a uterus to prevent endometrial hyperplasia and cancer. Estradiol can be delivered orally (an micronized estradiol, estradiol valerate estrone, estriol or conjugated equine estrogens) or transdarmally 17beta-estradiol. Topical vaginal administration of estrogen is used for localized symptoms. Various progestogen are used in combination with estradiol, either is a sequential cyclical regimen or as continuous combined therapy (CCT). Progestogen is mostly administered orally. Only two formulations being available one is transdarmal and another one is levonorgestril intrauterine system. Tibolone is an oral synthetic steroid with estrogenic, androgenic and progestogenic actions that can be used as HRT in postmenopausal women. The role of supplemental testosterone will not be covered in this article[3].

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Discussion:

Epidemiology-

Mean age of menopause is different in different region of the world. Median age of 42.1-49.5 years South Asian countries but in European countries median age is (50.1-52.8) is 51.4 years. Vasomotor symptoms (hot flushes and night sweats) are common, affecting about 70% of women (severely in about 20%), for a median duration of 5.2 years, but may continue for many more years in about 10% of women[4]. Menopausal symptoms adversely affect quality of life. In the 1970s epidemiological studies identified that the most common cause of death in women with early onset of menopause is cardiovascular diseases (CVD). The possibility that estrogens may be protective to the female cardiovascular system led to much research into looking at the effect of estrogen on the cardiovascular system[5-6]. Since epidemiological studies was the heart and estrogen/ progesterone replacement study designed to identify of HRT prevented recurrence of coronary heart disease in women with established coronary heart disease.

Pathophysiology:

Menopause is due to the depletion of ovarian follicles secondary to apoptosis or programmed cell death along with changes in the hypothalamic and pituitary hormones, the ovary fails to respond to the pituitary hormones. Menopause also occurs due to premature ovarian insufficiency which includes genetic, infection, autoimmune and metabolic factors or due to surgery. Women born with around seven million oocytes but during their reproductive lifespan only release up to 500 oocytes. Therefore ovarian insufficiency may be due to lower number of follicles present in the ovary or increase rate of follicle loss. Another possibility is that abnormal pairing during meiosis may result in oocytes apoptosis. Surgical menopause occurs due to surgical removal of ovaries, commonly ovarian malignancy, cervical cancer radical hysterectomy or severe endometriosis. It also occur due to chemotherapy (Anthraycline, cyclophosphamide) and or radiotherapy.

Randomized control trial on post menopausal women ($\bar{e}$ an average age of 66.7 years) with conjugate equine estrogen and medroxy progesterone acetate did not showed any benefit but increase various thromboembolism more pronounced is the first year of use and gall bladder disease.[7]

Effect of HRT

Premature ovarian insufficiency

In the developed world menopause under 45 years in classified as premature ovarian failure[8-9]. Women with premature ovarian insufficiency have an earlier onset of both CVD and osteoporosis. They are also noted to have reduced breast cancer risk compared with their menstruating peers. The risk of breast cancer with HRT use in these women in deemed to be not greater than population risk for their age, while the benefits are greater by prevention of long term morbidity. Hence it is strongly advised that these women should consider taking HRT, at least until the age of 50

Effect of HRT on cardiovascular events in recently post menopausal women:

A randomized study by Schaerbeek et al.[10] that was carried out in Denmark in 1990-1993, has been the first one to address the correct timing and the long term effect of HRT on CVD in recently postmenopausal women. After 10 years women on HRT were found to have had a significant reduction in mortality and CVD related events, with no apparent increased risk of VTE, stroke or cancer. The health benefits were seen up to 6 years after stopping. 2012 Cochrane collaboration systemic review[11] assessed the clinical effects of using HRT for 1 year or more. Twenty three randomized double blind studies were included involving 42830 women aged 26-91 yrs. Since 70% of data were derived from the women's health initiative and HTRS most participants were post menopausal. This review included that there was no indication to use HRT for primary or secondary prevention of CVD or dementia or for protection of cognitive function. There was a significant benefit and reduction in the risk of bone fracture after 5 years use. So no single recommendation for optimum duration of treatment or safe upper age limit for use of HRT is therefore possible because they will be specific to every woman's circumstances. For most women, short term treatment will be sufficient to relieve vasomotor symptoms for others; HRT may need to be continued for longer. For all women the lowest effective dose should be used for the shortest possible time and the need to continue HRT should be reviewed at least yearly.

3. Practical guidance on prescribing HRT :

HRT in Low risk women:

There are few women in whom HRT is an absolute contraindication. The fear of increased breast cancer risk is foremost for most women and physicians. The risk as a result of taking HRT is much lower than the risk associated with obesity, moderate alcohol intake or delaying first pregnancy until after 35 years.[12] The absolute increase in breast cancer risk is 6 times per 1000 women for 5 years of estrogen and progestogen and reverts back to the population risk 5 years after stopping[13]. Three months trial of HRT will enable a women to assess her quality of life, whether HRT has been of benefit or not and the decide on duration, having been made aware that the breast cancer risk will be duration dependent.

A full history will reveal any existing medical problems or family history or CVD or cancer. This information will point the clinician to the correct regimen, dose and route of administration. Baseline measurement of body mass index (BMI) and blood pressure give guidance as to the need for further investigation. There is no indication for a pretreatment mammogram or breast examination pelvic examination, cervical smear or endometrial thickness measurement by transvaginal scan.

Once established on HRT a women should not discontinue abruptly but should wean of treatment gradually .Continuing or restarting on HRT is a decision based on quality of life.

Troublesome menopausal symptoms can start in the perimenopausal state. To avoid unnecessary investigation or unscheduled bleeds these women should be commenced on sequential (cyclical) HRT for 12-14 days per months. If periods are reasonably frequent, the HRT should start with the next bleed, but if infrequent (more than three months apart) the HRT can be commenced without awaiting a period.

The most common adverse effects include headache breast tenderness, bloating and muscle cramps. Weight gain is not an adverse effect of HRT[14]. Adverse effects are transient and usually resolve by 3 months. Any unscheduled bleeding should be investigated. Persistent progestogen adverse effects can be addressed by altering the progestogen or by using an intrauterine system. This will give the benefit of contraception, reduction to periods and endometrial protection with continuous estrogen use.

Once established on HRT an annual review is all that is necessary. HRT does not increase blood pressure and there is no indication to monitor more frequently. Women who wish to stay on HRT for more than 5 years should be encouraged to switch to combined contraception to avoid an increased risk to endometrial hyperplasia seen in women on long term sequential therapy. Lower doses may be evaluated prior to switching and if tolerated. Then the women can switch to a lower dose of CCT by completing the month of sequential treatment. So that the withdrawal bleeding occurs before starting the CCT. As a rule, women aged 54 years would be advised to switch as 80% of women at this age will be postmenopausal.

CCT (continuous combined therapy) or Tibolone are used in postmenopausal women (amenorrhea for 12 months). Such women will have been estrogen deficient for this time and starting with a low dose combination will minimize adverse effects and breakthrough bleeding. The dose can be increased after 3 months if menopausal symptoms remain. Initial breakthrough bleeding is common but usually reduces and ceases with time. Persistent bleeding should be investigated after 6 months with an ultrasound scan and / or endometrial biopsy. The risk of endometrial cancer is lower in those using CCT than in those not using HRT. If bleeding occurs after a time of amenorrhea, then investigation is still required even if a causative factor is identified causative factors included :

- Forgotten pills, poor patch adhesion, poor compliance.
- Introduction of new medication or over the counter predations.
- All other cases of post menopausal bleeding.[15]

Patients with relative contraindication to HRT could be referred to specialist service for advice. Quality of life may be the deciding factor for women with contraindication and in such circumstance a written statement from the women in helpful and may avoid any future medico-legal complication.

Thrombosis risk:

According to Canadian society incidence of VTE and PE increased from 0.12 %(in general population) to 0.2%

in HRT user. The risk of VTE associated with HRT use is mostly seen after using 12 months. This risk depends upon type of HRT ,dose of drugs and route of administration.Transdermal HRT is associated with a lower risk of VTE than oral but lower doses may be less likely to promote this risk. Women who are sedentary, overweight and smoker increased risk of VTE[16-17].

Other benefits of HRT :

Other observed benefits of HRT other than those affecting vasomotor symptoms, include improvement of low mood and protection against loss of tooth. Several studies have identified a risk reduction of bowel cancer in women using HRT, but this is not deemed to be as indication to prescribe HRT as preventative for this disease. Some forms of Estrogen replacement therapy appear to be neuroprotective, preserving cognitive function and reducing the risk of Alzheimer's disease. Some protection against Parkinsonism disease has also been seen. . It is suggested that there may be a 'Window of opportunity' for preserving cognitive function if HRT is used early in the menopause.[18] HRT is effective in preventing the bone loss normally associated with the menopause.[19]

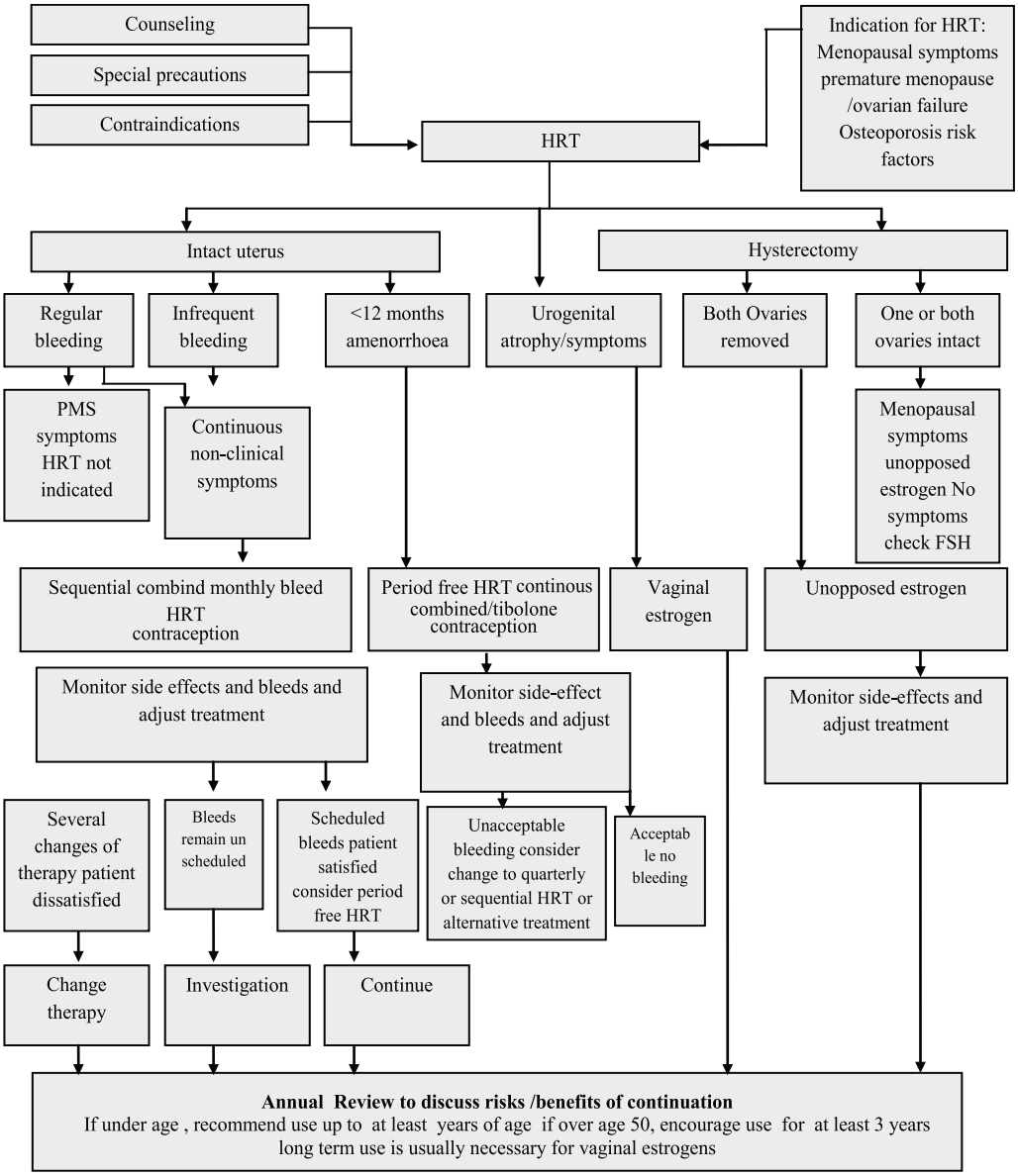

Fig.-1: *Guidance on HRT prescribing with permission from the West Midlands Menopause Society.*

Topical vaginal estrogen

Atrophic vaginitis is treatable with topical estrogen, resulting in cornification and regeneration of the vaginal epithelium. This improves lubrication and sexual function. Systemic absorption is insignificant with low-dose topical estrogen. Additional systemic progestogen is not required. Vaginal estrogen may reduce symptoms of urgency of micturition and recurrent urinary tract infections. Vaginal symptoms can persist even when on adequate systemic HRT; in such cases both topical and systemic are required. The safety of topical vaginal estrogen has not been assessed in patients with breast cancer, where theoretically the risks are small. The benefits to the genitourinary tract along with improved sexual intimacy may outweigh the risk.

HRT after breast cancer[20-23]

Breast cancer is a common condition that affects women of all ages. The vast majority of breast cancers are estrogen receptor positive (ER+) and require adjuvant tamoxifen or aromatase inhibitors, the adverse effects of which can be exacerbated and debilitating menopausal symptoms. Many breast cancers and precancerous change (ductal carcinoma in situ) are screen detected and caught at an early stage, with excellent prognosis. Adequate studies have not been done where such individuals have continued on adjuvant treatment with the addition of HRT. Some case-control studies 3S have shown no defrayment to the mortality rate or recurrence rate with HRT.

Therefore, HRT use is a patient choice. There is inadequate information on the risks and benefits of herbal and alterative over-the-counter preparations.

The specialist needs to consider the following factors when discussing management in order to predict prognosis:

- Stage of the disease at diagnosis (size, ER status, grade of tumor and lymphnode status). This gives a guide to the prognosis.
- Type of adjuvant therapy currently or previously used.
- Time since diagnosis.
- The woman's attitude to her symptoms.
- The woman's fear of recurrence/fear of using hormones.
- What she has tried already.

Non-hormonal treatments

Women in need of treatment may be offered clonidine, selective serotonin reuptake inhibition (SSRI)(if not on tamoxifen) or selective nor adrenaline reuptake inhibitors(SNRI) (unlicensed indication for vasomotor symptoms), or gabapentin, along with self-help tips for a trial period of 3-4 months. If this is ineffective, then the next option may be evaluated. When all alternative prescribed medications have been tried, then a discussion about quality of life and survival is relevant. Should the patient wish to try HRT, it is recommended that this is discussed with her oncologist and care providers.

TIBOLONE

Tibilone, a selective tissue estrogenic activity regulator, is effective in treating symptoms in postmenopausal women. The evidence of a reduced stimulatory effect on breast tissue compared with other HRT preparations meant that it was feasible to evaluate its safety in a randomized controlled trial in women with recently diagnosed breast cancer[24]. Quality of life was improved in the treatment group, but a higher rate of breast cancer recurrence was seen only in the women with ER+ disease. There are no data on whether it is safe to use in disease-free survivors who still experience menopausal symptoms many years after their initial treatment.

Family history of breast cancer

As seen in the Nurses' Health study[25] HRT did not increase the risk of breast cancer in those women with a family history. Therefore a family history of breast cancer is not a contraindication to HRT, rather an opportunity for the clinician to identify whether the history is significant and warranting a referral to 'the clinical geneticist and additional screening under 50 years of age.

Carriers of BRCA mutations

BRCAI and BRCA2 mutation carriers are at increased risk of breast and ovarian cancer. Risk-reducing surgery with mastectomies and bilateral salpingooophorectomy (BSD) is usually carried out when the family is complete[26]. Surgical menopause in these premenopausal women causes acute and severe symptoms. Preoperative counseling will help the patient decide between BSO only, or hysterectomy plus BSO. The progestogen required when the uterus remains may influence the decision. HRT is indicated in these young women to

avoid the early onset of osteoporosis and CVD associated with a premature menopause. The use of HRT following risk-reducing surgery appears to be safe with no additional increase of breast cancer, especially if estrogen-only therapy is used.[27-28]

FIGO recommendation in menopausal syndrome, 2017[29]

1) Certain type of HRT may protect memory loss
2) Biphosphonate continue significantly prevent hip fracture in compare with no user or stop use more than 2 years
3) Soya protein an reduce coronary heart diseases.
4) Avoidance of caffeine significantly reduces menopausal symptoms.
5) HRT does not shorten the lives.

American menopausal society recommendation of HRT [30]

The 2017 hormone therapy position statement of the north American menopause society recommend that hormone therapy remains the most effective treatment for vasomotor symptoms and genitourinary syndrome of menopause and has prevent bone loss and fracture . The risk of hormone treatment differ depending on type ,dose, duration of use, route of administration, timing of initiation and whether a progestogen is used.. For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture. For women who initiate hormone treatment more than 10 or 20 years from menopause onset or aged 60 years or older, the benefit risk ratio appears less favorable because of greater risk of coronary heart diseases, stroke VTE, and dementia. Longer duration of therapy must be periodic reevaluation.

Conclusion:

Symptomatic women benefit from the use of HRT. Strictly speaking, there are no absolute contraindications to HRT.Relative contraindications are personal or family history of VTE, cardiovascular diseases. Alternative therapies are limited in there effectiveness and safety .Combined HRT should not routinely recommended for all postmenopausal women. It can be offered in symptomatic postmenopausal women for reduce distressing menopausal symptoms, for prevention of hip fracture, vaginal dryness when alternatives are ineffective. It should not offer for protection and prevention of CVD, breast carcinoma, colorectal diseases.

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