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Review Article

Prescribing Hormone Replacement Therapy: To Whom, When, What and How?

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Received: September 17, 2021; **Published:** October 27, 2021

Abstract

Increase in life expectancy has increased the number of years women live their life in menopausal period. Estrogen deficiency in the menopausal phase, brings along many health ailments that can affect the quality of life. Use of hormone replacement therapy (HRT) to ameliorate the menopausal symptoms is like a double-edged sword with its inherent risks and advantages. However, judicious use of HRT in this difficult phase of a woman's life may bring respite, with minimum side effects and enhanced efficacy. The present review aims to provide currently available evidence regarding the use of HRT, so that the practicing gynecologists are empowered to use it aptly without any reservations.

Keywords: *Menopause; Hormone Replacement Therapy; Vasomotor Symptoms; Urogenital Atrophy*

Introduction

Menopausal period is associated with estrogen deficiency and nearly one-third life of a woman is spent in this deficient state.

Menopause is diagnosed retrospectively as a period of amenorrhea for 1 year after the last menstruation cycle [1]. Biochemically it is confirmed by two serum FSH levels more than 40 IU/ml done at least 4 weeks apart [2]. The average age of menopause in India is 46 years [3]. This early age as compared to western population, predisposes women in India, to increased incidence of chronic health conditions known to be associated with menopause. These chronic diseases along with other menopause related symptoms affect the quality of life of the women. These problems are also faced by women following surgical menopause as well as women diagnosed with premature ovarian insufficiency. Premature ovarian insufficiency (POI) is diagnosed when ovarian function ceases before the age of 38 years. As per European Society of Human Reproduction and Embryology (ESHRE) 2005 guidelines, POI is defined as oligomenorrhea or amenorrhea over a period of 4 months and serum FSH levels more than 25 IU/L on two occasions 4 weeks apart [4].

Hormone replacement therapy (HRT) is a viable option to improve the quality of life in these women, but inadequate knowledge and fear of adverse effects makes the gynecologists hesitant in prescribing it. It has also been shown to have favorable effects on serum lipid profile, glucose homeostasis and bone health. In this review, the authors aim to simplify the indications, contraindications, doses, duration and side effects of HRT so that the gynecologists are empowered to use this modality of treatment in postmenopausal women with confidence and manage them optimally.

Miseries of menopausal transition and menopause

Women in perimenopause and menopause period suffer from many distressing problems known as climacteric symptomatology. These are subdivided into somatic symptoms such as vasomotor symptoms; psychic disorders; organic symptoms such as skin changes; urogenital changes; weight changes; and metabolic symptoms such as lipid metabolism abnormalities, atherosclerosis, osteoporosis. Some of the important symptoms are discussed below:

- Vasomotor symptoms (VMS): These include hot flushes and excessive sweating, which could include both cold or night sweats. These appear usually within 1 - 2 years of final menstrual period and may continue for 4 - 5 years. Incidence of vasomotor symptoms is reported to be around 75% [5]. Grading of VMS is important in order to plan treatment and its follow up [6]. It can be graded according to the severity of symptoms as follows:
    - Mild- mild feeling of heat without sweating.
    - Moderate- feeling of heat with sweating.
    - Severe- feeling of heat with sweating and palpitation which disrupts usual activity.
- Urogenital symptoms: These occur secondary to changes caused by estrogen deficiency in bladder, urethra, vagina and genitalia; and include symptoms like dysuria, sexual discomfort, vaginal dryness and increased risk of urinary tract infection. The prevalence of these symptoms has been found to be approximately 15%. However, women usually do not present with these complaints. Therefore, history taking has to be elaborate in order to elicit the real cause of distress in these women [5,7].
- Osteoporosis, osteopenia, osteoarthritis: Bone loss is associated with estrogen deficiency. This, along with loss of muscle strength and impaired balance, may be the underlying cause for increase in incidence of fractures in postmenopausal women.
- Loss of cognition/dementia or depression: Loss of cognition has been related to estrogen deficiency and women may suffer from dementia. Dementia is characterized by loss of any of the two-core mental functions which include memory, communication, language, ability to focus, do reasoning and do daily routine activities. Usually dementia is progressive, so early diagnosis and timely treatment is important. Depression is also diagnosed in menopausal transition and postmenopausal phase more frequently as compared to in premenopausal phase.
- Cardiovascular diseases: Risk of cardiovascular diseases increases after menopause, more so in women with metabolic syndrome. The prevalence of metabolic syndrome in Indian women is estimated to be 40% [8]. Prevention is the best strategy to mitigate this risk.

HRT-To whom?

The chief indications for starting HRT are mentioned in table 1. The women with any of the stated conditions should be prescribed HRT if no contraindications exist. HRT has been found to be associated with improvement in quality of life of the women by causing improvement in VMS symptoms, psycho sociological and physical changes [9-11].

Prevention and treatment of symptoms due to estrogen deficiency which include: • Vasomotor symptoms • Urogenital symptoms • Osteopenia/osteoporosis
Menopausal transition phase if symptoms are debilitating.
Following surgical menopause, even if asymptomatic, until the mean age of menopause.
Premature ovarian insufficiency, even if no symptoms, until the mean age of menopause

Table 1

The contraindications for HRT have been listed in table 2.

• Active endometrial or hormone dependent gynecological cancer
• Active breast cancer or high risk for developing breast cancer
• Active liver or gall bladder disease
• Venous thromboembolism
• Cardiovascular disease or at high risk of developing the CVD
• Undiagnosed abnormal vaginal bleeding

Table 2: *Contraindications for HRT.*

Hrt-When?

The decision to start HRT should be individualized for each patient depending on the indications and contraindication, in order to ensure maximum benefit to the patient. Any woman presenting with menopause related complaints should be evaluated systematically starting from proper history and culminating in detailed examination and laboratory tests. It is a must before starting HRT.

The salient features to consider are [12-14]:

History

- History of smoking or alcohol intake.
- History of depression and treatment taken.
- History of malignancy, cardiovascular diseases, venous thromboembolism, diabetes, thyroid, liver disease.
- Family history of Alzheimer's disease.

Examination

- Height, weight, BMI.
- Blood pressure

- Thyroid and breast examination.
- Pelvic examination.

Laboratory tests

- Complete blood count
- Liver and kidney function tests.
- Blood sugars
- Lipid profile
- Mammography
- Bone mineral density
- PAP smear
- Pelvic ultrasonography.

Optional tests, if required as per history and examination, are:

- Thyroid function test
- Endometrial biopsy.

Optimum time to start HRT

- In cases of premature ovarian insufficiency (POI), HRT should be started immediately and continued till the average age of menopause. Further need for continuation has to be decided as per the need and risk-benefit analysis.
- In cases of surgical menopause, same regime as POI should be followed.
- In cases of natural menopause and indications of starting HRT, it is preferable to start within 10 years of menopause or age less than 60 years as it is involved with least risk to the patient. This is known as the "Timing hypothesis" [8]. As per the findings of the Cochrane database, the risk ratio of ischemic heart disease and overall mortality are 0.52 and 0.7 respectively when HRT is started within a period of 10 years of menopause [15,16].

HRT-What and how?

HRT or menopausal hormonal therapy includes estrogen, progesterone, combined therapies, androgen therapy, SERMs (selective estrogen receptor modulators- raloxifene, bazedoxifene), Tissue selective estrogen complex {Bazedoxifene and Conjugated Equine Estrogen (CEE)} and gonadomimetic -tibolone.

- **Estrogens:** Estrogens can be administered orally, transdermally, percutaneously, intramuscularly, intranasally, subcutaneously or locally i.e. vaginally with dosing and timing of administration as per the women's need. Estrogen has three forms, E1- estrone, E2- estradiol, E3- estriol. Estradiol is FDA approved and is the most potent of all the forms. Thus, it is also the preferred estrogen for HRT as it is effective in small doses, thus reducing the incidence of adverse effects of the drug. Estriol is not FDA approved but still forms a part of vaginal creams.

Oral

Usually, estrogen is used orally in single daily dose. Estrogen should always be started in lowest dose. Effect takes 1 month to be seen and maximum effect is seen in 3 months' time. The various formulations available are: CEE- (0.3 mg, 0.625 mg), 17 β estradiol- (1 mg, 2 mg), Ethinyl estradiol- (0.02 mg, 0.05 mg), Estradiol valerate- (1 mg, 2 mg) etc. Oral route of HRT is avoided in cases of conditions like hypertriglyceridemia > 400 mg/dl, obesity, DVT or history of DVT, varicose veins, tobacco use, active gall bladder disease and migraine with aura [17].

Transdermal patches

These contain 0.05 mg of ethinyl estradiol. These were designed with the idea of bypassing the first-pass effect seen with oral route of administration and providing better bio-availability. They were considered to be better in cases of intolerance to oral preparation, in cases with diabetes mellitus, hypertriglyceridemia, cardiovascular or liver disease. But, these are not used these days owing to high rates of expulsion due to sweating.

Gels

These contain 0.75 mg or 1.25 gm E2 and can be applied on arm or forearm.

Vaginal creams

Vaginal creams containing E3, CEE or E2 are applied at bedtime for 10 days followed by bi-weekly for the desired duration depending on symptoms resolution. These are the agent of choice for urogenital symptoms.

Metered dose transdermal sprays

These are the newest methods available. In a recent study, it was found that with 1.53 mg of transdermal spray, the levels of estradiol, estrone or estrone sulphate gradually showed an increase and stable levels of estrogen levels were achieved on the 7^{th} - 8^{th} day of application. This combined the advantages of transdermal application with precise dosing [18].

Use of estrogen therapy in isolation is reserved for women without the uterus; as unopposed estrogen increases the risk of endometrial malignancy in women with intact uterus:

- **Progesterone:** It is available in natural form as micronized progesterone or as synthetic form like dydrogesterone, medroxyprogesterone acetate (MPA), norethisterone acetate (NEA) or levonorgesterol. Natural progesterone and dydrogesterone have a better safety profile as compared to MPA as well as NEA, which have been found to be more androgenic and associated with increased risk of breast cancer [8]. Progesterones alone are usually not effective in managing the menopausal symptoms. However, they form an important part of HRT in women with intact uterus as they mitigate the adverse effects of estrogen on the endometrium. Thus, dydrogesterone or natural micronized progesterone in combination with 17 β estradiol should be the HRT of choice for women with intact uterus. The indications for adding progesterone in hysterectomized women include history of endometriosis, endometrioid ovarian cancer and partial hysterectomy.

Formulations are available in the form of oral, vaginal and intrauterine system.

The various progesterone formulations available are [17]:

- Oral progesterone: 200 mg or 300 mg for 12 days for sequential regimens.
- Vaginal progesterone: 100 mg or 200 mg for 12 days.
- Dydrogesterone: 5 mg daily or 10 mg for 12 days.
- Levonorgestrel intrauterine system (LNG-IUS).

Combined HRT regimes

- **Cyclical hormone replacement therapy:**
    - Monthly- Estrogen is used every day with progesterone added for 10 - 14 days each month. This regimen is most suitable for perimenopausal women. It contains CEE 0.625 mg daily and MPA 5 - 10 mg for 10 - 14 days. Withdrawal bleeding occurs following progesterone finishes in the regimen.
    - 3- Monthly- Estrogen is used every day with progesterone added for 14 days at the end of three month.
- Continuous-combined regimen- Estrogen and progesterone in same dose is given over the entire regime. This regimen is most suitable for postmenopausal women. Withdrawal bleeding can happen in unpredictable manner in some women and usually stops in 6-8 months following endometrial atrophy.
- Low dose OCP's can also be used in perimenopausal period with distressing menopausal symptoms mainly VMS, irregular vaginal bleeding and also provide an effective contraception. Formulation in low dose OCP's are ethinyl estradiol 20-35 micrograms and norethindrone acetate 0.5 - 1 mg:
    - Tibolone: It is a synthetic steroid molecule which is basically a progesterone. After absorption, its metabolites have estrogenic, progestogenic and androgenic properties with different action on different body tissues. It has an estrogenic effect exerted on brain, bone and vaginal tissues as well as progestogenic and antiestrogenic action on endometrium and breast. Androgenic action is seen on mood and libido. The dose is 2.5 mg/day (1.25 mg/day is equally effective dose). The International Tibolone consensus Group 2005 and Asia Pacific Tibolone Consensus Group 2010 implied that Tibolone shows a positive effect on mood disorders, sexual function and sleep and have less side effects in the form of breast pain or abnormal vaginal bleeding [19,20]. Specific indications for using tibolone include depressed mood and libido, adverse effects with convention HRT, older women (>60 yrs) and family history of breast cancer or history of endometriosis. However, one should not prescribe tibolone for long duration in older women owing to the increased risk of stroke in them. It is also known to be associated with increased recurrence in women with history of breast cancer.
- SERMS: These act by having beneficial effect of estrogen on bone and lipid metabolism and have antagonist action in reproductive tissue. Tissue-selective estrogen complex is a combination of SERM and CEE i.e. bazedoxifene 20 mg and CEE 0.45 mg This has no effect on endometrium and positive effect on bones. It also has a mild side effect profile and so is better tolerated.

Alternatives to HRT (non-hormonal therapy)

Non-hormonal therapy helps in treating climacteric symptoms to certain extent, but long-term effect if not proven. These include [21]:

1. Antidepressants like SSRI's used in cases of hot flushes.
2. Phytoestrogen like isoflavones or lignans. These are non-steroid plant derived compounds which are able to produce an estrogenic effect.

Symptom wise treatment options for menopausal ailments

Vasomotor symptoms

It has been seen that use of HRT helps 62.7% women in combatting the symptoms and help in improving quality of life (QOL) [22]. Studies have shown that estrogen reduces the frequency of symptoms by 75% and its intensity by 87%. Any form of estrogen therapy requires 6 - 8 weeks to reach its maximum effect. Discontinuation of therapy may lead to return of symptoms in 50% of women [18]. For women presenting with vasomotor symptoms, various options are available as highlighted below:

- Low dose oral contraceptive pills. This is effective in menopausal transition phase. There can be worsening of symptoms in 7-day pill free period, in that scenario, continuous regime can be used.
- Estrogen + Progesterone therapy (EPT).
- Only progesterone like micronized progesterone in a dose of 300 mg/day or dydrogesterone 5 mg/day can also be used, but long term safety data are lacking.
- SSRI's like Paroxetine in low dose of 10-12.5 mg can be used in women with VMS and with known case of depression or sleep deprivation. Other indications are where estrogen is contraindicated or not well tolerated. SSRI's are known to be effective in improving VMS in 40-65% cases [23]. Some small studies have also shown positive effects with gabapentin as well in 50% cases in a dose of 900 mg/day [24].

Urogenital symptoms

- In women suffering from mild vaginal atrophy, topical estrogen therapy is known to be effective. It also helps in reducing vaginal acidity and maintaining vaginal flora and reducing the risk of recurrent urinary tract infections postmenopausal women. In women with severe symptoms, both vaginal and systemic therapy is required. Vaginal application with estriol cream (Evalon) in the dose of 0.5 mg daily is done at bedtime for 10 days followed by bi-weekly for the desired duration (usually not more than 12 weeks total) depending on symptoms resolution. Estrogen helps in increasing blood flow and maturation index of vaginal epithelium and thus relieving symptoms. The use of only estrogen therapy should be continued till symptoms resolves. If continuation is necessary, the endometrial should be evaluated before deciding to continue the therapy [25]. Continuous testosterone therapy has shown benefits in women with hypoactive sexual desire disorders but their availability is limited and is also associated with side effects owing to its known virilizations effects [26].
- Oral ET/EPT may be used in cases with sexual dysfunction.
- SERM (Selective estrogen receptor modulator) like Ospemifene in a dose of 60 mg/day may be effective. This is suited for women not candidates for estrogen therapy. It helps in relieving moderate to severe symptoms.

- Combination of SERM with CEE is also effective in decreasing vaginal dryness and dyspareunia.
- Tibolone- It improves vaginal dryness, sexual desire, sexual arousal and thus frequency of sexual intercourse. It helps by increasing bioavailability of testosterone through reduction of direct androgen effect. This is found to be better than ET or EPT for improvement of libido. Optimal starting dose is 2.5 mg/day. Maximum effect is seen in 12 weeks.
- Vaginal testosterone alone or combined with estrogen may be prescribed.
- Vaginal DHEAS is also FDA approved for the treatment of urogenital symptoms. It help in decreasing vaginal dryness and reducing sexual dysfunction [27].
- Vaginal lubricating creams or regular sexual intercourse can also help in mild cases, especially those women who don't want to start HRT.

Osteoporosis/osteopenia/osteoarthritis

- ET/EPT when started in early premenopausal women, may help in prevention and also treatment of osteoporosis. It increases BMD (bone mineral density) of lumbar spine by 7.6% and femoral neck by 4.5% over a period of 3 years. Decrease in the risk of osteoporosis fracture by 33 - 40% is also seen. Similar findings were seen in Postmenopausal estrogen/progestin Intervention trial and WHI Intervention Trial [27,28]. HRT acts by decreasing bone resorption and decreasing bone remodeling [8]. It also helps in improving muscle strength combined with exercise. However, ET/EPT should not be used solely for the treatment of osteoporosis and other treatment options should be adopted such as SERM's i.e. raloxifene in the dose of 60 mg/day or ospemifene.
- Tibolone which has estrogenic, progestogenic and androgenic properties has also been found to be effective in cases of osteoporosis. It acts by its estrogenic property on bones by decreasing its osteoclastic activity. Its usual dose in 2.5 mg, but a lower dose of 1.25 mg is also effective. It should be prescribed after one year of menopause.

Dementia/depression

- There is no role of HRT in dementia and in improving cognitive functions in postmenopausal women if started late i.e. more than 10 years after menopause. Following timing hypothesis, it may be effective only if started immediately with decline in ovarian function [29-31]. In the MIRAGE study, the risk of Alzheimer's disease was found to decrease by 65% for the age range of 50 - 63 years as compared to more than 63 years. North American menopause society and Indian menopausal society, recommend starting HRT immediately following surgical menopause to prevent Alzheimer's disease and cognitive decline [32].

Cardiovascular disease, metabolic syndrome and stroke

HRT users have been found to have decreased incidence of onset of type 2 diabetes mellitus in a study by Hauvais Jarvis F., *et al* [33]. Similar results were found in WHI (Women's Health Initiative) study as well, where continuing HRT in perimenopausal period for 3 years have been found to prevent android deposition of fat and maintaining weight [34]. During early postmenopausal phase, HRT may decrease cardiovascular risk by 32% [35]. Early versus late intervention trial and Kronos early estrogen prevention study, have proven that the use of hormone therapy in early postmenopausal year can decrease carotid intima media thickness [36,37]. Thus, HRT is known to have cardioprotective effect, only if started in healthy women and in the "Window of Opportunity". This was also emphasized in the study done by IMS, 2016 [23]. HRT is known to increase the risk of stroke when started late in the postmenopausal women. Standard oral combined HRT increases the risk by one-third in healthy postmenopausal women. No such increased risk has been seen with low dose ET or transdermal

preparations [8]. Incidence of ischemic stroke is increased more as compared to hemorrhagic stroke especially above the age of 60 years. WHI study, showed no increased risk of stroke when HRT was initiated in the window period [34].

When to stop HRT?

There is no set limit which can be applied to all women. Usually, the therapy should be prescribed for the shortest duration possible. If continued use is required, then careful re-evaluation and supervision is warranted. There is no consensus on whether to stop HRT abruptly or gradually and an individualized decision may be taken depending on the duration of HRT use [38]. In cases of POI or surgical menopause, the HRT should be continued till the average age of menopause.

Risks involved in prescribing HRT

- Breast cancer- Use of HRT may increase the risk of breast cancer in susceptible women. Long term use of HRT for more than 10 years may increase the risk of breast cancer by 10 - 30%. HRT acts as promoter genes for the cancer cells present. Relative risk of 1.035 per year of use was found in use of less than 5 years and of 1.35 with use of more than 5 years as per the reanalysis of 51 epidemiological studies [39].

- Venous thromboembolism- Conjugated equine estrogen is known to increase the risk of VTE as compared to estradiol. Similarly, medroxyprogesterone acetate is associated with increased risk as compared to micronized progesterone. The ESTHER study showed a significant increased risk of thromboembolic events following use of MHT (RR 3.5 [CL: 1.8 - 6.8]) as compared to controls [40]. In the US Preventive services task force along with the meta-analysis with WHI and HERS study, there was increased risk venous thromboembolism especially in early years of starting estrogen therapy [40-42]. The timing hypothesis may prove protective in terms of VTE as well. In women with BMI > 25, the risk of VTE increases and so thorough examination before starting HRT is must.

- Endometrial cancer- Risk of endometrial cancer is increased only in cases of estrogen only therapy upto the RR of 2.3 - 9.5. This has been proved in the WHI study as well [43].

- Risk of gall bladder disease is also increased in women on estrogen only therapy or combined HRT.

Follow up after prescribing HRT

Follow up is advisable after one month of HRT use for the side effects and then after three months for the efficacy of the regime used. Annual review is required to assess requirement of the continuation of HRT and this has to be followed by thorough examination and investigations as per the need.

Conclusion

Prescription of Hormone replacement therapy has two sides of the coin with both positive and negative effects. Positive effects are improvement in vasomotor and urogenital symptoms, prevention of bone density and fractures and decrease in the risk of colorectal cancer. Negative effects are related to increased risk of breast cancer, venous thromboembolism, cardiovascular diseases and stroke. Time of starting HRT has also been found to be critical to decrease mortality related to coronary artery disease as well as onset and severity of Alzheimer's disease. The importance of critical window of opportunity should be emphasized and utilized efficiently. The HRT should preferably be prescribed in the lowest possible dose with the shortest possible duration and local therapy should be preferred wherever feasible. A meticulous follow up is essential to determine the efficacy and timely identify the adverse effects, if any. Importance of adopting healthy lifestyle should be emphasized and women visiting in menopausal transition or postmenopausal phase should be screened for

chronic diseases or malignancy. All attempts should focus on counselling postmenopausal women regarding importance of maintaining healthy life style, exercise, treatment of diabetes and hypertension and avoiding alcohol intake. It is suggested that specialized menopausal clinics should be established where menopause related issues are recognized timely and addressed appropriately.

Bibliography

1. De Carvello BR., *et al*. "Ovarian Reserve assessment for infertility investigation". *Obstetrics and Gynecology* (2012): 576385.
2. Fritz MA and Speroff L. "Menopause and the perimenopause transition". In: Speroff L, Glass RH, Kase NG, editors. Clinical Gynecological Endocrinology and Infertility. 8th edition. Philadelphia, PA, USA: Lippincott Williams and Williams (2011): 681.
3. Sharma S., *et al*. "Menopausal signs and symptoms in urban women". *JK Science: Journal of Medical Education and Research* 9 (2007): 13-17.
4. Stuenkel CA., *et al*. "Treatment of symptoms of the menopause: An endocrine society clinical practice guideline". *The Journal of Clinical Endocrinology and Metabolism* 100 (2015): 3975-4011.
5. Government of India: Ministry of Home Affairs 2011, Office of Registrar General and Census commissioner, India (2011).
6. Sloan JA., *et al*. "Methodological lessons learned from hot flash studies". *Journal of Clinical Oncology* 19 (2001): 4280-4290.
7. Aggarwal M., *et al*. "Faridabad, Souvenir: 17th National Indian Menopause Society; study of urogenital complaints in postmenopausal women over 45 years in Safdarjung Hospital" (2012): 48.
8. Meeta M., *et al*. "Clinical practice guidelines on menopause. An executive summary of recommendations: Indian menopause society 2019-2020". *Journal of Mid-Life Health* 11 (2020): 55-95.
9. Kim OM and Lee YS. "The climacteric symptoms and quality of life in climacteric women according to hormone replacement therapy". *Korean Journal of Women Health Nursing* 7 (2001): 642-656.
10. Cho HH., *et al*. "Influences of hormone therapy to tissue mineral concentration and quality of life in menopausal women". *The Journal of Korean Society of Menopause* 13 (2007): 209-216.
11. Kim JY., *et al*. "Assessment about quality of life in menopausal women with HRT". *Korean Journal of Obstetrics and Gynecology* 41 (1998): 2429-2435.
12. Cobin RH and Goodman NF. "AACE Reproductive endocrinology Scientific Committee. American Association of clinical endocrinologists and American college of endocrinology position statement on menopause. 2017 update". *Endocrine Practice* 23 (2017): 869-880.
13. The 2017 Hormone therapy position statement of the North American Menopause Society". *Menopause* 25 (2018): 1362-1387.
14. Jane FM and Davis SR. "A practioner's toolkit for managing the menopause". *Climacteric* 17 (2014): 564-579.
15. Collin P., *et al*. "Management of cardiovascular risk in perimenopausal woman". *European Heart Journal* 28 (2007): 2028-2040.
16. Hodis HN., *et al*. "The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future perspectives". *Climacteric* 15 (2012): 217-228.
17. Ratner S and Ofri D. "Menopause and hormone replacement therapy: Part 2. HRT regimen". *WJM* 175 (2001): 32-34.
18. Fait T., *et al*. "The use of estradiol metered-dose transdermal spray in clinical practice". *Climacteric* 21.6 (2018): 1-5.

19. Somnunkiran A., *et al*. "The effect of tibolone versus 17-beta estradiol on climacteric symptoms in women with surgical menopause: a randomized cross over study". *Maturitas* 56 (2007): 61-68.

20. Kenemens P and Speroff L. "International Tibolone consensus group. Tibolone: clinical recommendations and practical guide. A report of the International Tibolone consensus group". *Maturitas* 51 (2005): 21-28.

21. Fait T. "Menopause Hormone therapy: latest developments and clinical practice". *Drugs in Context* (2019).

22. Park HM., *et al*. "The HRT awareness and acceptance in Korean postmenopausal women: result of Korean Gallup epidemiological survey on menopause and HRT". *Journal of the Korean Physical Society* Menopause 8 (2002): 3-18.

23. Baber RJ., *et al*. "IMS writing group. 2016 IMS. Recommendations on women's midlife health and menopause hormone therapy". *Climacteric* 19 (2016): 109-150.

24. Birkhauser MH., *et al*. "Updated Practical recommendations for HRT in the peri and postmenopausal". *Climacteric* 11 (2008): 108-123.

25. Lee SR., *et al*. "The 2020 Menopausal hormone therapy guidelines". *Journal of Menopausal Medicine* 26 (2020): 69-98.

26. Weirman ME., *et al*. "Androgen therapy in women". *The Journal of Clinical Endocrinology and Metabolism* 99 (2014): 3489-3510.

27. Labrie F., *et al*. "VVA Prasterone Research group. Efficacy of intravaginal DHEAS on moderate to severe dyspareunia and vaginal dryness, signs and symptoms of vulvovaginal atrophy and of the genitourinary syndrome of menopause". *Menopause* 23 (2016): 243-256.

28. Effort of hormone therapy on bone mineral density: results from postmenopausal estrogen/progesterone interventions (PEPI) trial. The writing group for the PEPI". *JAMA: The Journal of the American Medical Association* 276 (1996): 1389-1396.

29. Cauley JA., *et al*. "Effects of estrogen plus progestin on risk of fractures and bone mineral density: the women's health initiative randomized trial". *JAMA: The Journal of the American Medical Association* 290 (2003): 1729-1738.

30. Whitman RA., *et al*. "Timing of hormone therapy and dementia: the critical window theory revisited". *Annals of Neurology* 69 (2011): 163-169.

31. Attarian H., *et al*. "Treatment of chronic insomnia disorder in menopause: evaluation of literature". *Menopause* 22 (2015): 674-684.

32. Greendale GA., *et al*. "Effects of the menopause transition and hormone use of cognitive performance in midlife women". *Neurology* 72 (2009): 1850-1857.

33. Hauvais Jarvis E., *et al*. "MHT and type 2 Diabetes prevention". *Endocrine Reviews* 38.3 (2017): 173-188.

34. Anderson GL., *et al*. "Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized trials". *JAMA: The Journal of the American Medical Association* 291 (2004): 1701-1712.

35. Salpester SR., *et al*. "Coronary Heart disease event associated with hormone therapy in younger and older women. A meta-analysis". *Journal of General Internal Medicine* 21 (2006): 363-366.

36. Harman SM., *et al*. "Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial". *Annals of Internal Medicine* 161 (2014): 249-260.

37. Hodis HN., *et al*. "Vascular effect of early versus late postmenopausal treatment with estradiol". *The New England Journal of Medicine* 374 (2016): 1221-1231.

38. NAMS 2017. Hormone therapy position statement Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society". *Menopause* 24 (2017): 728-753.

39. Collaborative Group on hormonal factors in Breast cancer. Breast cancer and HRT". *Lancet* 350 (1997): 1047-1059.

40. Canonico M., *et al*. "Estrogen and thromboembolism among postmenopausal women. The ESTHER study". *Circulation* 115 (2007): 840-845.

41. Canonica M., *et al*. "Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis". *British Medical Journal* 336 (2008): 1227-1231.

42. Cushman M., *et al*. "Women's Health Initiative investigators. Estrogen plus progestin and risks of venous thrombosis". *JAMA: The Journal of the American Medical Association* 292 (2004): 1573-1580.

43. Writing group for the Women's Health Initiative Investigators". *JAMA: The Journal of the American Medical Association* 288.3 (2002): 321-333.

Volume 10 Issue 11 November 2021