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REVIEW

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HORMONE REPLACEMENT THERAPY- KEY FOR IMPROVING LIFE'S QUALITY

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**ABSTRACT**

*Menopause is the most important transition period in a woman's life, and its symptoms significantly affect the quality of life. Hormone replacement therapy (HTR) is the most effective treatment of postmenopausal symptoms and also for women with primary ovarian failure or bilateral oophorectomy. This treatment has specific indications and contraindications, respectively. Also, particular investigations are required before initiating therapeutic measures. Many variables must be factored in the decision to choose the appropriate management.*

**KEYWORDS:** *hormone replacement therapy, menopause, postmenopausal symptoms*

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**INTRODUCTION**

Menopause is the most significant shift in a woman's life. As life expectancy continuously increases, menopause represents more than a third of women's lives. During this period, symptoms such as cardiovascular, bone, metabolic disorders, and others significantly alter their quality of life. However, a question that has not yet been considered is: "Is the moment of natural menopause an indicator of health or aging?" The menopause beginning was regarded as the perfect moment to institute preventive measures to enhance the postmenopausal women life's quality and longevity. Current hormone replacement therapy (HRT), consisting mainly of estrogen and progesterone, has a decades-long tradition to treat postmenopausal disturbances. The ability to replace ovarian function and hormones side effects have been repeatedly

reanalyzed. Up-to-date facts in estrogen and progesterone-based therapies and their diverse delivery routes have developed HRT benefits; however, directly comparing, the function of premenopausal women normal ovaries is still higher. The ovaries produce eggs, secrete several hormones, including estrogen, progesterone, testosterone, inhibin, activin, insulin-like growth factor 1, and anti-Müllerian hormone, which have crucial importance on a woman's physiology [1]. These hormones' function and secretion are elaborate. Thus, the ovary isn't just a static endocrine organ, which begins to live and act into puberty and shrinks in menopause. We should see it as a lively organ whose rhythm is counted in weeks. The benefit on women's health is huge. It is acknowledged as the main facet of lower morbidity and mortality, as shown by the research of premenopausal women paralleled to men in the same group of age [2],[3].

Disturbances like hot flashes, mood disorders, sleeping problems, and vaginal dryness that arise in menopause substantially impact millions of women's life quality around the world [4], [5].

## RESULTS AND DISCUSSION

### *HRT and Clinical Practice*

There is controversy about the hormone replacement therapy effects on health-related life's quality. Studies demonstrated HRT to enhance the quality of life in general by diminishing both the number and severity of menopausal symptoms [6],[7].

So far, hormone replacement therapy mainly consists of estrogen and progesterone, differing in doses and administration routes, each with benefits and risks. The symptoms' alleviation is induced primarily by estrogen, prescribed in monotherapy to women who underwent a hysterectomy. Estrogen is administered with progestin for women with an intact uterus in order to combat the risk to ensue endometrial hyperplasia and even carcinoma [8],[9].

#### *HRT indications:*

- For menopausal issues including:
  1. Treatment of vasomotor symptoms
  2. Treatment of the genitourinary syndrome
  3. Prevention of osteoporosis [10],[11]
- FDA (Food and Drug Administration)-approved indications for progestogens include:
  1. Dysfunctional uterine bleeding
  2. Amenorrhea, either primary or secondary
  3. Assisted reproductive technology treatment
  4. Endometrial hyperplasia [10]

#### *HRT contraindications:*

1. breast cancer history
2. coronary heart disease
3. history of venous thromboembolism (VTE) or stroke
4. active liver disease
5. unidentified vaginal bleeding
6. high-risk endometrial cancer
7. endometrial cancer history
8. transient ischemic attack

9. history of blood clotting disease, Factor V Leiden mutation carriers - the most common [10-12]

#### *Calculating risk*

Endocrine Society's 2015 Clinical Practice Guideline suggests calculating cardiovascular and breast cancer risks before commencing treatment [12]:

- for women with moderate risk of cardiovascular disorders (CVD; 5 to 10% 10-year risk), transdermal estrogen is preferred over oral.
- in symptomatic women who present a moderate (1.67 to 5 percent 5-year risk) to major risk (>5 percent) for breast cancer or high risk (>10 percent 10-year risk) for CVD, nonhormonal medicines are advocated [12].

#### *Investigations before starting HRT*

1. Dosing FSH (for primary ovarian insufficiency - FSH with menopausal values at two determinations at intervals of at least one month) [13]
2. Endometrial biopsy preceded by transvaginal ultrasound (for endometrial hyperplasia)
3. Breast screening (mammography)
4. Lipid profile
5. Hematological examination

#### *Estrogens*

All kinds of estrogen preparatives effectively alleviate hot flashes [14]. It is procurable in many forms: transdermal, oral, topical gels and lotions, and vaginal rings [15]. Adequate daily doses of estrogen, e.g., 17-beta estradiol (transdermal 0.05 mg/day or oral 1 mg/day), are used to suppress symptoms in most women [16],[17]. Higher doses are prescribed two to three years after bilateral oophorectomy surgery for younger women (e.g., 0.1 mg transdermal estradiol or 2 mg oral estradiol or their substitutes), which afterward may be decreased [18].

A significant reduction in hot flashes has been observed in women who received estrogen compared to placebo; this was demonstrated in a meta-analysis of 24 trials that administered estrogen in 3329 postmenopausal women (a reduction in 75%) [16].

Another meta-analysis illustrated the similarity between equivalent doses of different estrogens (such as conjugated estrogen 0.625 mg/day and 17-beta estradiol either orally in the amount of 1 mg/day or transdermal - 0.05 mg/day), both forms seemed to be effective in treating hot flashes [17]. These doses annihilated hot flashes completely in approximately 80 percent of women decreased the frequency and severity in the rest [16].

In order to relieve symptoms, current treatments begin with small doses (e.g., oral estradiol (0.5 mg/day) or transdermal estradiol (0.025 mg)), which can be increased if required. The treatment does not cover all women, as primary ovarian insufficiency necessitates a more significant daily dose [19].

#### *Progestins*

Progestins must be administered for women who have the uterus in order to prevent endometrial hyperplasia, which usually arises after six months of treatment with unopposed estrogen. Women with total hysterectomy do not require progestin because it has no benefit [20],[21].

The natural oral micronized progesterone (200 mg/day for 12 days/month "cyclic regimen that mimics the normal luteal phase" or 100 mg daily "continuous regimen") is the first approach. The progesterone should be taken at bedtime, as few of its metabolites induce drowsiness. Current information sustains that natural progesterone is reliable regarding the cardiovascular system and breast side effects. A reduced amount of progesterone (a 12-day course every 6 to 12 months) is needed for women who take lower doses of estrogen (e.g., 0.014 mg transdermal estradiol) [22],[23].

#### *Tibolone*

Tibolone is a synthetic steroid, and its metabolites demonstrated androgenic, progestogenic, and estrogenic effects. This therapeutic agent has been utilized mainly in Europe and other countries for many years to treat hot flashes. It diminishes vasomotor symptoms compared to placebo but is not equally efficient as estrogen therapy. Other usages: tibolone proved effective on bone mineral density and displayed a modest improvement of sexual dysfunction [24].

### ***The relationship between symptoms in postmenopausal women and HRT***

#### *Vasomotor symptoms*

The perimenopausal phase includes the most common vasomotor symptoms (hot flashes or night sweats) and is endured by about 60–80% of postmenopausal women [25],[26]. These symptoms severely affect women's sense of well-being and quality of life [27]. A study shows that patients who receive hormone replacement therapy notice a reduction in symptoms. Hormone replacement therapy is also justified for all women with moderate and severe symptoms [28].

#### *Genitourinary syndrome*

Both topical and systemic estrogens have been shown to improve symptoms like vaginal dryness, superficial dyspareunia, itching, and vaginal stenosis. Long-term therapy is required to achieve these benefits. Symptoms commonly recur after treatment is stopped [29]. Urinary tract infections incidence and overactive bladder symptoms are reduced after topical estrogen therapy [29],[30].

#### *Osteoporosis*

Osteoporosis is the most frequent bone problem in menopausal women, and it is connected to diminished bone mass with raised susceptibleness to fractures. Reduced estrogen levels in the postmenopausal period account for more than 75% of bone density loss rather than only aging [31].

Hormonal therapy reduces the number of all osteoporosis-related fractures, including vertebral and hip fractures. The therapy's effect is evident in average women not at high-risk of fracture and not diagnosed with osteoporosis [32].

#### ***HRT Risks***

##### *Venous Thromboembolism (VTE) and Stroke*

Hormonal replacement therapy increases VTE risk by 2-fold, mainly at the treatment inception, the first two years of treatment [33],[34]. Combination therapy with estrogen and progesterone raises the risk of venous thromboembolism relative to estrogen alone [35]. Tibolone is associated with a steep rise in stroke risk [36].

### *Breast cancer risk and recurrence*

An increased breast cancer risk has been demonstrated in women who have received  $\geq 5$  years of continuous treatment with estrogen and progestin, which flourishes further with prolonged administration [37],[38]. Tibolone was linked to an elevated risk of recurring breast cancer [24].

### *Endometrial hyperplasia*

Postmenopausal women treated with estrogen alone have a considerable risk of endometrial hyperplasia and carcinoma [20],[39]. The use of estrogen combination and progesterone treatment decreases the risk of developing endometrial hyperplasia and endometrial cancer, provided if progestin is prescribed for a sufficient number of days, for example, 10-12 days a month [41].

### *Ovarian cancer*

Results of a systematic review on mainly observational studies showed that therapy with estrogen alone and with estrogen and progesterone might be associated with an elevated risk of initiating ovarian cancer [41]. Also, in a separate study, links between ovarian cancer and both estrogen replacement therapy (a 20% increase) and therapy with estrogen and progesterone (a 10% increase) have been observed [42]. One observational study revealed an increased risk of both serous tumors and endometrioid tumors but a decreased risk of mucinous tumors in women using estrogen replacement therapy or combined therapy with estrogen and progesterone [43].

### *Health-related quality of life*

Estrogen demonstrated a varied effect depending on the woman's age and presence of symptoms and/or comorbid conditions on life's quality in postmenopausal women. In postmenopausal women with vasomotor flushes, estrogen appears to improve their quality of life [16],[44].

### *Cognitive function*

Studies have shown that estrogen exhibits a neuroprotective effect and that HRT improves cognitive function. This is only possible on the condition that HRT is initiated early [45],[46].

The risk of dementia and Alzheimer's disease increases if started over the age of 65 years [47].

## **CONCLUSION**

Besides the quality-of-life improvement, hormone replacement treatment also presents some risks which may be harmful. Before undertaking this treatment, we need to establish that the benefits outweigh the risks. A woman who follows this therapy needs to be informed and aware of these risks. Treatment needs to be initiated with small doses and on a fixed time interval in order to ameliorate ensuing symptoms.

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