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Perspectives in hormone replacement therapy

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Abstract

Estrogens have been convincingly shown to be highly effective in preventing and reversing menopause-related conditions, such as hot flushes, urogenital complaints, and postmenopausal bone loss. Observational studies report that long-term, estrogen-containing, postmenopausal hormone replacement therapy (HRT) leads to a substantial reduction in hip fractures, myocardial infarction, and possibly colonic cancer, with important consequences for health and quality of life. Estrogen replacement may postpone the onset of Alzheimer's disease and extend life. While many of these effects are biologically plausible, with a variety of cellular mechanisms being involved, only ongoing and future large-scale randomized clinical trials can and should define the effects of HRT more precisely. Long-term compliance is a key issue for long-term benefits, and offering women a choice of administration routes and regimens can only be beneficial in this respect. Pills, patches, gels, and implants are all widely prescribed. Intravaginal or intranasal forms of administration, which are very easy to use and adaptable on an individual level, are among the new options which could improve long-term continuation of HRT use. Fear of breast cancer and recurrence of vaginal bleeding are real concerns for many women considering HRT. This has led to research into lower-dose, estrogen-containing regimens, into continuous combined regimens, and into the potential of estrogen receptor α or β binding molecules that may help to prevent such problems from arising. The prospects for safe and effective postmenopausal HRT with either estrogens or estrogen-like drugs are very promising when these drugs are used in a patient-tailored, risk profile-based manner.

Keywords: HRT, Hormone replacement therapy; Menopause; Estrogens

1. Introduction

Menopause is the point of no return within the endocrinological, psychological and social transition from the reproductive years to the non-reproductive years. At this point, nearly all follicles have reached atresia and those remaining are insufficient to sustain the cyclic hormonal process [1]. Formally, menopause is the moment of the final menstruation, directly preceded by the permanent cessation of ovarian follicular function. The median age at natural menopause is close to 50 years [2]. Life expectancy for modern women in developed countries is such that the postmenopausal period represents more than one third of their lives.

Years before the actual moment of the last menstrual period, the process of the transition from fertility to sterility can already be leaving its

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mark. This period, the climacteric, is characterized by the specific changes that take place in a woman's body, linked to the aging process of the ovaries. For many modern women, this period is one of blood (menstrual cycle disorders), sweat (hot flushes and night sweats), and tears (mood swings). Urogenital complaints like vaginal dryness start in this period, while other more atypical climacteric complaints can also be present, such as joint and muscle pains, tiredness, palpitations, headache, dizziness, irritability, and insomnia. The climacteric is also a period of accelerated bone loss and an inconspicuous shift in cardiovascular risk factors to a more male-like atherogenic profile (Table 1). The postmenopausal period, therefore, is associated with an increased risk of osteoporotic fractures and myocardial infarction, and possibly also with an early onset of Alzheimer's disease [3].

In general, mid-life age is associated with a variety of symptoms that might influence the general well-being of women. The physical changes are often accompanied by changes in the family and social environment, which may have a profound influence on psychosocial functioning. However, vasomotor complaints show a clear relationship with the changing serum levels of sex hormones that occur in the climacteric [4]. Many of the so-called atypical symptoms cannot be readily associated with the hormonal situation as such.

The climacteric cannot simply be described as the phase of constantly declining estrogens, nor can the postmenopausal state be characterized solely as a state of estrogen deficiency. Nevertheless, many of these symptoms of the climacteric and the postmenopausal period have been shown to disappear with the administration of exogenous estrogens, either alone or in combination with progestogens. This approach, hormone replacement therapy (HRT), can be defined as perimenopausal and postmenopausal medication with estrogens, or a combination of estrogens and progestogens (or any other substance with a sex steroid receptor affinity, such as raloxifene or tibolone) for the treatment of climacteric symptoms or for the prevention of postmenopausal diseases, such as osteoporosis and cardiovascular disease.

Table 1
Menopause-induced and hormone replacement therapy (HRT)-induced changes related to mechanisms of coronary artery disease in postmenopausal women[a]

Parameter	Menopause-induced changes	HRT-induced changes
Lipid and lipoprotein metabolism	TC ↑, HDL-C ↓, LDL-C ↑ Lp(a) ↑	TC ↓, HDL-C ↑, LDL-C ↓, Lp(a) ↓
Homocysteine metabolism	Homocysteine ↑	Homocysteine ↓
Hemostatic factors	Fibrinogen ↑, factor VII ↑ PAI-1 ↑, t-PA ↓	Fibrinogen ↓, factor VII ↓ PAI-1 ↓, t-PA ↑
Glucose metabolism	Insulin sensitivity ↓ insulin elimination ↓ insulin secretion ↓	Insulin sensitivity ↑ Insulin elimination ↑ insulin secretion ↑
Peripheral vascular resistance	Increased	Decreased
Endothelium-dependent vasomotion	Endothelin-1 ↑ NO ↓	Endothelin-1 ↓ NO ↑
Endothelium-independent vasomotion	Ca influx into vascular smooth muscle ↑	Ca influx into vascular smooth muscle ↓

[a] TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); PAI-1, plasminogen activator inhibitor-1; t-PA, tissue plasminogen activator; NO, nitric oxide; Ca, calcium. Modified after Practical HRT with permission [3].

Table 2
Determinants of HRT uptake

Determinant	HIGH uptake in women characterized by being	LOW uptake in women characterized by being
Menopausal status	Perimenopausal	Late postmenopausal
Ovarian status	Castrated	Still ovulating
Uterine status	Hysterectomized	Non-hysterectomized
Contraception status	Former oral contraceptive users	Natural method users
Social status	Female doctors	Without high-school graduation
Health status	Healthy, exercising women	Cancer patients or diabetics
Fear of cancer	A low-anxiety type	Carcinophobic
Attitude to vaginal bleeding episodes	Indifferent as to bleeding	Negative to the idea of starting to menstruate again
HRT options	Approached in an individually tailored way	Approached uniformly

2. Hormone replacement therapy

Postmenopausal supplementation of estrogens is becoming increasingly popular. Progestogens are added to estrogens, sequentially or continuously, to prevent endometrial neoplasia. Routes of administration are multifold: pills, patches, gels, implants, vaginal rings, and nasal sprays are among the options. Estradiol has been shown to be a highly effective treatment option for women with vasomotor complaints independent of the route of administration. Other steroids such as progestogens and tibolone have been shown to be effective. Raloxifene is not effective and tamoxifen often worsens the symptoms. Other treatment options are exercise and clonidine [5].

In many women who have atypical symptoms in conjunction with severe vasomotor symptoms, HRT for vasomotor complaints will also be effective for the atypical symptoms.

Systemic administration of estrogens including oral estradiol (E2) is effective for urogenital atrophy, which includes genital atrophy with vaginal dryness, irritation, dyspareunia, and problems related to micturition, like dysuria, incontinence, and recurrent urinary tract infections. Vaginal administration of estradiol is also highly effective for the relief of these symptoms, but can occasionally significantly increase serum and endometrial levels of estradiol [6].

HRT given for the treatment of climacteric symptoms can be continued for preventive reasons, as long-term HRT leads to a substantial reduction in hip fractures [7,8], myocardial infarction [9], and possibly colonic cancer [10,11], with important consequences for health and quality of life. Estrogen replacement may also postpone the onset of Alzheimer's disease [12,13] and extend life [14].

3. Uptake of HRT

Despite these well-documented advantages of both short- and long-term HRT, the HRT uptake and continuation rates are generally poor. The proportion of peri- and postmenopausal women using HRT varies considerably, even within the developed regions of the world (e.g. Italy 3%, UK 7%, France 12%, Germany 25%, USA 38%) [15–17].

HRT uptake is influenced by many factors (Table 2). Prominent factors, both in peri- and in postmenopausal women, include fear of breast cancer, return of vaginal bleeding, weight gain, and other side effects [18]. Although the majority (around 75%) of peri- and early postmenopausal women experience menopausal symptoms, only a minority (around 20–25%) report their complaints as being severe [19]. In a Danish survey of all women with symptoms, two-thirds had consulted a physician, half of these women had then been prescribed HRT (34% of the total) and 94% of these actually started treatment [20]. Thus,

women with severe climacteric symptoms are far more often inclined to start HRT than those without symptoms. A minor fraction start HRT because of preventive reasons, mostly osteoporotic concerns [20,21].

In many countries, the uptake of HRT has increased considerably in recent years, for instance, in the UK, the uptake increased from less than 5% in 1987 to almost 30% in 1994 [22]. Generally, perimenopausal women use HRT more often than postmenopausal women [15,16], while current use is three times more common after hysterectomy [17] and especially after bilateral oophorectomy [20,21].

Social status and health status are also important factors. HRT uptake is more common among higher-educated women [17] and in female doctors [23], while HRT use is less common among women with a disease such as diabetes mellitus or a history of breast cancer [17]. Uptake of HRT is more frequent in previous oral contraceptive users and in women who regularly exercise or do sports [20].The availability of new technologies has also been shown to be a factor. The use of HRT increased with the introduction of the transdermal patch. A similar effect is expected to be seen with the new introduction of the medicated intrauterine contraceptive device (IUCD) and with the introduction of the intranasal route of administration.

4. Continuation rate of HRT

Generally, HRT is continued for less than 2 years. Factors influencing the continuation rate are also diverse (Table 3). Both effective therapy with disappearance of complaints as well as ineffective therapy are reasons for discontinuation [20]. Often, successful therapy for climacteric complaints is not continued for preventive reasons, as the awareness of preventive reasons for HRT use is low in climacteric women [20,24]. In the majority of women, side effects are the reason for discontinuation. Side effects can be real (bleeding, breast tenderness) or presumed (weight gain). Continuation of HRT is much higher in hysterectomized women [17,20] and with regimens that do not induce withdrawal bleeding, such as continuous combined HRT or tibolone [20].

With increasing age, continued HRT use generally declines. Previous oral contraceptive use is not a factor. Sadly, a considerable number of women stop on the basis of advice from their general practitioner; in general, gynecologists are highly in favor of HRT, although some negativity towards HRT might result from omission bias (more concern about harmful acts than harmful omissions), proportionality bias (attention to relative risk rather than risk differences), and natural bias (preference for the natural) [25].

5. HRT in perspective

It is important to look at HRT from the proper perspective, because the way we look at HRT is changing. Also, the way we look at postmenopausal women is changing. There is no such thing anymore as general HRT, neither is there a normal postmenopausal woman. Paraphrasing George Orwell [26], one could say that while all animals are equal (and some are more equal than others), it certainly is true that all women are different (and some are more different than others).

Table 3
Reasons for discontinuation of HRT

1	Ineffective therapy	No relief
2	Effective therapy	No need anymore
3	Real side effects	Bleeding, breast tenderness, bloating
4	Presumed side effects	HRT-related weight gain
5	Emerging insight	Breast cancer risk
6	Information deficit	Lack of awareness of preventive HRT
7	Medicalization issue	Biased preference for the so-called natural
8	'Primum non nocere' bias	More concern about harmful acts than about harmful omissions
9	Doctor's bias	Better (legally) safe than (financially) sorry

In view of this, hormone replacement has developed over the last 10 years from simple to complex and from uniform to individual. This is true for the indications of HRT, for the duration of HRT, and also for the practical options of HRT. Before advising a woman to start HRT, many questions have to be asked, such as "what indications does this woman have?" "what risks does she have without HRT and what risks with HRT?" and "what are her present complaints and what are her fears?"

For many doctors and women, the indications for HRT are no longer simply the treatment of climacteric symptoms, as they have been for a long time, but increasingly attention is being paid to the prevention of postmenopausal diseases with a fully informed, individually tailored approach based also on an individual risk-benefit score [27].

For the prevention of severe osteoporosis in osteopenic postmenopausal women, HRT is the gold standard. Primary prevention of cardiovascular disease can be obtained with postmenopausal hormonal use as reported in several meta-analyses [28–30]. However, the results may have been overestimated, due to selection bias [31], although two studies failed to demonstrate the presence of such a healthy-user effect [32,33]. The list of proposed mechanisms for the cardioprotective effect of HRT is still expanding. Available data indicate that cardiovascular risk factors, such as cholesterol, lipoprotein (a), and homocysteine can be favorably modulated by HRT [34,35]. The strongest reduction can be achieved in postmenopausal women with the highest concentrations [36]. The data from the Heart and Estrogens/progestin Replacement Study (HERS), a secondary prevention trial of coronary artery disease in postmenopausal women, however, seem to suggest the opposite [37]. Although several mechanisms could explain the adverse effect seen in the HERS study [38,39], this trial also had some severe limitations that need to be considered [40–42]. Moreover, the HERS trial is a secondary prevention trial and its results should not be extrapolated to primary prevention.

As to duration of HRT use, for preventive purposes, a shift is necessary from short-term perimenopausal use for 1–2 years to long-term postmenopausal use that lasts at least for 5 years, but probably life-long. This is because the benefits lie with long-term and current HRT use, although there are also problems associated with long-term, current use, especially in relation to endometrial and breast cancer [43,44]. As for endometrial cancer, the risk incurred with sequentially combined HRT is still a point of discussion. With an appropriate duration of progestogen use each cycle (10 or more days), most studies find no substantial increase in risk [45], while a recent study found a substantial reduction with the use of continuous combined HRT [46]. Others showed that hyperplastic endometrium also responds to progestogen therapy in a favorable manner [47], unless cytologic atypia had developed [48].

The breast cancer risk with HRT is a real issue for concern. The largest re-analysis, which used 90% of the world data, showed an increased risk (particularly among leaner women) with both estrogen only and combined HRT recent use, although many single studies did not find any increase in risk [49]. Tumors found on HRT were clinically less advanced. There does not seem to be a synergistic effect of the combined risks of HRT on the one hand, and reproductive risk factors of breast cancer on the other, such as early menarche, late menopause, and late first delivery or nulliparity [50]. It is still a matter of dispute as to whether sequentially combined or continuous combined HRT differ in their risk of breast cancer morbidity and mortality compared with estrogen replacement users [51]. Indeed, some data suggest a reduction in E2-induced proliferation of breast epithelial cells by exposure to progesterone [52], but a recent cohort study found the opposite [53].

It should be noted that HRT reduces the sensitivity of mammographic screening [54].

It should be realized that some adverse effects reported with HRT, in relation to thromboembolism, coronary artery disease, and breast and endometrial cancer, are highly related to the drugs, dosage, regimen or route of administration used, and to the duration and recency of use.

The last decade has seen a large increase in practical options for HRT. Estrogens now available for hormone replacement include, in addition

to the well-known conjugated equine estrogens and the synthetic ethinylestrogens, the option of micronized 17β-estradiol. Available progestogens offer a very wide choice that includes, in addition to the old nortestosterone derivatives (like norethisterone acetate) and the old progesterone derivatives (like medroxyprogesterone acetate), new ones such as levonorgestrel and dydrogesterone, while micronized progesterone with an improved cardiovascular profile has also become available [55]. In addition, other drugs for hormone substitution have become available, like androgens, tibolone, and raloxifene. Recently, raloxifene has been shown to decrease breast cancer risk [56].

With many of the drugs used for HRT, a similar trend is seen with respect to the dosage advised. In general, estrogen dosages are lower than they used to be, and there is a trend towards offering the possibility of an individualized dosage. The latter approach has been very successful with the matrix patch, the gel and, quite recently, with the nasal spray [57,58]. Although the optimal estrogen dose for osteoprotection, cardioprotection, and neuroprotection has not been established unequivocally, and might be different for overweight women compared with lean women, there is a general trend to use a lower dosage. For instance, for micronized estradiol, the standard dose has been reduced from 2 to 1 mg. For modern HRT, not only is a multitude of different drugs available, but there is also a large variety of routes of administration to choose from, both for estrogens and for progestogens. These include oral tablets, subcutaneous implants, percutaneous creams, transdermal patches, vaginal tablets, creams and rings, intranasal sprays, and intrauterine devices.

Drawing conclusions about the last 10 years, we can say, retrospectively, that HRT has gone from being simple to varied and complex, and from uniform to varied and individualized. This is true for the indications for HRT, for the duration of use, and for the practical options (drug dosages, regimens and routes) available for postmenopausal hormonal supplementation. In the near future, women and doctors will together make the decision about whether or not to use HRT. When the choice is made to use HRT, they will then choose a patient-tailored way to treat climacteric complaints and prevent postmenopausal diseases, on the basis of an individualized risk-benefit profile. DNA-chip technology might help to obtain a more precise definition of this individual profile in establishing relevant hereditary risks, such as those for breast cancer, cardiovascular disease, and osteoporosis.

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