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REVIEW

Hormone Replacement Therapy for the South African healthcare provider: Part I

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Menopausal symptoms are due to a lack of circulating oestrogen in women. Hormone replacement therapy (HRT), also called menopausal hormone therapy (MHT) is very controversial, misunderstood and as a result often underutilised by clinicians. Hormonal therapy is instituted to improve quality of life in peri- and postmenopausal women by reducing hot flushes and improving sexual function. Oestrogen therapy does not improve muscle mass and muscle function. HRT is prescribed as a first-line treatment to prevent and treat osteoporosis. Oral oestrogens increase the risk for venous thromboembolism (VTE) but the risk with the use of transdermal oestradiol delivery systems is comparable to the risk in non-users. The lipid profile and carbohydrate metabolism in post-menopausal women is improved with oestrogen replacement therapy.

Keywords peri- and postmenopausal, quality of life, oestrogen, oestradiol, vasomotor symptoms, vulvovaginal atrophy, sexual dysfunction, depressive mood, cognition, dementia, osteoporosis, venous thromboembolism, transdermal hormone delivery

Introduction

In this first part the of the series the most common symptoms of the peri- and postmenopausal period – osteoporosis, venous thromboembolism, implications for liver disease and the lipid profile, as well as the carbohydrate metabolism – will be discussed. The second part will focus on stroke, the cardiovascular implications of hormone replacement therapy (HRT), as well as the malignancies that are commonly encountered and influenced by HRT in peri- and postmenopausal women. Attention will also be given to abnormal uterine bleeding and postmenopausal bleeding. Thirdly, preference will be given to hormonal and non-hormonal treatment options, the different routes of hormone administration and the safety implications of the different treatment options. In the last part the series general pointers and a summary of indications and contraindications for the use of HRT will be discussed.

As is well known, the peri- and postmenopausal period can cause significant physical and psychological distress and up to 75% of women complain of symptoms that reduce their quality of life (QoL).[1-2] In a significant number of women symptoms may persist for several years.[3] As the life expectancy of women has increased over the past few decades, women often spend half their lives in the peri- and postmenopausal states.[4] Furthermore, hormone replacement therapy (HRT) has been marred in controversy since the publication of the Women's Health initiative (WHI) in 2002. The use of HRT has decreased to such an extent that only 5% of women still used HRT in 2010.[4-5] Since then, re-analysis and subgroup analysis of the data gathered by the WHI was done and several new studies were published. To complicate matters even more there is a myriad of new treatment options and routes of hormone delivery available to clinicians.

The menopause is characterised by a state of hypoestrogenism with circulating oestradiol (E2) levels decreasing five to ten fold compared to the hormonal levels of women in their reproductive years.[6] The most common symptoms and complications of the peri- and postmenopausal periods are vasomotor symptoms (VMS), an increase in mood and depressive disorders, vulvovaginal atrophy (VVA), lower urinary tract symptoms, changes in body fat distribution, decreased libido, palpitations, sarcopenia, arthralgia, and osteoporosis.[3,6] Other disease processes in postmenopausal women which require consideration are cardiovascular disease, cerebrovascular incidents (stroke), venous thromboembolism and malignancies. The lipid and carbohydrate metabolism are altered in the peri- and postmenopausal states and the effect of HRT needs to be carefully evaluated.

Vasomotor symptoms

Hot flushes and night sweats are the most common complaints during the perimenopausal period and possibly the reason for which HRT is mostly prescribed. The afore mentioned symptoms lead to a disturbance in sleeping patterns which aggravates feelings of anxiety and tiredness. These symptoms often start two years before the onset of menopause and generally last for a mean period of five to seven years.[2-3] Unfortunately, up to 20% of women may report symptoms for 15 years or more.[3] The use of oestrogen replacement results in a 75% reduction in the intensity and frequency of hot flushes and night sweats. In the hypothalamus of women, groups of neurons with oestrogen receptors were recently discovered and shown to become enlarged in postmenopausal women.[7] These neurons produce kisspeptin, neurokinin B and dynorhine.[7] For this reason, they are called KNDy-neurons (pronounced "candy"). Animal research revealed that the above neurons play an important role in temperature regulation and as oestrogen levels decrease, these neurons become more active.[7] Current research is focused

on blocking neurokinin-3 receptors (NK3R) on the KNDy-neurons, and phase 2 and phase 3 trials with fezolinetant and elinzanetant are currently in progress. Receptor antagonists on the KNDy-neurons could provide relief of the vasomotor symptoms (hot flushes) for women in which hormonal therapy is contraindicated.[8]

Mood disorders

Menopause is often associated with being irritated, easily agitated, and having a depressed mood. Women with a history of postnatal depression (PND), premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are at an even greater risk of developing such symptoms.[3,9] Although studies showed conflicting results regarding improvement in mood symptoms, most studies reported a positive effect.[3,10] But as the progestogen component in HRT might have a negative effect on mood symptoms the clinician should consider it when prescribing HRT. It has been shown that androgenic derived progestogens, when compared to micronised progestogens, are associated with more negative mood disorders.[3,9]

The vagina, bladder, and sexual function

Since the female urogenital tract and pelvic floor have the same embryological origin, oestrogen receptors are present in the vagina, uterus, and lower urinary tract.[9] The decrease in circulating oestradiol in the peri- and postmenopausal periods causes vaginal atrophy and subsequently causes dyspareunia as well as overactive bladder symptoms in 50% of women.[3] Consequently, the North American Menopause Society (NAMS) and the International Menopause Society (IMS) have both advocated that the term "genitourinary syndrome of the menopause" be used.[3,11] Oestrogen that is topically applied to the vagina improves vaginal blood supply, which in turn results in improved lubrication and less dyspareunia.[3] Oestrogen also restores the lactobacilli dominance and as a result the vaginal acidity returns to the premenopausal state, which in turn may reduce urinary tract infections as well as dysuria, frequency and nocturia.[9] Because of the limited systemic absorption of topically applied vaginal oestrogen, the development of endometrial hyperplasia is unlikely, thus the need for concomitant progestogen treatment is negated.[3,9] Vaginally applied topical oestrogen therapy is more effective in relieving vulvovaginal atrophy than systemic oestrogen.[9] Although female sexual function is complex and influenced by several other factors, systemic oestrogen replacement can improve sexual desire and libido. Even though some menopausal societies support the use of testosterone or other androgens such as dehydroepiandrosterone (DHEA) in women with hypoactive sexual desire disorder (HSDD), the use thereof remains controversial as most of these preparations are manufactured, and only licenced, for use in men thus the prescription of androgens is "off-label". Importantly, when used, the testosterone levels should be monitored and maintained within the normal female physiological range to prevent androgenic side-effects such as acne, hirsutism, and sometimes even irreversible voice changes.[3] Currently the use of vaginal laser therapy might be an effective treatment for genitourinary syndrome, but as its efficacy and safety have not been established, menopausal societies do not endorse its use.[12]

Sarcopenia and arthralgia

Sarcopenia, defined as a progressive and generalised loss of muscle mass and strength resulting in a weaker physical performance, is due to a decline in circulating oestrogen levels in the postmenopausal period.[9] Resistance therapy, two to three times per week, is beneficial to maintain muscle mass, but the use of HRT has not been proven to enhance musculoskeletal function.[9] Cartilage metabolism is partly regulated by oestrogen. Declining oestrogen levels results in not only increased osteoarthritic joint changes but also in thinning of intervertebral discs. Data from the WHI reported a significant improvement in arthralgia with the use of oestrogen.[13] It is important to note that lifestyle changes, which include weight loss and exercise, are important in maintaining joint mobility.

Memory, cognition and dementia

During the menopausal transition women often complain of a loss in short-term memory and difficulty in concentrating.[12] This can be explained by the fact that oestrogen receptors are present in the central as well as the peripheral nervous systems.[9] Despite the above, the use of HRT has not been shown to reduce the risk of dementia. Evidence from WHI neither showed any significant improvement nor worsening in cognition or memory in women older than 50 on HRT.[3,9] Subsequent subgroup analysis, however, showed that the risk of developing dementia was increased in women in whom HRT was initiated after age 65.[9] In a Finnish study using data from a period encompassing 14 years, almost 85 000 postmenopausal women with a diagnosis of Alzheimer's disease were compared to roughly the same number of controls; it was concluded that women younger than 60 who were exposed to more than ten years of HRT had an increased risk of developing dementia.[3] Current guidelines suggest that women who were started on HRT before the age of 60 and used it for less than 10 years, can be reassured that its use is unlikely to have any negative effect on cognition or the development of dementia.[9] Importantly studies do not support the initiation of HRT to improve cognition, nor to prevent dementia.

Osteoporosis and bone mineral density

Osteoporosis is marked by a reduced bone mineral density (BMD) and a change in micro-architectural structure of bone leading to an increased incidence of hip, vertebral and forearm fractures.[9] Presently HRT is regarded as the first-line intervention for the prevention and treatment of osteoporosis as studies have shown relative risk reduction of 0.72 (95% CI 0.53–0.98) in hip and 0.63 (95% CI 0.44–0.91) in vertebral fractures.[3,9] The protective effect of HRT seems to be dependent on duration and dose of treatment. Most studies showed a decline in BMD after discontinuation of HRT, although some reports claimed that HRT may provide long-term protection against fractures even after stopping treatment.[3] Importantly, lifestyle interventions, such as weight-bearing exercise, reducing alcohol intake, smoking cessation and adequate calcium and vitamin D supplementation

play an equally important role in the prevention and treatment of osteoporosis.[3] The recommended Ca^{2+} and Vitamin D intake for postmenopausal women are respectively a 1 000 mg and a 1 000IU daily, but remember, supplements should be given per indication, rather than routinely.[3] Furthermore, it is not recommended to start HRT after the age of 60 years for the prevention of osteoporotic fractures.[9] In these patients anti-resorptive agents, namely bisphosphonates, are recommended.

Venous thromboembolism

There is a two to four fold increase in the risk of venous thromboembolism (VTE) and pulmonary embolism (PE) in women taking oral HRT, and the risk of developing an embolic event is at its highest within the first year of use.[2-3,9,11] Additional factors such as obesity, thrombophilia, a personal previous thrombotic or embolic event and a family history of VTE increase the risk even further.[9] Routine screening for thrombophilia is not recommended and should be reserved for patients with a family history of VTE.[3] All oral oestrogens are not equal since the risk of VTE events is higher with the use of conjugated equine oestrogen (CEE), as it is more thrombogenic than oestradiol.[9] Similarly medroxyprogesterone acetate and norpregnane synthetic progestogens convey a higher risk for developing VTE and PE than micronised progestogens.[3,9] The single most important risk factor in developing VTE when on HRT is the route of administration.[9] Meta-analyses, observational and laboratory studies have shown that there is no increase in risk of developing a VTE and PE when comparing transdermal HRT to non-users.[2,11] Transdermal oestrogen preparations are directly absorbed systemically and bypass first-pass metabolism in the liver.[1,5,9,11] This equates to a lower dosage for a similar physiological effect when using transdermal preparations in comparison to oral oestrogens.[5] Oral oestrogens are metabolised in the liver and metabolites are mostly excreted in the bile. The oral oestrogens and their metabolites (such as oestrone) generated from the first pass metabolism in the liver is implicated in VTE due to its effects on fibrinogen, antithrombin III and activated protein-C resistance.[1,5] Hospitalised women on HRT and women on HRT undergoing elective surgery should receive adequate thromboprophylaxis.[3] Controversy exists whether HRT should be stopped in the aforementioned women if proper thromboprophylaxis is instituted, as some authors propose that it can be continued, others suggest changing from oral to transdermal preparations and a third group advocate temporary cessation of HRT.[3] Personal opinion would be to rather err on the safe side.

HRT the liver and the lipid profile

During the perimenopausal period there is an increase of abdominal adiposity, dyslipidaemia, and non-alcoholic fatty liver disease (NAFLD). With the cessation of ovarian function an increase in triglycerides, low density lipoprotein (LDL) cholesterol and the total cholesterol serum levels follows, but on the flip side of the coin, high density lipoprotein (HDL) cholesterol and lipoprotein a (Lp[a]) levels remain mostly unchanged.[14] Oestrogens taken orally increase triglycerides, HDL cholesterol and decrease LDL cholesterol and Lp(a).[14] The effect of transdermal oestrogen on the lipid profile is less pronounced (more neutral) compared to the oral administration thereof.[4,14] In women with an intact uterus, where progestogens are co-administered, the positive effect of oestrogens on the lipid profile are diminished, albeit the overall effect is still beneficial.[14] Important to note is that not all progestogens are equal, as dydrogesterone and micronised progesterone have lesser of a negative effect on the lipid profile compared to synthetically derived progestogens. Although HRT may improve NAFLD, their use is still only experimental. As mentioned earlier, oestrogen taken orally undergoes first-pass metabolism in the liver before entering the bloodstream, with the metabolites being mostly excreted through bile.[5,11] In contrast, transdermal oestrogen bypasses this initial first-pass metabolism in the liver, allowing for lower doses to achieve similar physiological effects.[5] The varying doses and concentrations of metabolites (such as oestrone) formed after oral oestrogen intake may account for the difference seen in menopausal hormone therapy and gallbladder disease when comparing oral and transdermal administration routes. Observational studies have shown that the transdermal administration of oestrogens in peri- and postmenopausal women is associated with a decreased risk for undergoing a cholecystectomy compared to women taking oral preparations.[15]

Carbohydrate metabolism

In a recent study, oral and transdermal HRT were both shown to reduce the risk for developing diabetes mellitus when compared to non-users, although the effect was more pronounced in women taking oral preparations.[4] Furthermore, it was also associated with an improvement of glycosylated haemoglobin (HbA1C) levels in these women.[4] Notably, medroxyprogesterone acetate and levonorgestrel are implicated with an increase in glucose intolerance and insulin resistance, but the overall effect of combined oestrogen-progestogen HRT is advantageous on the carbohydrate metabolism.[4]

Key points

- Hormone replacement therapy (HRT) is also called menopausal hormone treatment (MHT).
- Hormone replacement therapy reduces vasomotor symptoms and improves vulvovaginal atrophy and sexual function in peri- and postmenopausal women.
- KNDy-neurons in the hypothalamus are implicated in thermoregulation in postmenopausal women and current research focuses on non-hormonal therapy options.
- Sarcopenia is due to oestrogen deficiency, but not improved by HRT.
- Arthralgia is improved by using HRT.
- HRT (oestrogen) is a first-line option for the prevention and treatment of osteoporosis.
- The use of HRT to prevent dementia is unsubstantiated and the long-term use thereof (> 10 years) may increase the risk of developing dementia.

- Oral oestrogen therapy is associated with an increased risk of VTE events.
- Transdermal oestrogen bypasses the first-pass metabolism in the liver and lower doses achieve similar physiological effects compared to oral oestrogens.
- Transdermal oestrogen does not increase the VTE risk.
- There is an increase in non-alcoholic fatty liver disease during the peri- and postmenopausal periods.
- HRT improves the lipid profile as well as the carbohydrate metabolism in postmenopausal women.
- Transdermal oestradiol is associated with a lower prevalence of cholecystectomy compared to oral oestrogens.

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