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Menopause, Hormone Replacement Therapy (HRT) and Obesity

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Abstract

Menopause is associated with a rapid increase in fat mass and a redistribution of body fat from the periphery to the abdomen, resulting in a transition from a gynoid to an android pattern of fat distribution. In postmenopausal women, increase in body mass index (BMI) and proportion of visceral fat are strongly correlated with the development of hypertension, dyslipidemia, insulin resistance and with a number of metabolic risk factors for cardiovascular disease (CVD). Central adiposity and visceral adiposity could influence the distribution of cardiovascular fat, defined as the fat surrounding the heart and arteries, and are correlates with CVD risk.

Adipose tissue could be an 'insulator' and interfere with normal thermoregulatory mechanisms of heat dissipation. Women with higher abdominal adiposity, particularly subcutaneous adiposity, report an increase of vasomotor symptoms (VMS) during the menopausal transition and in early post menopause. Healthy weight in midlife women early in the menopausal transition may help to prevent VMS. Overweight women may suffer from psychosocial consequences, with a significant impact on self-esteem and general well-being: obese postmenopausal women have lower health-related quality of life, in physical functioning, energy, and vitality compared with normal-weight women. Obesity is also a major risk factor for pelvic floor dysfunction, some cancers (endometrial, breast and colon) and musculoskeletal disorders, especially osteoarthritis (a highly disabling degenerative disease of the joints). It could be necessary to encourage lifestyle measures in addition to therapeutic interventions throughout the menopausal transition in order to controlling menopausal obesity and to manage menopause- related symptoms, with minor side effects.

Keywords: HRT; Menopause; Obesity; Metabolic syndrome

Abbreviations: HRT: Hormone Replacement Therapy; BMI: Body Mass Index; VMS: Vasomotor Symptoms; CVD: Cardiovascular Disease; DXA: Dual-Energy X-Ray Absorptiometry; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; ERs: Estrogen Receptors; E2: Estradiol; FSH: Follicular Stimulating Hormone; LH: Luteinizing Hormone; FMP: Final Menstrual Period; SHBG: Sex Hormone-Binding Glob¬ulin; VTE: Venous Thromboembolism; PAI-1: Plasminogen Activator Inhibitor-1; GSM: Genitourinary Syndrome of the Menopause; POP: Pelvic Organs Prolapsed; DRSP: Drospirenone; DNG: Dienogest; NOMAC: Nomegestrol Acetate; DHEA: Dehydroepiandrosterone; SERM: Selective Estrogen Receptor Modulator; WHI: The Women's Health Initiative

Introduction

The menopausal transition marks a period of physiologic changes as women approach reproductive senescence. Evidence supports the clinical importance of the transition for many women as a period of temporal changes in health and quality of life (vasomotor symptoms, sleep disturbance, depression) and longer-term changes in several health outcomes (urogenital symptoms, bone, lipids) that may influence women's quality of life and the likelihood of healthy aging [1].

Loss of sex hormones during ageing contributes to changes in body mass, musculoskeletal integrity, sexual dysfunction and long-term risks of health and disease. The metabolic syndrome increases in prevalence after menopause and consists of insulin resistance, abdominal obesity, dyslipidaemia, elevated blood pressure and proinflammatory and prothrombotic states. This syndrome, also known as insulin resistance syndrome, usually precedes the development of diabetes mellitus and carries a twofold increased risk for cardiovascular events [2].

The prevalence of obesity (BMI >30kg/m^2) is higher in postmenopausal women than in premenopau¬sal women. This is a consequence of a multifactorial process that involves reduced energy expenditure due to physical inactivity, which is sometimes compounded by depression, as well as due to muscle atrophy and a lower basal metabolic rate. Whereas menopause per se is not associated with weight gain, it leads to an increase of total body fat and a redistribution of body fat from the periphery to the trunk, which results in visceral adiposity. Increased BMI and upper body fat distribution (indicated by waist-to-hip ratio) and meno-pausal estrogen decline are associated with adverse metabolic changes such as insulin resistance, a pro-pensity to develop type 2 diabetes mellitus and dys¬lipidaemia

characterized by high triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels and an increased frequency of small, dense low-density lipoprotein (LDL) particles. Altered adipokine secretion, which leads to chronic inflammation, is a possible mechanism that links abdominal obesity to its metabolic consequences.

Cross-sectional and longitudinal studies using waist circumference or the waist-to-hip ratio show no effect of menopause on body fat distribution. By contrast, studies using dual-energy X-ray absorptiometry (DXA) showed increased trunk fat in postmenopausal women. Moreover, studies using computed tomography (CT) and magnetic resonance imaging (MRI) show that postmenopausal women have greater amounts of intra-abdominal fat compared to premenopausal women. Collectively, these studies confirm that the menopause transition is associated with an accumulation of central fat and, in particular, intra-abdominal fat. Postmenopausal women had 36% more trunk fat, 49% greater intra-abdominal fat area, and 22% greater subcutaneous abdominal fat area than premenopausal women. The menopause-related difference in intra-abdominal fat persisted after statistical adjustment for age and fat mass, whereas no differences were noted in trunk or abdominal subcutaneous fat [3]. *In vivo* and *in vitro* studies indicate that the estrogen receptors are mechanistically implicated in endocrine-related diseases. Recent studies with estrogen receptor knockout mice have helped to unravel the role of the estrogen receptors in brain degeneration, osteoporosis, cardiovascular diseases and obesity [4].

In humans, the hormones help integrate metabolic interaction among major organs that are essential for metabolically intensive activities like reproduction and metabolic function. Sex steroids are required to regulate adipocytes' metabolism and also influence the sex-specific remodeling of particular adipose depots. Sex hormones concentrations partially control fat distribution: men have less total body fat but more central/intra-abdominal adipose tissue, whereas women tend to have more total fat in gluteal/femoral and subcutaneous depots. Weight and fat abdominal distribution differ among women of reproductive age and menopausal women.

Estrogens function is mediated by nuclear receptors that are transcription factors that belong to the superfamily of nuclear receptors. Two types of estrogen receptors (ERs) have been identified, the alpha (ERα) and beta (ERβ) receptors. Human subcutaneous and visceral adipose tissues express both ERα and ERβ, whereas only ERα mRNA has been identified in brown adipose tissue. ERα plays a major role in the activity of adipocytes and sexual dimorphism of fat distribution. Polymorphism of ERα in humans have been associated with risk factors for cardiovascular diseases. Lipolysis in humans is controlled primarily by the action of β-adrenergic receptors (lipolytic) and α2A-adrenergic receptors (antilipolytic) [5].

Genazzani [6] evaluated the effects of climacteric modifications on body weight and fat distribution: he selected 2175 untreated normal healthy women attending a menopause clinic. He divided them into three groups: premenopausal, perimenopausal and postmenopausal, and compared them with 354 postmenopausal women receiving different forms of HRT. The total body fat tissue mass and distribution were analyzed using DXA. Body weight and BMI were significantly higher in perimenopausal and postmenopausal than in premenopausal women. Fat tissue and regional fat tissue as a percentage of total fat tissue were higher in the trunk and arms in perimenopausal and postmenopausal than in premenopausal women. Instead, in age-matched HRT-treated postmenopausal women, the fat tissue was similar to that in the premenopausal group. Perimenopausal and postmenopausal women show a shift to a central, android fat distribution that can be counteracted by HRT [6].

Discussion

A number of studies looked at the pattern of hormonal changes during the menopausal transition between obese and non-obese women. In both Study of Women's Health across the Nation (SWAN) and Penn Ovarian Aging Study (POAS), obese women had lower Estradiol (E2) and Follicular Stimulating Hormone (FSH) levels than nonobese women, and in the POAS, lower Luteinizing Hormone (LH) and Inhibin B levels as well. More rigorous analysis of hormonal changes before and after the final menstrual period (FMP) between obese and non-obese women has found that the patterns of change in FSH and E2 in relation to the FMP were not statistically different when comparing obese to non-obese women, although significant differences in the mean FSH and E2 levels were observed. The E2 change was less pronounced in obese women when compared with non-obese women, because obese women had lower premenopausal mean E2 levels but higher postmenopausal mean E2 levels. The rate of E2-blunted decline observed among obese women is physiologically corroborated by a similarly blunted FSH rise surrounding the FMP in obese versus non-obese women. Ultrasound data have shown no difference in antral follicle count between obese and non-obese women in their late reproductive age (40-52 years). This lack of difference does not support low ovarian reserve as the mechanism underlying lower E2 levels in obese women premenopausally, and this mechanism is currently unclear. In POAS, AMH was found to be lower in obese women compared to non-obese women in the late reproductive years, demonstrating the complex relationship between obesity and reproductive hormones in women approaching menopause. Follicular dysfunction and alterations in central nervous system regulation of hormonal levels among obese women may be factors, but additional research in this area is needed. The blunted magnitude of change in reproductive hormones in obese women during menopausal transition may be related to the change in the primary source of circulating E2 as the menopause transition progresses; the primary source of circulating E2

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premenopausally is the ovary, whereas in post menopause, the primary source of circulating E2 is the aromatization of androgens within the adipose tissue. This change in E2 source provides postmenopausal obese women with a non-ovarian reservoir of estrogen that normal-weight women do not have, which may blunt the gonadotropin rises and mitigate ovarian estrogen loss with menopause. These hormonal alterations may also blunt menopause-associated adverse health effects [7].

Data from the Women's Healthy Lifestyle Project provide clear evidence that weight gain and increased waist circumference, along with elevations in lipid levels and other CVD risk factors, are preventable through use of lifestyle intervention in healthy menopausal-aged women. In fact although these changes are inevitable with age and menopause, physical activity may attenuate the impact of both events. Thus, weight gain prevention should be recognized as an important health goal for women before they approach menopause and women should make regular physical activity [8].

All women at midlife should be encouraged to maintain or achieve a normal body weight, be physically active, adopt a healthy diet, limit alcohol consumption and not smoke. Some women find that avoidance of spicy food, hot drinks and alcohol lessens their vaso¬motor symptoms. Obesity is associated with a greater likelihood of vasomotor symptoms, although women who are overweight (BMI from 25 to <30kg/m^2), as opposed to obese (BMI ≥30kg/m^2), are more likely to have severe symptoms [9]. For obese women, weight loss may lessen vasomotor symptoms, as well as reduce the risks of cardiovascular disease, diabetes, urinary incon¬tinence, breast, pancreatic and endometrial cancer, dementia.

Estrogens seem to influence glucose homeostasis through increased glucose transport into the cells, whereas lack of estrogens has been associated with a progressive decrease in glucose-stimulated insulin secretion and insulin sensitivity as well as with insulin resistance. These may explain why HRT administration to postmenopausal women is associated with a significant decrease in the incidence of type II diabetes. Estrogen deficiency is the principal pathophysiologi¬cal mechanism that underlies menopausal symptoms and various estrogen formulations are prescribed as menopausal hormone therapy, which remains the most effective therapeutic option available. The addi¬tion of progesterone aims to protect against the con¬sequences of systemic therapy with estrogen only in women with intact uteri [10]: namely, endometrial pathol¬ogies, including hyperplasia and cancer. The risk-benefit ratios of all treatment options must be considered, tak¬ing into account the nature and severity of symptoms, and individual treatment-related risks.

In the systemic circulation, E2 and es¬trone are partly bound to sex hormone-binding glob¬ulin (SHBG), as well as to albumin, as is testosterone. Increasing or decreasing SHBG levels will affect the amount of unbound estrogen and testosterone in the circulation [11]. Obesity is a biologically plausible risk factor for venous thromboembolism (VTE) but the mechanisms underlying the relation of obesity with VTE arenot totally understood. A strong positive correlation between plasminogen activator inhibitor-1 (PAI-1) level and BMI has been reported. PAI-1 is the main fibrinolytic inhibitor and reduced plasma fibrinolytic potential may be a risk factor for venous thrombosis. Decreased fibrinolysis because of a high level of PAI-1 could explain in part the association of VTE with overweight and obesity. Moreover, other studies suggested that an increased BMI was associated with higher levels of prothrombotic factors such as fibrinogen and factor (F) VII. Thus, both oral estrogen and obesity may have synergistic effects on the unbalance between procoagulant factors and antithrombotic mechanisms. By contrast, transdermal estrogen appears to have little or no effect on hemostasis. Alternatively, increased C reactive protein levels have been reported in obese individuals with a history of VTE and low grade inflammation could explain in part our findings. In addition to the effects on hemostasis and inflammation, obesity may also have direct mechanic effects on the venous area. An increased BMI may result in a higher VTE risk through an increased intra-abdominal pressure and a decreased venous return. These effects may result in venous hypertension, varicose veins and venous stasis which promote the development of VTE [12].

For those who require pharmacological therapies, average dose HRT is the most effective treatment for VMS [13] with reductions in both frequency and severity in the order of 75% [14] and HRT may improve quality of life in symptomatic women [15]. HRT should be avoided in those with unexplained vaginal bleeding, active liver disease, previous breast cancer, coronary heart disease, stroke, personal history of thromboembolic disease or known high inherited risk. CVD risk factors do not automatically preclude HRT but should be taken into account. Up regulation of the hepatic synthesis of procoagulants is another known effect of oral estrogens. Trans-dermal estradiol does not seem to increase the risk of venous thromboembolic events. Evidence show that trans-dermal estrogen (≤50μg) is associated with a lower risk of deep vein thrombosis, stroke, and myocardial infarction compared to oral therapy [16] and may be the preferred mode of treatment in women with an increased thrombosis risk, such as obese women and smokers In addition, unlike oral estrogen, transdermal estradiol does not increase the risk of gallbladder disease [17,18].

Genitourinary syndrome (GSM) is a relatively new terminology describing vulvovaginal changes at menopause, as well as urinary symptoms of frequency, urgency, nicturia, dysuria and recurrent urinary tract infections. Vaginal dryness is common after menopause and unlike VMS usually persists and may worsen with time [19]. Urogenital symptoms are effectively treated with either local (vaginal) or sys¬temic estrogen therapy [20]. Pelvic floor dysfunction is more common in the overweight and obese women. Risk factors for developing

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pelvic organs prolapse (POP) can be divided into obstetric, lifestyle, comorbidity, aging, social, pelvic floor factors and surgical factors. The most important lifestyle factor is a higher BMI. Obesity may impair pelvic floor function increasing intra-abdominal pressure, that damages pelvic musculature and nerve, this is linked to conduction abnormalities and obesity related co-morbidities including diabetic neuropathy and intervertebral disc herniation.

Estrogen therapy restores normal vaginal flora, lowers the pH, and thickens and revascularizes the vaginal lining. The number of superficial epithelial cells is increased and symptoms of atrophy are alleviated. Importantly, low-dose vaginal estrogen improves vaginal atrophy without causing proliferation of the endometrium. Given the docu¬mented efficacy and proven safety, vaginal estrogen is the first-line approach to treat symptoms of vaginal atrophy in the majority of women: vaginal estrogen is effective and whilst systemic absorption does occur, it does not induce endometrial hyperplasia. Concerns about systemic absorption mean that vaginal estrogens may be avoided in breast cancer patients taking aromatase inhibitors. The relationship between HRT and urinary incontinence depends on the delivery route. Systemic HRT worsens urinary incontinence but vaginal treatment may improve urge incontinence and prevent recurrent urinary tract infections. Using very low doses for the first few weeks is helpful if irritation occurs and indeed lower doses of vaginal estrogens, with less frequent administration, often yield satisfactory results [21].

In conclusion, initiation of hormone therapy is usually contraindicated in women with a personal history of breast cancer or venous thromboembolism, or those with a high risk for breast cancer, thrombosis or stroke. Trans-dermal estrogen therapy may be considered and preferred when highly symptomatic women with type 2 diabetes mellitus or obesity, or those at high risk of cardiovascular disease, do not respond to non-hormonal therapies. In general, commencement of hormone therapy is not recommended for women who are aged >60 years [22].

In order to avoid undue chronic stimulatory effects on the endometrium, control menstrual bleeding, avoid abnormal bleeding and avoid cancer development, the combination of the estrogen with a progestogen is needed. Endometrial cancer is the most common gynecologic cancer: it is estimated that risk of endometrial cancer increases about 59% for every 5 unit increase in body mass index (BMI, kg/m^2), and overweight and obesity are responsible for 57% of all case of endometrial cancer in USA. Obesity increases exposure to estrogen unopposed by progesterone in pre and postmenopausal women. The inclusion of progesteron appears to increase breast cancer risk, but progestogens are still indicated to prevent endometrial hyperplasia and cancer risk [21].

Progesterone, which is naturally produced in women in the ovaries(particularly the corpus luteum), in the placenta and to a certain extend in the adrenals, there are a variety of synthetic progestogens . One of these progestogens, dydrogesterone, is a retro-progesterone, and another, drospirenone (DRSP), is spironolactone derivative. The “newer” progestogens belong to different classes based on their structure. For each of them the progestogenic, as well as the antiestrogenic action, is common. The antiandrogenic effect is relevant for dienogest (DNG) and DRSP and minor for nomegestrol acetate (NOMAC). None of them have a glucocorticoid effect. DRSP is different due to its strong antimineralocortocoid action, and has a favourable effect on blood pressure. In addition, these progestogens do not interfere with the positive effect of estrogens on lipid and carbohydrate metabolism, do not augment hemostasis processes as monotherapy and avoid induction of abnormal proliferation of the endometrium in doses clinically tested. Therefore, all three progestogens appear to be suitable for treatment of menopausal women [23].

Nonetheless, considering that HRT could create important health risks, it is highly desirable to discover new alternatives in the menopause- related symptoms management, with minor side effects. Over the past 15 years, hormone preparations of Dehydroepiandrosterone (DHEA) have been available over-the-counter and have been sold as the ‘‘fountain of youth’’ [24]. DHEA serves as a precursor for estrogens and androgens from fetal life to postmenopause, and many people believe that DHEA is merely an inactive precursor pool for the formation of bioactive steroid hormones. DHEAS represent the most abundant sex steroid in plasma in humans (more than 1000 times higher than estradiol and testosterone levels), but its serum concentration goes down to 10-20% of its maximum level by around the age of 70 years. The large difference between low and high serum DHEA levels has a major clinical impact. Among postmenopausal women with coronary risk factors, lower DHEA levels were linked with higher mortality from cardiovascular disease and all-cause mortality [25]. Several studies had previously demonstrated that 1-year treatment [26,27], using administration of 10mg DHEA daily in symptomatic postmenopausal women with lower (5^{th} percentile) baseline DHEAS levels, improved climacteric and sexual symptoms and directly reversed some age-related changes in adrenal enzymatic pathways, including adrenal DHEA and progesterone synthesis.

In the past 2 years, two new pharmaceutical prepa¬rations were approved in the United States and Europe for the treatment of menopausal symptoms. An oral selective estrogen receptor modulator (SERM), Ospemifene, has been approved for the treatment of moderate to severe pain during intercourse associated with vulvovaginal atrophy [28], and a tissue-specific SERM-estrogen complex (a combination of oral con¬jugated equine estrogen and bazedoxifene (a SERM) has been approved for the management of moderate to severe vasomotor symptoms in women with an intact uterus [29]. Tissue selectivity is achieved through the con-current use of estrogen and a SERM, which replaces a progestogen and selectively blocks the undesirable

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actions of estrogen. In the case of conjugated equine estrogen-bazedoxifene, the proliferative effects of estrogen are blocked in the uterus and possibly also the breast, whereas the bone-sparing actions of es¬trogen are preserved. The role of testosterone for the treatment of postmenopausal desire or arousal disorders and the long-term implications of such a therapy in postmenopausal women are unclear. The rationale for combining estrogens with a SERM (T-SEC, combination of conjugated equine estrogen and BZA (SERM)) is to retain beneficial effects of estrogens on VMS, VVA, and bone while incorporating the anti-estrogenic effects of the SERM on the breast and endometrium to improve the overall safety profile [30]. The tissue selective estrogen complex (combination of 0.45mg of oral conjugated equine estrogen and 20mg bazedoxifene (a SERM)) has been approved for the management of moderate to severe VMS in the US and Europe [31].

Tibolone is a synthetic steroid that is rapidly converted to two metabolites with estrogenic activity and to a third metabolite characterized by a mixed progestogenic/androgenic activity. Tibolone controls hot flushes, sweating, mood symptoms and is effective in improving libido, due to its androgenic component. Randomized, controlled studies show that tibolone increases bone mineral density and reduces fracture risk. These beneficial effects are seen over long-term treatments [32] (over 10 years) and both in early and late postmenopausal women as well as in women with established osteoporosis. The combined analysis of randomized clinical studies on Tibolone indicates no increase in risk of breast cancer development compared with placebo. Tibolone treatment is associated with a reduction of proliferation and a stimulation of apoptosis in normal breast cells that is possibly attributable to the impact of this compound on the activity of estrogen-metabolizing breast enzymes [33]. The metabolization of Tibolone is tissue selective, and the conversion to the progestogenic metabolite is particularly active in the endometrium. Investigation of endometrial histology in women treated with tibolone shows no hyperplasia and a high level of atrophic endometrium, indicating no proliferative effect of this molecule.

A number of non-hormonal therapies are efficacious against menopausal vasomotor symptoms and should be considered for women who do not wish to take estrogen or those with contraindications. For vasomotor symptoms, many drugs have dem¬onstrated efficacy in several studies: paroxetine, fluox¬etine and citalopram (which are selective serotonin reuptake inhibitors); venlafaxine and desvenlafaxine (selective noradrenaline reuptake inhibitors); clonidine (α_2-adrenergic receptor agonist); and anticonvulsants (gabapentin and pregabalin). Paroxetine and fluoxe¬tine are potent cytochrome P450 2D6 (CYP2D6) inhibi¬tors, and as they decrease the metabolism of tamoxifen (a SERM used in the treatment of breast cancer)-which may reduce its anticancer effects -these drugs should be avoided in tamoxifen users. However, consistency of treatment response and efficacy of the various alternative options remain questionable.

Conclusion

Estrogen therapy may partly prevent menopause-related change in body composition and the associated metabolic sequelae. The decision to start HRT in a woman transitioning toward menopause requires a personalized discussion on the unique balance of risks and benefits in that particular individual. Thorough counseling on the relevance of improving lifestyle, dietary habits and implementing physical activity should be provided. Menopause physicians should appropriately stress how these behavioral changes are far more important to prevent cardiovascular risk than any pharmacologic or hormonal intervention.

Within this frame, the available evidence shows that the balance of benefits and risks for HRT is most favorable within the first 10 years of menopause. Expert agreement is that HRT should still be primarily initiated for the management of climacteric symptoms to improve quality of life. Long-term preventive strategies, particularly cardiovascular protection, should not be a primary goal even if HRT has long-term protective effects on the cardiovascular system, reflected in an approximate 40-50% reduction in cardiovascular events in most clinical studies, when started during this “window of opportunity”.

New and emerging menopausal therapies have the potential to fill an unmet need in the post-WHI era for effective relief of menopausal symptoms with improved safety profiles. Based on the WHI, the greatest risk appears to be associated with combined estrogen-progestin therapy; therefore, recent strategies have focused on eliminating the need for progestins either through use of topical estrogens without a progestin for VVA or by combining estrogen(s) or DHEA with potentially safer options (e.g., micronized progesterone, SERMs) to reduce endometrial stimulation.

Menopausal hormone therapy remains the most effective treatment of VMS, and is also indicated for GSM (previously called vulvovaginal atrophy) and bone protection. With no fixed duration of treatment, the guidelines now state that HRT should be individualized to account for each patient’s unique risk-benefit profile. The ultimate goal is to get closer to the profile of the ideal menopausal therapy -- that is, to relieve bothersome menopausal symptoms and reduce the risk of osteoporosis and cardiovascular disease, without increasing the risk of endometrial or breast cancer.

References

1. Roberts H, Hicke M (2016) Managing the menopause: An update. Maturitas 86: 53-58.

2. Salpeter SR, Walsh JME, Ormiston TM, Greyber E, Buckley NS (2006) Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab 8(5): 538-554.

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3. Toth MJ, Tchernof A, Sites CK, Poehlman ET (2000) Menopause-related changes in body fat distribution. Ann NY Acad Sci 904: 502-506.

4. Mueller SO, Korach KS (2001) Estrogen receptor and endocrine disease: lessons from estrogen receptor knock out mice. Curr Opin Pharmacol 1(6): 613-619.

5. Lizcano F, Guzmán G (2014) Estrogen deficiency and the origin of obesity during menopause. Biomed Res Int 2014: 757461.

6. Genazzani AR, Gambacciani M (2006) Effect of climacteric transition and hormone replacement therapy on body weight and body fat distribution. Gynecol Endocrinol 22(3): 145-150.

7. Al Safi ZA, Polotsky AJ (2015) Obesity and Menopause. Best Practice & Research Clinical Obstetrics and Gynaecology 29(4): 548-553.

8. Marioribanks J, Farquhar C, Roberts H, Lethaby A (2012) Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev (7): CD004143.

9. Davis SR, Castelo Branco C, Chedraui P, Lumsden MA, Nappi RE, et al. (2012) Understanding weight gain at menopause. Climacteric 15(5): 419-429.

10. Woods DC, White YA, Tilly JL (2013) Purification of oogonial stem cells from adult mouse and human ovaries: an assessment of the literature and a view toward the future. Reprod Sci 20(1): 7-15.

11. Dunn JF, Nisula BC, Rodboard D (1981) Transport of steroid hormones. Binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-steroidbinding globulin in human plasma. J Clin Endocrinol Metab 53(1): 58-68.

12. Canonico M, Oger E, Conard J, Meyer G, Le´ Vesque H, et al. (2006) Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. J Thromb Haemost 4(6): 1259-1265.

13. Gartoulla P, Worsley R, Bell RJ, Davis SR (2015) Moderate-severe vasomotor and sexual symptoms remain problematic for 60-65 year old women. Menopause 22(7): 694-701.

14. MacLennan AH, Broadbent JL, Lester S, Moore V (2004) Oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev (4): CD002978.

15. Welton AJ, Vickers MR, Kim J, Ford D, Lawton B, et al. (2008) Health related quality of life after combined hormonereplacement therapy: randomised controlled trial. BMJ 337: a1190.

16. North American MenopauseSociety (2012) The 2012 Hormone Therapy PositionStatement of the North American Menopause Society. Menopause 19(3): 257-271.

17. Olie V, Plu Bureau G, Conard J, Horellou MH, Canonico M, et al. (2011) Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause 18(5): 488-493.

18. Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrøm E, et al. (2000) Increased risk of recurrent ven ous thromboembolism during hormone replacement therapy-results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost 84(6): 961-967.

19. Palacios S, Castelo Branco C, Currie H, Mijatovic V, Nappi RE, et al. (2015) Update on management of genitourinary syndrome of menopause: a practical guide. Maturitas 82(3): 308-313.

20. Santen RJ (2014) Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. Climacteric 18(2): 121-134.

21. Roberts H, Hickey M, Lethaby A (2014) Hormone therapy in postmenopausalwomen and risk of endometrial hyperplasia Cochrane review summary. Maturitas 77(1): 4-6.

22. Davis SR, Lambrinoudaki I, Lumsden M, Mishra GD, Pal L, et al. (2015) Menopause. PRIMER.

23. Schindler AE (2014) The “newer” progestogens and postmenopausal hormone therapy (HRT). J Steroid Biochem Mol Biol 142: 48-51.

24. Pluchino N, Carmignani A, Cubeddu A, Santoro A, Cela V, et al. (2013) Androgen therapy in women: for whom and when. Arch Gynecol Obstet 288(4): 731-737.

25. Shufelt C, Bretsky P, Almeida CM , Johnson BD, Shaw LJ, et al. (2010) DHEA-S levels and cardiovascular disease mortality in postmenopausal women: results from the National Institutes of Health-National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women’s Ischemia Syndrome Evaluation (WISE) . J Clin Endocrinol Metab 95(11): 4985-4992.

26. Genazzani AR, Stomati M, Valentino V, Pluchino N, Pot E, et al. (2011) Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality. Climacteric 14(6): 661-668.

27. Pluchino N, Ninni F, Stomati M, Freschi L, Casarosa E, et al. (2008) One-year therapy with 10mg/day DHEA alone or in combination with HRT in postmenopausal women: effects on hormonal milieu. Maturitas 59(4): 293-303.

28. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA (2014) Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric 18(2): 226-232.

29. Pinkerton JV, Abraham L, Bushmakin AG, Cappelleri JC, Racketa J, et al. (2014) Evaluation of the efficacy and safety of bazedoxifene/conjugated estrogens for secondary outcomes including vasomotor symptoms in postmenopausal women by years since menopause in the Selective Estrogens, Menopause and Response toTherapy (SMART) trials. J Womens Health (Larchmt) 23(1): 18-28 .

30. Pickar JH, Yeh IT, Bachmann G, Speroff L (2009) Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil Steril 92(3): 1018-1024.

31. Genazzani AR, Komm BR, Pickar JH (2015) Emerging hormonal treatments for menopausal symptoms. Expert Opinion on Emerging Drugs 20(1): 31-46.

32. Rymer J, Robinson J, Fogelman I (2002) Ten years of treatment with tibolone 2.5mg daily: 283 effects on bone loss in postmenopausal women. Climacteric 5: 390-398.

33. Valdivia I, Campodonico I, Tapia A, Capetillo M, Espinoza A, et al. (2004) Effects of 287 tibolone and continuous combined hormone therapy on mammographic breast density and 288 breast histochemical markers in postmenopausal women. Fertil Steril 81: 617-623.

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