Bioidentical hormone therapy in menopause: relevance in dermatology

Luis J Borda MD, Lulu L Wong BS, Antonella Tosti MD

Affiliations: Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA

Corresponding Author: Luis J Borda MD, Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, 1600 NW 10th Avenue, RMSB 2023A, Miami, FL, 33136, Tel: 305-243-6734, Email: lborda@med.miami.edu

Abstract Hormone replacement therapy has been shown to be effective in alleviating menopausal symptoms. However, its use is controversial owing to potential health risks, such as thromboembolism and cancer. Bioidentical hormone therapy has recently become popular as an alternative to conventional hormone replacement therapy. These bioidentical hormones have a molecular structure identical to endogenous hormones found in a woman's body. A claimed advantage of bioidentical hormone therapy is the compounding practice in order to individualize therapy depending on patient's own hormone levels and symptoms. However, there is no scientific evidence to assess the validity of these claims. Bioidentical hormone therapy has also been used by dermatologists for its anti-aging effects on the skin, but little is known about efficacy and side effects of bioidentical hormones in this field. This review illustrates the main purpose of bioidentical hormone therapy for dermatological uses and its potential side effects, serving as a tool for dermatologists when facing these patients.

Keywords: hormone replacement therapy, bioidentical hormone therapy, anti-aging, bioidentical

Introduction

Menopause is a natural condition that occurs between the ages of 48 and 55 years [1]. It is defined as the termination of menses owing to the loss of ovarian follicular activity; it is diagnosed after 12 consecutive months of amenorrhea not related to pathological cause. Symptoms of menopause affect up to 80% of post-menopausal women in the United States, with hot flashes being the most commonly reported (60-85% within this group). Other symptoms attributed to the decline of estrogen include bone loss, vaginal atrophy, and skin aging [1, 2]. Although hormone replacement therapies (HRT) demonstrate effectiveness in alleviating these symptoms, potential health risks including cancer and thromboembolism make its use controversial [2, 3]. In recent years, the use of custom-compounded bioidentical hormone therapy (BHT) has become increasingly popular as an alternative to conventional HT. However, although some non-compounded BHTs have been approved by the Food and Drug Administration (FDA) for the treatment of menopausal symptoms [4, 5], (**Table 1**), compounded BHT custom-prepared by pharmacists have not been regulated or approved by this entity [6].

Compounded BHT may include various dosage levels of estrogen, progesterone, and sometimes testosterone, which can be combined into single dosing formulation for oral, transdermal, or vaginal delivery [7]. Both estrogen and progesterone are effective for improving mood symptoms and resolving hot flashes, whereas testosterone helps improve libido. Additionally, estrogen effectively treats vaginal atrophy and prevents osteoporosis [3].

Hormone replacement therapies consist of conjugated estrogen and progesterone containing extra structural groups without altering the molecular properties. In contrast, bioidentical

hormones do not have added moieties and their molecular structure is identical to endogenous hormones produced by a woman's body. Though marketed to be natural, safer, and more effective than traditional options, these molecules are still synthesized in the laboratory from soy or yam-based products [1]. There is no scientific evidence to evaluate the validity of these marketing claims [8]. There are currently several forms of estrogens used in BHT including estradiol, estriol, and estrone. Bioidentical progesterone and testosterone are available in one naturally found form and testosterone is sometimes replaced by its precursor dehydroepiandrosterone (DHEA), [3]. Commonly compounded products include bi-estrogen, a combination of estradiol and estriol, and tri-estrogen, a combination of estradiol, estriol, and estrone [2].

A claimed advantage of BHT is the practice of compounding to personalize therapy based on a patient's own hormone levels, preferences, and symptoms [2]. Compounding can allow for lower concentrations of hormones to be used compared to commercially available products. Though there is no standard way to determine how compounded BHT should be prescribed, some providers determine initial dosing based on patient symptoms, whereas others measure levels of hormones in saliva or serum [3]. Compounding pharmacies often work closely with prescribers to determine best dosing formulations for each particular patient [2]. However, there are no evidence-based guidelines for determining optimal dose based on hormone levels. Additionally, there are risks arising from the compounding process itself, as stated by major medical societies, such as the American College of Obstetrician and Gynecologists, the Endocrine Society, and the North American Menopause Society [1]. Part of the issue is the lack of regulation, as compounding pharmacies are exempt from having to register with the FDA as a drug manufacturer [5].

Dermatologists treat many women that take menopausal hormone therapy, which includes both HRT and BHT. Little is known about the use of BHT for dermatological uses, including potential anti-aging effects and potential side effects. This review will describe the main application of BHT in dermatology practice, including any adverse effects that its consumption carries or might carry.

Methodology of search

A review of the English-language published work was performed via PubMed database (i.e. http://www.ncbi.nlm.nih.gov/pubmed/). The search was carried out by using the following terms: "bioidentical hormone therapy," "bioidentical compounded hormone," and "menopausal hormone therapy" separately. Activating the limit "review," "clinical trial," "systematic review," and "guideline" narrowed the search for relevant articles. We also used the search field tag "Title/Abstract." Thirty-five articles and documents were selected to inform this review after exclusion of those that reflected duplication of information, did not present current evidence, or deviated from the topic of BHT. To establish the relevance and fit of the literature, abstracts and summaries were read and keywords were highlighted. Thorough reading and reflection of the selected publications were used to create a framework for the extraction and synthesis of information.

Main use of BHT in dermatology practice

Skin manifestations of estrogen deficiency and menopause

Menopause is a deficient estrogen state that affects the skin through accelerated collagen breakdown, decreased elastin, dehydration, and impaired wound healing. Loss of collagen results in skin that is more distensible and lacking tone, resulting in a decreased recoil from stretching [9]. Low estrogen is also associated with decreased water retaining capacity of skin tissues, resulting in dry and itchy skin [10], which leads to a more fragile skin riddled with deeper and more numerous wrinkles. Hirsutism has also been associated with menopause, which is possibly related to an increased impact of androgens on hair follicles [11]. Ali et al. revealed diffuse generalized hair loss as the most frequent type of scalp hair loss in 26% of post-menopausal women. Frontal hair loss was also shown in 9% of post-menopausal women. Hirsutism, especially facial hair gain was shown in 39% with the chin being the most common site (32% of women), [12].

Female androgenetic alopecia, also known as female pattern hair loss (FPHL), has a peak incidence following menopause with a prevalence of up to 29% in women aging between 70 and 89 years [13, 14]. The mechanism through which follicular miniaturization happens in FPHL is not completely clear. Some authors have theorized that the effects of dihydrotestosterone on hair follicles contributes to the development of FPHL [15], which is supported by cases that women with hyperandrogenism may develop early-onset FPHL [16]. Nevertheless, levels of androgens are normal in most women with FPHL. Several theories have been proposed to explain why women with normal androgen levels could develop FPHL, such as increased sensitivity of hair follicles to androgens and the influences of estrogens on its development [17, 18]. Furthermore, the increased prevalence of FPHL especially in postmenopausal women indicates the possible role of estrogen in its pathogenesis; but there is still conflicting evidence on whether estrogens inhibit or promote hair growth [17].

Skin flushing occurs in 70-85% of women throughout the peri-menopausal stage. Abrupt feeling of intense heat, reddening of face, neck, and chest, and sweating is known to be caused by a dysfunction in the central catecholaminergic system. It can be associated with nausea, waking at night, and throbbing pain in neck and head [19]. Estrogen deficiency is also detrimental to wound healing, specifically in inflammation and re-granulation, whereas exogenous therapy can reverse these effects [20]. Keratoderma climactericum was originally reported as having a particular association with menopause [21]. Its main features involve hyperkeratosis of soles and palms, specifically at level of the heels at the beginning of menopause. Walking may be painful for these patients and it is most commonly found in hypertensive and obese menopausal women [22].

Anti-aging effect with use of hormone replacement therapy

The impact of HRT on the skin thickness and dermal density has been shown when estrogens were first used for menopausal women. Therefore, this therapy was deemed as an effort to partly alleviate skin atrophy and xerosis in postmenopausal women [23]. Wolff et al. reported that women receiving long-term postmenopausal HT have more elastic skin and less severe wrinkling than women who never used HT, indicating that HT may have cosmetic benefits [24]. In addition, treatment with conjugated estrogen for 12 months has been shown to increase the thickness of the skin (i.e. reduction of atrophy), thus providing further evidence for the potential use of conjugated estrogens in preventing skin aging. Both the barrier function and water-retaining capacity of the menopause-associated xerotic stratum corneum were restored partially following HRT [25]. Furthermore, these changes are associated with change in the keratinocyte turn-over. Currently, no consensus has been established about the effects of HRT on dermal climacteric aging. Overall, the dermal collagen density, content, and thickness have been reported to be likely maintained in HRT recipients compared to age-matched untreated women [23]. Finally, estrogen was also found to revert age-related reduction in wound healing rates, specifically via increase of TGF-β1 [26].

Dehydroepiandrosterone supplementation has shown several positive effects, including an increase in sebum production. This is especially helpful for improving the skin of patients who are older than 70 years of age, as they are often physiologically

Table 1. *Non-Compounded Bioidentical Hormone Therapies Approved by the FDA*.*

BHT†	Presentation	Dose
Estradiol	Tablet	0.5; 1.0; or 2.0mg
	Transdermal Patch	14; 25; 37.5; 50; 75; 100µg
	Transdermal Emulsion, Gel, Spray	1.0; 1.25; 1.53-4.59g, respectively
	Vaginal Ring	0.05-0.1mg
Micronized Progesterone	Capsules	100, 200mg

*: Food and Drug Administration.

†: Bioidentical Hormone Therapy.

hyposeborrheic [27, 28]. Increase in skin surface hydration has also been found mostly in men less than 70-years old, which could be related to a concurrent improvement of skin roughness and stratum corneum water content. A decrease in facial skin pigmentation (i.e. yellowness) has also been reported, which compared with the increase of around 5% noticed between young and old people [29] should be deemed as a trend towards rejuvenation of skin color [27]. A randomized controlled trial (RCT) found that skin atrophy is significantly decreased (i.e. increased epidermal thickness) in post-menopausal women by DHEA oral supplementation at a dosage of 50mg daily for 365 days, particularly on the dorsal surface of hands [27]. Therefore, effects induced by oral DHEA supplementation may ameliorate physical appearance of aging skin.

Safety and efficacy of using custom-compounded bht

Use of compounded BHT still carries similar risks comparable to that experienced by women taking HRT. The Women's Health Initiative (WHI) study showed that use of estrogen and progesterone replacement therapy increased risks for stroke, venous thromboembolism, and breast cancer. Additionally, these risks were more pronounced in post-menopausal women over the age of 60 [8]. Other reported adverse effects include gall bladder disease, urinary incontinence, and an increased risk for endometrial cancer [8]. Owing to the lack of FDA regulation on the compounding process, there are also risks for contamination, dosage inconsistency, and lack of sterility with compounded BHT. Previous investigations of compounded hormone therapies have revealed that some products contain lower levels of active hormone than prescribed alternatives, and inadequate doses of progesterone could potentially increase the risk of endometrial cancer [30]. Compounding risks were also unfortunately made clear when 64 deaths and over 750 cases of fungal meningitis were linked to the use of contaminated intrathecal steroids, prepared by a New England compounding pharmacy [30]. Compounded products such as BHT are in need of better regulatory processes to ensure safety for patients using these formulations. Additionally, randomized controlled trials should be done to assess and compare the efficacy and safety profile of compounded BHT versus traditional hormone therapy. Currently, there are three clinical trials investigating bioidentical hormone replacement therapy for the treatment of menopause. The REVERT study is investigating improvement of vasomotor symptoms in women taking any new regimen involving bioidentical hormones (NCT01862861). Another study evaluates safety and outcomes in women taking bioidentical estrogen and progesterone compared with conventional hormone combinations and placebo (NCT00302731). A third study investigates pharmacokinetics and tolerability of compounded bioidentical estrogen cream and progesterone that are currently on the market (NCT00864214).

Dermatological Side Effects

Dermatological side effects will vary depending on the kind of hormones the patient is receiving. Though there is no clinical data to assess side effect profile in BHT, a survey of 401 pharmacists found that approximately 25% believed BHT carried less risk of side effects compared to non-bioidentical hormone therapy [31]. Despite this belief, there have been some case reports of cutaneous side effects that may be associated with BHT use (**Table 2**).

Most cutaneous adverse events associated with hormone therapy are androgenic and likely related to aberrant levels of testosterone and its derivatives [1, 32]. Testosterone replacement was associated with hirsutism in a dose-dependent manner with a reported prevalence of up to 36% in two different placebo-controlled trials [33, 34]. Acne was an adverse event with a wide range of incidence reported as high as 50% in different studies including randomized controlled trials, literature reviews, and case series [33-36]. Androgenetic alopecia has been associated with use of testosterone [37], but was actually reported at a higher incidence in the placebo-control arm in one study [34].

A case of frontal fibrosing alopecia that began after a patient began BHT of unknown formulation has also been reported [38]. Other major dermatological adverse events associated with bioidentical

Table 2. *Dermatologic adverse effects attributed to bioidentical hormone replacement therapies.*

Dermatologic side effect	Prevalence	Study design	References
Testosterone and other related anabolic steroids			
Unspecified	2.6 unadjusted OR, 4.9 adjusted OR	RCT, DB	[54]
Acne	1-50%	Literature review	[33]
	5.6%-6%	DB, placebo-controlled trial	[34]
Hirsutism	1-30%	Literature review	[33]
	4-6% women	Literature review	[36]
	0.8-11.7% dose dependent	Literature review	[55]
Increased facial hair growth	11.6%-19.6% dose dependent	DB, placebo-controlled trial	[34]
Testosterone and estrogen combination			
Acne	3-30%	Literature review	[33]
	5.6%	RCT, DB	[35]
	3-8%	Literature review	[36]
Hirsutism	6-36%	Literature review	[33]
DHEA			
Skin pigmentation	N/A (reported as a median)	RCT, DB	[27]
Increase sebum production (skin spots on tape test)	N/A (reported as a median)	RCT, DB	[27]
	64% female	DB, placebo-controlled trial	[56]
Skin oiliness and elasticity changes	41-89% dose dependent	RCT, DB	[57]
	13.33% female, 0% male	RCT, DB	[58]
	45% female	DB, placebo-controlled trial	[56]
Greasy hair	13.33% female, 0% male	RCT, DB	[58]
Acne	23.08% (6.66% male, 84.21% female)	DB, Randomized, placebo-controlled cross over study	[59]
Androgenic effects, unspecified	84%	RCT, DB	[57]
	16.67% female, 0% male	RCT, DB	[58]
Increased axillary and/or pubic hair	69-100%, dose dependent	RCT, DB	[57]
	58% male	DB, placebo-controlled trial	[56]
Increased perspiration with exercise	63%	RCT, DB	[57]
Estrogen +/- progesterone			
Skin irritation (topical treatments only)	20%	RCT	[40]
	<1%	RCT	[42]
Localized allergic reaction	<1%	RCT	[43]
	4.5%	RCT	[44]
Nonspecific Pruritus	2.80%	RCT	[41]
Unspecified bioidentical hormone therapy			
Frontal fibrosing alopecia	1 patient	Case report	[38]
Multiple melanomas	1 patient	Case report	[46]

RCT: randomized placebo-controlled trial, DB: double-blinded.

hormone replacement are reported in patients using DHEA replacement and include oiliness of the skin, greasy hair, skin pigmentation, increased sebum production, and increased perspiration with exercise as summarized in **Table 2**.

Estrogen in the form of estradiol, estrone, and estriol are commonly found in compounded BHT formulations. However, cutaneous side effects associated with use of these compounds have not been widely reported in the literature. The most

common adverse skin reactions mentioned in literature include localized erythema or irritation at the site of topical application. One Cochrane review concluded that skin reactions were more common in women using transdermal estradiol or placebo [39]. One small study reported 20% incidence of local irritation in patients using transdermal estradiol, whereas another reported nonspecific pruritus in 2.8% of patients taking micronized estradiol tablets orally [40, 41]. Another larger study found a lower incidence of application site irritation, with only 3 patients experiencing this adverse effect [42]. Two studies reported local allergic reaction in one patient out of 80 receiving vaginal cream and one patient out of 22 using an estradiol patch [43, 44]. However, despite dozens of clinical trials investigating use of estrogens in menopausal women in the past decade, very few reported any cutaneous adverse effects.

Although melanoma is not considered a risk when taking BHT, it was reportedly associated with BHT in one case report. A woman with no other alarming risk factors for melanoma was found to develop multiple melanomas in situ and dysplastic nevi

within three years of receiving BHT for her perimenopause [45, 46]. Authors concluded that sex hormones were likely to contribute to melanoma pathophysiology, yet contradicting studies suggest an inhibitory effect of estrogen and progesterone on melanoma growth [47]. Furthermore, a randomized clinical trial found no increased incidence of non-melanoma or melanoma skin cancers in patients using traditional menopause hormone therapy [48]. In vitro experiments have also reported progesterone-induced autophagy and growth inhibition in melanoma cells [49]. It is unclear whether BHT contributes to the development of melanoma and dysplastic nevi.

Lastly, though the etiology is not well studied on a molecular level, melasma is associated with hormonal influences such as pregnancy, oral contraceptives, and hormone replacement [50-52]. Pathogenesis of the hyperpigmentation may involve high estrogen and progesterone levels stimulating melanogenesis [50, 53]. Although the literature does not mention melasma as a side effect of BHT, it is important to consider this as a potential effect for any person using exogenous female sex hormones.

Conclusion

Postmenopausal women have certain cutaneous alterations resulting in dry, itchy, thin, and fragile skin. Several studies suggest benefit in using BHT in alleviating these symptoms, such as increase of cutaneous hydration and reduction of skin atrophy, providing evidence for the use of BHT in the prevention of skin aging. However, treatment with any kind of hormone carries the risk of skin side effects, which will depend on the type of hormones the patient is receiving. Even though BHT is used in dermatology practice, particularly for its anti-aging effects, yet more research needs to be carried out in order to evaluate and extend the use of BHT in this field. Additionally, though compounded BHT is marketed to be natural, safer, and more effective than traditional alternatives, there are no well-run RCTs available to support these claims.

References

1. Cirigliano M. Bioidentical hormone therapy: a review of the evidence. *J Womens Health (Larchmt).* 2007;16(5):600-31. [PMID: 17627398].
2. McBane SE, Borgelt LM, Barnes KN, Westberg SM, Lodise NM, Stassinos M. Use of compounded bioidentical hormone therapy in menopausal women: an opinion statement of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy.* 2014;34(4):410-23. [PMID: 24390902].
3. Ruiz AD, Daniels KR, Barner JC, Carson JJ, Frei CR. Effectiveness of compounded bioidentical hormone replacement therapy: an observational cohort study. *BMC Womens Health.* 2011;11:27. [PMID: 21651797].
4. Stuenkel CA, Manson JE. Compounded Bioidentical Hormone Therapy: Does the Regulatory Double Standard Harm Women? *JAMA Intern Med.* 2017;177(12):1719-20. [PMID: 29052690].
5. Egras AM, Umland EM. The role of transdermal estrogen sprays and estradiol topical emulsion in the management of menopause-associated vasomotor symptoms. *Int J Gen Med.* 2010;3:147-51. [PMID: 20531974].
6. Dubaut JP, Dong F, Tjaden BL, Grainger DA, Duong J, Tatpati LL. Prescribing Bioidentical Menopausal Hormone Therapy: A Survey

of Physician Views and Practices. *J Womens Health (Larchmt).* 2018;27(7):859-66. [PMID: 29583064].

7. Sood R, Warndahl RA, Schroeder DR, Singh RJ, Rhodes DJ, Wahner-Roedler D, et al. Bioidentical compounded hormones: a pharmacokinetic evaluation in a randomized clinical trial. *Maturitas.* 2013;74(4):375-82. [PMID: 23384975].
8. Santoro N, Braunstein GD, Butts CL, Martin KA, McDermott M, Pinkerton JV. Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement. *J Clin Endocrinol Metab.* 2016;101(4):1318-43. [PMID: 27032319].
9. Calleja-Agius J, Brincat M. The effect of menopause on the skin and other connective tissues. *Gynecol Endocrinol.* 2012;28(4):273-7. [PMID: 21970508].
10. Thornton MJ. Human skin: a mirror for estrogen action? *Menopause.* 2016;23(2):119-20. [PMID: 26757275].
11. Mofid A, Seyyed Alinaghi SA, Zandieh S, Yazdani T. Hirsutism. *Int J Clin Pract.* 2008;62(3):433-43. [PMID: 18081798].
12. Ali I, Wojnarowska F. Physiological changes in scalp, facial and body hair after the menopause: a cross-sectional population-based study of subjective changes. *Br J Dermatol.* 2011;164(3):508-13. [PMID: 21128905].
13. Blume-Peytavi U, Blumeyer A, Tosti A, Finner A, Marmol V, Trakatelli M, et al. S1 guideline for diagnostic evaluation in androgenetic alopecia in men, women and adolescents. *Br J Dermatol.* 2011;164(1):5-15. [PMID: 20795997].
14. Norwood OT. Incidence of female androgenetic alopecia (female pattern alopecia). *Dermatologic surgery.* 2001;27(1):53-4. [PMID: 11231244].
15. Price VH. Androgenetic alopecia in women. *J Investig Dermatol Symp Proc.* 2003;8(1):24-7. [PMID: 12894991].
16. Futterweit W, Dunaif A, Yeh HC, Kingsley P. The prevalence of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. *J Am Acad Dermatol.* 1988;19(5 Pt 1):831-6. [PMID: 3192772].
17. Yip L, Rufaut N, Sinclair R. Role of genetics and sex steroid hormones in male androgenetic alopecia and female pattern hair loss: an update of what we now know. *Australas J Dermatol.* 2011;52(2):81-8. [PMID: 21605090].
18. Camacho-Martinez FM. Hair loss in women. *Semin Cutan Med Surg.* 2009;28(1):19-32. [PMID: 15009320].
19. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. *Health Qual Life Outcomes.* 2005;3:47. [PMID: 19341939].
20. Horng HC, Chang WH, Yeh CC, Huang BS, Chang CP, Chen YJ, et al. Estrogen Effects on Wound Healing. *Int J Mol Sci.* 2017;18(11). [PMID: 29099810].
21. Deschamps P, Leroy D, Pedailles S, Mandard JC. Keratoderma climactericum (Haxthausen's disease): clinical signs, laboratory findings and etretinate treatment in 10 patients. *Dermatologica.* 1986;172(5):258-62. [PMID: 2943612].
22. Nair PA. Dermatosis associated with menopause. *J Midlife Health.* 2014;5(4):168-75. [PMID: 25540566].
23. Pierard GE, Humbert P, Berardesca E, Gaspard U, Hermanns-Le T, Pierard-Franchimont C. Revisiting the cutaneous impact of oral hormone replacement therapy. *Biomed Res Int.* 2013;2013:971760. [PMID: 24455744].
24. Wolff EF, Narayan D, Taylor HS. Long-term effects of hormone therapy on skin rigidity and wrinkles. *Fertil Steril.* 2005;84(2):285-8. [PMID: 16084862].
25. Guinot C, Malvy D, Ambroisine L, Latreille J, Mauger E, Guehenneux S, et al. Effect of hormonal replacement therapy on skin biophysical properties of menopausal women. *Skin Res Technol.* 2005;11(3):201-4. [PMID: 15998332].
26. Ashcroft GS, Dodsworth J, van Boxtel E, Tarnuzzer RW, Horan MA, Schultz GS, et al. Estrogen accelerates cutaneous wound healing associated with an increase in TGF-beta1 levels. *Nat Med.* 1997;3(11):1209-15. [PMID: 9359694].
27. Baulieu EE, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci U S A.* 2000;97(8):4279-84. [PMID: 10760294].
28. Diamond P, Cusan L, Gomez JL, Belanger A, Labrie F. Metabolic effects of 12-month percutaneous dehydroepiandrosterone replacement therapy in postmenopausal women. *J Endocrinol.* 1996;150 Suppl:S43-50. [PMID: 8943786].
29. Andreassi L, Casini L, Simoni S, Bartalini P, Fimiani M. Measurement of cutaneous colour and assessment of skin type. *Photodermatol Photoimmunol Photomed.* 1990;7(1):20-4. [PMID: 2371166].
30. Pinkerton JV, Pickar JH. Update on medical and regulatory issues pertaining to compounded and FDA-approved drugs, including hormone therapy. *Menopause.* 2016;23(2):215-23. [PMID: 26418479].
31. Siyam T, Yuksel N. Beliefs about bioidentical hormone therapy: a cross-sectional survey of pharmacists. *Maturitas.* 2013;74(2):196-202. [PMID: 23265304].
32. Conaway E. Bioidentical hormones: an evidence-based review for primary care providers. *J Am Osteopath Assoc.* 2011;111(3):153-64. [PMID: 21464264].
33. Gelfand MM, Wiita B. Androgen and estrogen-androgen hormone replacement therapy: a review of the safety literature, 1941 to 1996. *Clin Ther.* 1997;19(3):383-404; discussion 367-8. [PMID: 9220205].
34. Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, et al. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med.* 2008;359(19):2005-17. [PMID: 18987368].
35. Lobo RA, Rosen RC, Yang HM, Block B, Van Der Hoop RG. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril.* 2003;79(6):1341-52. [PMID: 12798881].
36. Shufelt CL, Braunstein GD. Safety of testosterone use in women. *Maturitas.* 2009;63(1):63-6. [PMID: 19250779].
37. Lattouf C, Miteva M, Tosti A. Connubial androgenetic alopecia. *Arch Dermatol.* 2011;147(11):1329-30. [PMID: 22106127].
38. Kimes KC, K. Frontal Fibrosing Alopecia. *J Dermatol Nurses Assoc.* 2015;7(4):216-8.
39. Gaudard AM, Silva de Souza S, Puga ME, Marjoribanks J, da Silva EM, Torloni MR. Bioidentical hormones for women with vasomotor symptoms. *Cochrane Database Syst Rev.* 2016(8):CD010407. [PMID: 27479272].
40. Honisett SY, Tangalakis K, Wark J, Apostolopoulos V, Stojanovska L. The Effects of Hormonal Therapy and Exercise on Bone Turnover in Postmenopausal Women: A Randomised Double-

Blind Pilot Study. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2016;37(2-3):23-32. [PMID: 27883319].

41. Honjo H, Taketani Y. Low-dose estradiol for climacteric symptoms in Japanese women: a randomized, controlled trial. *Climacteric*. 2009;12(4):319-28. [PMID: 19330598].
42. Hedrick RE, Ackerman RT, Koltun WD, Halvorsen MB, Lambrecht LJ. Transdermal estradiol gel 0.1% for the treatment of vasomotor symptoms in postmenopausal women. *Menopause*. 2009;16(1):132-40. [PMID: 18971794].
43. Fernandes T, Costa-Paiva LH, Pedro AO, Baccaro LF, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. *Menopause*. 2016;23(7):792-8. [PMID: 27116462].
44. Aguirre W, Chedraui P, Mendoza J, Ruilova I. Gabapentin versus. low-dose transdermal estradiol for treating post-menopausal women with moderate to very severe hot flushes. *Gynecol Endocrinol*. 2010;26(5):333-7. [PMID: 20050764].
45. Shelton M. Estradiol/testosterone. *Reactions Weekly*. 2015(1556):120. doi: 10.1007/s40278-015-2594-2.
46. Shelton MA, S.; Chon, S. Multiple melanomas developing after bioidentical hormone replacement therapy. *J Am Acad Dermatol*. 2015;72(5, Sup 1):AB173. doi: 10.1007/s40278-015-2594-2.
47. Marzagalli M, Casati L, Moretti RM, Montagnani Marelli M, Limonta P. Estrogen Receptor beta Agonists Differentially Affect the Growth of Human Melanoma Cell Lines. *PLoS One*. 2015;10(7):e0134396. [PMID: 26225426].
48. Tang JY, Spaunhurst KM, Chlebowski RT, Wactawski-Wende J, Keiser E, Thomas F, et al. Menopausal hormone therapy and risks of melanoma and nonmelanoma skin cancers: women's health initiative randomized trials. *J Natl Cancer Inst*. 2011;103(19):1469-75. [PMID: 21878677].
49. Leder DC, Brown JR, Ramaraj P. In-vitro rescue and recovery studies of human melanoma (BLM) cell growth, adhesion and migration functions after treatment with progesterone. *Int J Clin Exp Med*. 2015;8(8):12275-85. [PMID: 26550137].
50. Files JA, Kransdorf LN, Ko M, Kling JM, David PS, Pruthi S, et al. Bioidentical hormone therapy: An assessment of provider knowledge. *Maturitas*. 2016;94:46-51. [PMID: 27823744].
51. FDA. Bio-Identicals: Sorting myths from facts 2012 [Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm049311.htm. Accessed on August 1, 2018.
52. Kim SW, Yoon HS. Tamoxifen-induced melasma in a postmenopausal woman. *J Eur Acad Dermatol Venereol*. 2009;23(10):1199-200. [PMID: 19192013].
53. Ortonne JP, Arellano I, Berneburg M, Cestari T, Chan H, Grimes P, et al. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. *J Eur Acad Dermatol Venereol*. 2009;23(11):1254-62. [PMID: 19486232].
54. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109-22. [PMID: 20592293].
55. Braunstein GD. Safety of testosterone treatment in postmenopausal women. *Fertil Steril*. 2007;88(1):1-17. [PMID: 17493618].
56. Gurnell EM, Hunt PJ, Curran SE, Conway CL, Pullenayegum EM, Huppert FA, et al. Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab*. 2008;93(2):400-9. [PMID: 18000094].
57. Johannsson G, Burman P, Wiren L, Engstrom BE, Nilsson AG, Ottosson M, et al. Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. *J Clin Endocrinol Metab*. 2002;87(5):2046-52. [PMID: 11994339].
58. Brooke AM, Kalingag LA, Miraki-Moud F, Camacho-Hubner C, Maher KT, Walker DM, et al. Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab*. 2006;91(10):3773-9. [PMID: 16849414].
59. Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JA, et al. Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab*. 2000;85(12):4650-6. [PMID: 11134123].