Feature

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{abstract}

This article reviews a collection of recent articles and published studies on sex hormone replacement therapy with the use of endogenous human hormones including estradiol, estriol, progesterone, and testosterone.

The past several years have been an exciting time in research on the various hormone replacement therapy (HRT) options for women. Current and emerging evidence on the use of HRT in the areas of cardiovascular disease, osteoporosis, and cancer is helping to eliminate the confusion practitioners and patients have experienced post-Women's Health Initiative Trial (WHI). In addition, research is ongoing to investigate the role of HRT in a variety of conditions not generally recognized as hormone related including colon cancer, postoperative complications, wound healing, sleep apnea, immune response, and eye health.

In wading through the literature on HRT, it becomes apparent that reporting habits in regards to nomenclature still pose a significant obstacle to interpreting the data presented. In many studies, the specific hormone utilized (i.e., which estrogen and what progestin, human, animal, or synthetic) is not identified. In addition, the literature continues to frequently "lump" all forms

of hormone replacement, synthetic, and human into the same category—making the resulting data ambiguous at best. The articles presented here represent a best effort to ensure accurate identification of the specific hormone(s) utilized, and, unfortunately, many studies of interest were omitted because of potential or actual ambiguity.

{2010 articles}

1

Canonico M, Alhenc-Gelas M, Plu-Bureau G et al. Activated protein C resistance among postmenopausal women using transdermal estrogens: Importance of progestogen. *Menopause* 2010; [Epub ahead of print].

One-hundred and eight healthy, postmenopausal women ages 45 to 70 were studied to determine the differential impact of activated protein C (APC) on endogenous thrombin potential in women on transdermal estrogens + micronized progesterone, transdermal estrogens + norpregnane derivatives, and non-HRT users. No significant changes in APC sensitivity were noted in women on transdermal estrogens + micronized progesterone when compared with non-HRT users. When compared to the transdermal estrogen + micronized progesterone or non-HRT users, women treated with transdermal estrogen + norpregnanes were less sensitive to APC. These findings support recent epidemiological data showing norpregnane derivatives but not micronized progesterone increase venous thromboembolism risk in women on transdermal estrogen replacement therapy.

2

Di Carlo C, Tommaselli GA, Gargano V et al. Transdermal estradiol and oral or vaginal natural progesterone: Bleeding patterns. *Climacteric* 2010; [Epub ahead of print].

Irregular cycles are a common complaint among perimenopausal women. Researchers at the University of Naples evaluated the changes in bleeding pattern over 12 cycles in 100 patients randomized into four groups and administered transdermal estrogen with two doses and two routes of natural progesterone (NP) therapy from the 14th day to the 25th day of each 28-day cycle.

- **Group A:** Transdermal 17beta-estradiol 50 mug/day + NP per os 100 mg/day
- **Group B:** Transdermal 17beta-estradiol 50 mug/day + NP per os 200 mg/day
- **Group C:** Transdermal 17beta-estradiol 50 mug/day + NP per vagina 100 mg/day
- **Group D:** Transdermal 17beta-estradiol 50 mug/day + NP per vagina 200 mg/day

Results indicated that all treatments were effective in balancing the effects of estradiol on endometrium as no significant differences in endometrial thickness were seen between groups. Patients in Groups C and D reported a higher number of episodes of regular bleeding and fewer episodes of spotting than Groups A and B. Di Carlo and team conclude that transdermal estradiol combined with 100 mg/day of micronized NP administered vaginally led to the best cycle control, excellent patient satisfaction and no serious side-effects. The therapy outlined is offered as a potential first-line treatment for irregular uterine bleeding in early postmenopausal patients.

3

Otto C, Fuchs I, Vonk R et al. Comparative analysis of the uterine and mammary gland effects of progesterone and medroxyprogesterone acetate. *Maturitas* 2010; 65(4): 386–391.

Researchers at Bayer Schering Pharma in Berlin, Germany assessed the balance between estradiol-induced uterine epithelial cell proliferation and adverse mammary gland effects in ovariectomized mice treated with estradiol, estradiol + increasing doses of progesterone, or medroxyprogesterone acetate (MPA). Results showed MPA inhibits uterine activity and stimulates breast tissue proliferation at the same dose, whereas progesterone inhibits uterine activity at doses lower than those required to significantly stimulate breast cell proliferation. Researchers concluded: "Progestins do not behave the same. Use of the natural hormone progesterone, but not MPA, in combined hormone therapy (HT) might offer a safety window between uterine effects and undesired proliferative activity in the mammary gland."

4

Panay N, Al-Azzawi F, Bouchard C et al. Testosterone treatment of HSDD in naturally menopausal women: The ADORE study. *Climacteric* 2010; 13(2): 121–131.

Hypoactive sexual desire disorder (HSDD) in women is characterized by a deficiency or absence of sexual fantasies and desire for sexual activity, which results in interpersonal difficulties or marked distress. Hormonal, neurobiological, and psychosocial factors appear to be contributory or causative factors. Researchers at the Imperial College Hospitals and Chelsea and Westminster Hospital in London, evaluated the safety and efficacy of transdermal testosterone (TT) in menopausal women (with and without concurrent hormone replacement therapy) with HSDD. Naturally menopausal women (n = 272) were randomized to receive 300 mcg/day of TT for six months in this placebo-controlled, double-blind, multicenter trial. The women receiving TT showed significant improvement in the number satisfying sexual episodes as well as sexual desire and diminished personal distress when compared to the women receiving placebo. Panay and colleagues concluded: "[Transdermal testosterone] was effective in treating HSDD and improving sexual function in this study of naturally menopausal women with and without concurrent hormone therapy."

{2010 articles continued}

5

North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010; 17(2): 242–255.

Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable for women who initiate HT close to menopause but decreases in older women and with time since menopause in previously untreated women.

6

Studd J. Ten reasons to be happy about hormone replacement therapy: A guide for patients. *Menopause Int* 2010; 16(1): 44–46.

Despite negative and conflicting press reports, the London PMS and Menopause Clinic is reassuring women that under correct circumstances hormone replacement therapy (HRT), particularly if initiated prior to the age of 60, is beneficial and safe. The author presents data supporting the following key points:

1. Transdermal estradiol is likely safer than oral estrogens
2. HRT is effective for hot flashes, sweats, and vaginal atrophy
3. Estrogens prevent osteoporotic fractures (and should be first-line, rather than bisphosphonates)
4. Estrogens + testosterone helps with depression, energy, and libido
5. HRT reduces the risk of heart attacks
6. Estrogen replacement has beneficial effects on collagen (improves nail and skin texture, intervertebral discs, and bone matrix)

7

Mahmud K. Natural hormone therapy for menopause. *Gynecol Endocrinol* 2010; 26(2): 81–85.

Mahmud details a 12 plus-month follow-up on 189 patients receiving natural estrogen plus human progesterone with or without DHEA and testosterone, depending upon patient need. The results demonstrated:

1. 97% of patients experienced varying degrees of symptom control
2. 3% of patients experienced minimal or questionable benefit
3. 90% of patients experienced an improvement in mental symptoms
4. 60% of patients who had gained weight during menopause lost weight (an average of 14.8 lbs [standard deviation, 11.98])

Researchers noted that complications commonly described with traditional HRT did not occur in this group of patients and cited a need for larger controlled trials with similar protocols.

8

Tint NL, Alexander P, Tint KM et al. Hormone therapy and intraocular pressure in nonglaucomatous eyes. *Menopause* 2010; 17(1): 157–160.

Researchers at Queen's Medical Centre, Nottingham University Hospitals, United Kingdom, investigated the influence of sex hormone replacement therapy on intraocular pressure (IOP) in 263 women. Compared with non-HRT users, women taking HRT had significantly lower IOP. Women taking combined estrogen-progesterone therapy had no significant difference in IOP when compared to women on estrogen mono-therapy. Further investigation is warranted to determine whether HRT may represent a new treatment modality for glaucoma.

9

Canonico M, Fournier A, Carcaillon L et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: Results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010; 30(2): 340–345.

While oral estrogen therapy is known to increase venous thromboembolism risk, recent data indicates transdermal therapy may be safe with respect to thrombotic risk. Using data from the E3N French prospective cohort of 80,308 postmenopausal women, researchers attempted to establish the impact of the route of estrogen administration and choice of concomitant progestogen on thrombotic risk. Highlights of this study, which included 549 women with documented idiopathic first venous thromboembolism, include:

1. Past HRT users had no increased thrombotic risk when compared to non-HRT users.
2. Oral (but not transdermal) estrogens were associated with increased thrombotic risk.
3. No significant thrombotic risk was associated with the use of progesterone, pregnanes, and nortestosterones.
4. Norpregnanes were associated with increased thrombotic risk.

Canonico and colleagues conclude: "Transdermal estrogens alone or combined with [bioidentical] progesterone might be safe with respect to thrombotic risk."

{2009 articles}

1

Dimitrakakis C, Bondy C. Androgens and the breast. *Breast Cancer Res* 2009; 11(5): 212

Research on the androgenic pathways in breast cancer pathology is still in its early phases and the data on the effects of androgens in breast cancer are conflicting. Clinical evidence suggests that androgens generally inhibit mammary epithelial proliferation. However, conventional estrogen replacement suppresses endogenous androgens, potentially enhancing estrogenic breast stimulation. Researchers purport that the addition of testosterone to hormone replacement therapy regimens could potentially diminish the increased risk of breast cancer.

3

Gadducci A, Biglia N, Cosio S et al. Progestagen component in combined hormone replacement therapy in postmenopausal women and breast cancer risk: A debated clinical issue. *Gynecol Endocrinol* 2009; 25(12): 807–815.

Researchers at the Division of Gynecology and Obstetrics at the University of Pisa, Pisa, Italy, looked at the importance of the choice of the progestagen component in combined hormone replacement therapy (HRT) for breast cancer risk. Studies on women taking combination HRT have indicated that androgenic progestin- or MPA-containing formulations are associated with increased breast cancer incidence, whereas micronized progesterone- or dydrogesterone-containing formulations are not. It is theorized that progestins can activate cancer stem cells in women with clinically undetected breast cancer. In estrogen receptor (ER)+ breast cancer cells, the addition of MPA, but not progesterone, to estradiol [E(2)] appears to result in significantly higher increases in mRNA levels and estrogen-activating enzymes. MPA + E(2) results in increased breast epithelium proliferation, whereas progesterone + E(2) does not.

2

Karakus S, Kiran G, Ciralik H. Efficacy of micronised vaginal progesterone versus oral dydrogestrone in the treatment of irregular dysfunctional uterine bleeding: A pilot randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2009; 49(6): 685–688.

In this study, 69 women with irregular uterine bleeding receiving either oral dydrogesterone or vaginal progesterone for three months, were evaluated by endometrial histology findings and menstrual cycle characteristics. Results found no significant differences between groups, suggesting vaginal micronized progesterone could be an alternative to oral synthetic progestins in the treatment of irregular menstrual bleeding.

4

Majhi P, Bagga R, Kalra J et al. Intravaginal use of natural micronised progesterone to prevent pre-term birth: A randomised trial in India. *J Obstet Gynaecol* 2009; 29(6): 493–498.

Pregnant women (n = 100) with a history of one or more spontaneous pre-term births were randomized to receive (Group 1) 100 mg/day of natural micronized progesterone intravaginally from 20 to 24 weeks gestation until 36 weeks or (Group 2) no treatment. Pre-term births <37 weeks were significantly lower in women receiving progesterone (12% vs 38%) while pre-term births <34 weeks were similar between groups. In addition, babies born to women receiving progesterone therapy had significantly higher birth weights (2800 g vs 2500 g).

{2009 articles continued}

5

Aboulghar M. Luteal support in reproduction: When, what and how? *Curr Opin Obstet Gynecol* 2009; 21(3): 279-284.

Although the use, type, dose, and duration of therapy for luteal phase support (LPS) is debated, it is an essential part of the *in vitro* fertilization (IVF) cycles. Aboulghar's report discusses the original as well as recent data on LPS.

The literature supports the necessity of LPS for IVF cycles. Progesterone is more commonly used than human chorionic gonadotropin for LPS because of the risk of ovarian hyperstimulation syndrome. Although some studies suggest that for LPS with progesterone, the intramuscular route is superior to vaginal administration, the majority of IVF centers use vaginal progesterone to avoid side effects of intramuscular injection. There appears to be no difference in pregnancy rate whether LPS is started on the day of human chorionic gonadotropin, oocyte retrieval, or embryo transfer. There is, however, strong evidence that LPS should be stopped either on the day of the pregnancy test or the first ultrasound (6 to 7 weeks of pregnancy). There is no evidence that the addition of estrogen will improve pregnancy rate. Researchers conclude that progesterone is the preferred option for LPS and that therapy should start within two days from triggering ovulation and should end on the day of beta human chorionic gonadotropin or the day of the first ultrasound (6 to 7 weeks of pregnancy).

6

Holtorf K. The bioidentical hormones debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med* 2009; 121(1): 73-85.

The use of bioidentical hormones, including progesterone, estradiol, and estriol, in HRT has been intensely debated. A January 2009 report in Postgraduate Medicine reviews the published evidence on the risks and benefits of bioidentical hormone replacement (BHRT) when compared with traditional synthetic and animal-derived HRT. Specifically, BHRT's relative safety when compared with conjugated equine estrogens (CEE), medroxyprogesterone acetate (MPA), and other synthetic progestins was reviewed.

Proponents for BHRT claim that the evidence consistently supports that they are safer and more effective than comparable synthetic and nonhuman versions of HRT. However, the U.S. Food and Drug Administration and The Endocrine Society have repeatedly claimed that there is little or no evidence to support claims that bioidentical hormones are safer or more effective.

This report evaluated the evidence comparing bioidentical hormones, including progesterone, estradiol, and estriol, with the commonly used nonbioidentical versions of HRT in the following key areas:

- Clinical efficacy
- Physiologic actions on breast tissue
- Risks for breast cancer and cardiovascular disease

Researchers reviewed published papers from PubMed/MEDLINE, Google Scholar, and Cochrane databases, which included keywords associated with bioidentical hormones, synthetic hormones, and HRT. Publications that compared the effects of bioidentical and synthetic hormones, including clinical outcomes and *in vitro* results were specifically selected.

Researchers compared both the symptomatic efficacy and physiological effects of bioidentical progesterone versus synthetic progestin. They focused on the risk of breast cancer and cardiovascular disease. When compared with its synthetic counterparts, bioidentical progesterone has some distinct, potentially opposite, physiological effects. Synthetic progestins are associated with an increased risk for breast cancer, whereas both physiological and clinical studies have demonstrated that bioidentical progesterone is associated with a diminished risk. The results of Holtorf's review indicate that compared with HRT containing a synthetic progestin, patients also report greater satisfaction with HRTs that contain bioidentical progesterone. Synthetic progestins also have a variety of negative cardiovascular effects, which may be avoided with progesterone.

Estriol differentiates itself from estradiol, estrone, and CEE with its unique selectivity at the estrogen receptor and differing physiological effects. Although no randomized controlled trials of estriol have been documented, estriol along with progesterone is associated with a significant long-term reduction in the risk for breast cancer. Progesterone, compared with MPA, is associated with greater efficacy, patient satisfaction, and quality of life. Physiological data and clinical outcomes demonstrate that bioidentical estriol, estradiol, and progesterone are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than the commonly used synthetic counterparts. Researchers concluded: "Until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT. Further randomized controlled trials are needed to delineate these differences more clearly."

7

Stanosz S, Zochowska E, Safranow K et al. Influence of modified transdermal hormone replacement therapy on the concentrations of hormones, growth factors, and bone mineral density in women with osteopenia. *Metabolism* 2009; 58(1): 1–7.

Researchers studied 75 women, average age of 52.4 (± 3.5 years) with primary osteopenia, in the early postmenopausal period using two forms of HT: (1) modified transdermal HRT (bioidentical estrogen and progesterone) and (2) oral hormone supplementary therapy (HST) with synthetic, nonbioidentical hormones. Researchers evaluated serum concentrations of the sex hormones, insulin-like growth factor I (IGF-1), prolactin (PRL), osteocalcin, and procollagen, as well as the degree of mineralization of the lumbar spine.

Participants were randomly assigned to three groups depending on the form and route of administration of therapy:

1. Group I (n = 25, control) received placebo in the form of patches.
2. Group II (n = 25) was treated with modified transdermal HRT (micronized 17beta-estradiol at increasing-decreasing doses and progesterone in the second phase of the therapeutic cycle).
3. Group III (n = 25) received oral HST (Clyclo-Menorette; Wyeth, Munster, Germany).

The therapy was dosed cyclically in each group, with 21 days of medication administration, followed by a 7-day medication-free interval.

In women receiving oral HST:

1. Serum estradiol increased 5-fold and estrone increased about 11-fold (P <.0001) compared with the control group.

{2009 articles continued}

2. Basal PRL concentration and PRL level after metoclopramide stimulation test significantly increased after 3 and 12 months of treatment.
3. A significant decrease of IFG-I after one year of therapy was found.
4. An increase of growth hormone was observed during the entire time of treatment.
5. Increase in bone mineral density L(2)–L(4) was insignificant in women receiving oral HST after 12 months of therapy as compared with baseline values.

In women receiving [bioidentical] transdermal HRT:

1. Estrone and estradiol levels increased 3-fold compared with the baseline values.
2. Increased IFG-I concentrations were statistically significant after 3 months of treatment.
3. Increase in bone mineral density L(2)–L(4) was statistically significant in the group receiving modified transdermal HRT (P <.01) after 12 months of therapy as compared with baseline values.

No significant changes were shown in osteocaclin and in carboxyterminal propeptide of type I procollagen in all groups.

Researchers concluded that:

1. Low-dose modified transdermal (bioidentical) HRT modulates concentration of hormones, growth factor, IGF-I, osteocalcin, procollagen, and bone metabolism.
2. The curve concentrations of estrogens and progesterone in serum are similar to the type observed in the physiologic menstrual cycle.
3. The lack of significant increase in bone mineral density of lumbar spine in women after oral [synthetic/nonbioidentical] HST may be a result of significantly lower concentration of IGF-I in serum and occurring hyperprolastinemia.

{2008 articles}

1

L'hermite M, Simoncini T, Fuller S et al. Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review. *Maturitas* 2008; 60(3–4): 185–201.

The selection of specific compounds, doses, or routes of administration can provide significant advantages in the clinical management of postmenopausal women.

L'hermite et al reviewed the role of transdermal administration of [bioidentical] hormones in postmenopausal women. Transdermal administration of estrogens minimizes the hepatic induction of clotting factors and is associated with potential improvements in cardiovascular risk. In comparison with oral estrogens, the risk of developing deep vein thrombosis or pulmonary thromboembolism is negligible. In addition, transdermal hormones have potential advantages for blood pressure control. Synthetic progestins, administered with estrogens do not appear to share the same favorable action on the vasculature and brain as endogenous progesterone displays. Evidence indicates that these physiologic and clinical differences between synthetic progestins and progesterone with estrogens confer less or even no risk of breast cancer when compared to the use of synthetic progestins. L'hermite and colleagues conclude:

> While all types of hormone replacement therapies are safe and effective and confer significant benefits in the long term when initiated in young postmenopausal women, in specific clinical settings the choice of the transdermal route of administration of estrogens and the use of natural progesterone might offer significant benefits and added safety.

{Flashback to 1973}

In January of 1973…37 years ago…the journal *Headache* published an article titled "Progesterone suppositories and pessaries in the treatment of menstrual migraine." Progesterone vaginal suppositories are still frequently compounded today for the treatment of menstrual migraines.

{Conclusion}

The past few years have been an exciting time in research on the various HRT options for women, and the use of the bioidentical hormones estradiol, estriol, progesterone, and testosterone in replacement therapy has been hotly debated. Despite claims that there is little or no evidence to support claims on the safety and efficacy on bioidentical hormones, current data is available comparing the use of bioidentical hormones with synthetic or nonbioidentical counterparts. The emerging data for efficacy, breast tissue activity, breast cancer risk, and cardiovascular disease is helping to eliminate the confusion practitioners and patients have experienced post-WHI. In addition, current investigations are evaluating the role of HRT in a variety of conditions including colon cancer, lung cancer, postoperative complications, wound healing, sleep apnea, immune response, and eye health. While further randomized controlled trials are needed to delineate the differences between bioidentical and nonbioidentical hormones more clearly, until evidence is presented to the contrary, bioidentical hormones remain first line for HRT.

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