



A Perspective on HRT for Women:

Picking Up the Pieces
After the Women's
Health Initiative Trial —
Part 2

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Note: In this article, bioidentical hormone replacement therapy will be referred to as BHRT, and conventional hormone replacement therapy will be referred to as CHRT. Progestins will be used throughout this article to refer to synthetic compounds that exert an antiproliferative effect on uterine endometrium. By this definition, progesterone is not a progestin, since it is natural (not synthetic). Testosterone replacement, although relevant, is beyond the scope of our discussion.

Progesterone and Progestins

There has been an almost abysmal failure on the part of the medical profession to recognize the difference between progesterone and synthetic progestins. While a detailed comparison of bioidentical progesterone and progestins (synthetic C-19 and C-21 derivatives) will not be provided here, a book by John Lee, MD, a recognized expert on progesterone, discusses this topic in detail.¹ A perusal of the literature indicates that the terms *progesterone* and *progestins* are often used interchangeably. Failure to make the crucial distinction between progesterone and progestins has led us to our present position that compliance with established forms of hormone replacement therapy (HRT) is poor (due to side effects) and that the most commonly prescribed form of combined HRT has been shown to be unsafe over the medium term (5 years) in a large controlled trial.

Synergy Between Estradiol and Progesterone

One rarely considered aspect of the use of progesterone versus progestins is the synergy between estradiol and progesterone; each is required for the optimal expression of the other's receptors. Progesterone turns on estradiol receptor expression and has also been shown to elevate serum estradiol levels.

Nahoul demonstrated that vaginal administration of progesterone resulted in an elevation of serum estradiol, which was similar in magnitude and duration to the oral administration of 0.5 mg of estradiol.² Therefore, concurrent use of progesterone with estrogen (estradiol or estrone) should allow for lower dosing of estrogen. Anecdotally, this has been the experience of many practitioners working with progesterone. In fact, the rule of thumb is to halve the dose of estradiol or estrone when the switch is made from progestins to progesterone. This is Lee's opinion, and he prescribed progesterone skin cream for thousands of women patients for more than 20 years.

Balance Between Estrone and Estrogen Sulfate Within Tumor Cells

Progesterone also impacts the balance between estrone and estrogen sulfate within tumor cells. It is well known that breast-cancer cells and breast fibroadenomas accumulate large amounts of estrone sulfate, which they then use as a source of estradiol (the sulfate is hydrolyzed to estrone, which is then converted to estradiol).³ Progesterone, along with some synthetic progestins such as danazol, blocks the conversion of estrone sulfate to estrone and prevents the cells from fueling themselves with estradiol.

Protection of Uterine Lining

The common feature of progesterone and progestin is their ability to protect the uterine lining from overgrowth/carcinogenesis caused by estrogens. Both progesterone and progestin, when given continuously in opposition to estrogen, produce a dormant or quiescent endometrium. Some critics of progesterone supplementation have focused on studies in which progesterone failed to produce a secretory endometrium. This is not a necessary or even desirable end point. A quiescent endometrium is both nonproliferative and nonsecretory. However, an atrophic endometrium (which may arise from progestin therapy) is also undesirable, as it may lead to bleeding and is a degenerate tissue state. Progestins were added to estrogen therapy once it was realized that unopposed estrogen caused uterine cancer, and the focus for many years was only on that aspect. Researchers did not realize that progestins were causing other serious negative effects, such as increased risk of breast cancer and cardiovascular disease.

Impact on Cardiovascular Function

Many human and animal studies have indicated that estradiol does exert positive effects on parameters influencing cardiac disease.⁴⁻⁶ These effects include vasodilation,⁴ reduction of vascular proliferative and inflammatory responses,⁵ and decreased sympathetic activity.⁶

However, the Women's Health Initiative (WHI) trial indicated that oral conjugated estrogens and oral medroxyprogesterone acetate increased cardiac risk. This apparent paradox is resolved by realizing that there are many studies that indicate that medroxyprogesterone acetate is detrimental to cardiovascular function. Clarkson has reviewed the adverse effects of medroxyprogesterone acetate on cardiovascular health in some detail.⁷ For examples of such studies, see sidebar.

Studies Showing Adverse Effects of Medroxyprogesterone Acetate on Cardiovascular Health

- A study by Miyagawa demonstrated that estradiol plus medroxyprogesterone failed to prevent coronary vasospasm in response to serotonin plus a thromboxane A2 mimetic in rhesus monkeys, whereas estradiol plus progesterone was protective against vasospasm.⁸
- A study conducted by Wakatsuki demonstrated that medroxyprogesterone acetate dose-dependently inhibited improvement in flow-mediated brachial artery vasodilation seen in postmenopausal women who were given oral estrogen.⁹
- Kojima demonstrated that medroxyprogesterone acetate interferes with the assemblage of cholesterol and phospholipids into high-density lipoprotein (HDL) particles by apolipoprotein A-1.¹⁰ Although progesterone also decreased HDL, the effect was smaller.
- In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, it was found that at the end of 3 years, oral estrogen increased HDL cholesterol (net increase 7%), but this increase was considerably reduced (net increase 2%) when medroxyprogesterone acetate was added.¹¹

On the other hand, evidence that progesterone exerts beneficial effects on cardiovascular function is accumulating. For examples of such studies, see sidebar.

Studies Showing Progesterone's Beneficial Effects on Cardiovascular Function

- With monkeys as test subjects, Adams demonstrated that, whereas medroxyprogesterone acetate substantially blunted the reduction in plaque induced by conjugated estrogens, progesterone had no effect on the reduction in atherosclerotic plaque induced by estradiol.^{12,13}
- A recent study by Rosano has shown that vaginally administered progesterone had a beneficial effect on cardiovascular health. The time to ischemia on a treadmill was increased in postmenopausal women who had cardiovascular disease.¹⁴
- In another recent study, Molinari indicated that an intravenous infusion of progesterone increased blood flow in porcine mesenteric, iliac and renal arteries via the release of nitrous oxide.¹⁵
- With the use of cynomolgus monkeys, a study has shown that medroxyprogesterone acetate blunts the estradiol-induced release of nitrous oxide, a potent vasodilator.¹⁶

Although it is reasonably clear that some progestins may be deleterious to cardiac health, a recent review article points out that not all progestins exert equivalent effects on HDL, triglycerides, and other relevant parameters.¹⁷ In fact, a recent small study by Sander-son demonstrated that estradiol plus

norethindrone acetate improved exercise tolerance, increased time to ST segment elevation on a treadmill and reduced the total number of ischemic events during 24-hour ambulatory electrocardiographic monitoring in patients with angina.¹⁸ Pharmaceutical companies will eventually find progestins that are safer and that

will more closely mimic progesterone. However, if we do find these synthetic molecules, they will likely be so close in effect to progesterone that we might as well use progesterone.

Bioidentical Progesterones

Oral Bioidentical Progesterone

Bioidentical progesterone in the form of off-the-shelf progesterone capsules (in peanut oil), as well as compounded micronized progesterone capsules, has already been accepted by many physicians; and various publications support the ability of oral progesterone to produce a quiescent endometrium. For examples of studies investigating bio-identical progesterone, see sidebar.

Studies of Bioidentical Progesterone

- In a 12-month study of 10 women, Hargrove showed that oral micronized progesterone (100 mg/twice a day or 100 mg/mornings and 200 mg/evenings) in conjunction with oral micronized estradiol (0.35 mg/twice a day or 0.35 mg/mornings and 0.7 mg/evenings) resulted in a quiescent endometrium.¹⁹ At 6 months, there was no uterine bleeding in this group, whereas four of five women in the same study who were on 0.625 mg/day conjugated estrogens plus medroxyprogesterone acetate (10 mg/day for 10 days each month) continued to have withdrawal bleeding throughout the study.
- In a study by Gillet,²⁰ 98 women received transdermal estradiol (1.5 mg/day) plus 100 mg/day oral micronized progesterone (21 to 25 days/month). Endometrial biopsies were performed after a minimum of 6 months of therapy. No endometrial hyperplasia was found in any woman after a minimum of 6 months of supplementation, and 92% of women were amenorrheic after 6 months.²¹ No endometrial biopsy could be classified as proliferative, and the mean number of mitoses/1000 cells was 0.5 (very low).
- In the much longer PEPI trial, oral micronized progesterone (200 mg/day) was as effective as Provera (10 mg/day) in suppression of endometrial hyperplasia, when used in conjunction with 0.625 mg/day of conjugated equine estrogen.¹¹

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Despite its efficacy, oral administration of bioidentical progesterone has several potential drawbacks. Since progesterone is suspended in peanut oil, it poses a problem for individuals who are allergic to peanuts. Oral progesterone is not well tolerated by some women, with side effects that include nausea, breast swelling, dizziness, drowsiness, and depression. As is the case for oral estradiol, progesterone undergoes a substantial amount of first-pass gut and liver metabolism.^{2,21} It is progesterone metabolites such as allopregnanolone and deoxycorticosterone that are thought to be responsible for the side effects.²²⁻²⁴

Topical Bioidentical Progesterone

Progesterone skin cream has been widely used over the past 20 years as an alternative to oral progesterone and

progestins. Leonetti reported that progesterone cream (20 mg/day) given to postmenopausal women for 1 year (without estrogen replacement therapy) relieved vasomotor symptoms in 25 of 30 women (83%), versus 5 of 26 women (19%) given placebo.²⁵ Progesterone is necessary to prime estradiol receptors and may elevate endogenous estradiol levels; therefore, provision of progesterone alone is able to affect symptoms such as vasomotor complaints thought to be related primarily to low estrogen levels.

Many physicians very rightly question whether enough progesterone can be absorbed through the skin to protect the endometrium. There are also concerns about the standardization of over-the-counter progesterone creams, although this is not an issue for compounded products. Considering the findings of

the following studies can help in drawing conclusions about these issues.

Levine measured total serum progesterone levels (via liquid chromatography/mass spectroscopy) after ingestion of 100 mg of progesterone in peanut oil. A peak serum level of 2.4 ng/mL was achieved 1 hour after ingestion, followed by a rapid decline to baseline.²¹ However, the previously mentioned study by Gillet showed that 100 mg/day oral progesterone is sufficient to produce a histologically quiescent endometrium.²⁰ Therefore, we can conclude that an average serum progesterone level of somewhat less than 2.4 ng/mL is likely sufficient to stabilize the endometrium, depending on the dose of estrogen being administered. Luteal-phase progesterone levels (10 to 30 ng/mL) may be required to produce luteal phase histology (ie, a secretory

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endometrium); but, evidently, daily exposure to a much lower progesterone level can stabilize the endometrium (depending on the estrogen drive that has to be overcome).

We must also consider whether transdermal delivery of progesterone can produce serum total progesterone levels in this range (1 to 3 ng/mL). Transdermal delivery includes intranasal and vaginal sites, as well as peripheral skin delivery. In a study by Cicinelli, the mean serum progesterone level in eight women after 9 days of nasally administered progesterone (11 mg/three times a day) was 3.9 ng/mL (a sixfold increase from baseline).²⁶ A mean serum progesterone level of 2.4 ng/mL was seen after 13 days of administration of vaginal progesterone gel (45 mg/day) to 14 women.²⁷ In both these studies, estrogens had been administered for 28 days prior to starting progesterone; and, in both these studies, secretory endometrium was found on biopsy. Therefore, these levels are actually likely higher than that needed to simply stabilize the endometrium in a quiescent mode.

Several studies also show the results of serum progesterone levels achieved after application of progesterone to the skin (see sidebar).

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Studies Showing Results With Topical Progesterone

- Mircioiu compared serum progesterone time profiles after a one-time application of 90 mg progesterone in gel (n=9), emulsion (n=16), and lipophilic base cream (n=7).²⁸ In all cases, serum levels peaked 3 to 4 hours after application and declined gradually over the ensuing 72 hours. Peak levels were in the range of 1 to 2.2 ng/mL.
- Burry administered progesterone cream to six women for 28 days (14 days:30 mg/day, 14 days:30 mg/twice a day) and measured serum progesterone time profiles (eight points in 24 hours) on each of 5 days (days 1, 8, 15, 22, and 29).²⁹ After 1 week of use, five of the six women sustained a progesterone level of at least 1 ng/mL for at least 8 hours after application. On day 29, the average progesterone level was 2.2 ng/mL. Serum progesterone level was dose related and consistent for each woman, although interindividual results varied by a factor of two.
- Carey measured serum progesterone time profiles after 6 weeks of progesterone cream (20 mg/twice a day, n=10; and 40 mg/day, n=10).³⁰ Both regimens resulted in average progesterone levels of roughly 0.7 ng/mL over 24 hours. Peak levels were approximately 1 ng/mL.
- O'Leary measured serum progesterone levels at several time points after a one-time application of progesterone cream (64 mg) in six premenopausal and six postmenopausal women.³¹ In the premenopausal group, serum progesterone did not increase from an average baseline of 6.6 ng/mL. Mean serum progesterone 4 hours after application increased slightly to 1.1 ng/mL from 0.75 ng/mL at baseline in the postmenopausal women.
- Wren administered cyclic (14 days/month) progesterone skin cream to postmenopausal women in varying doses for 3 months.³² Nine women received 16 mg/day, eight received 32 mg/day, and ten received 64 mg/day. Curiously, the average serum progesterone level achieved was only 0.4 ng/mL, and one has to question the degree of absorption of the cream used in that study.

The majority of published literature indicates that transdermally delivered progesterone can produce serum total progesterone levels in the range of 1 to 3 ng/mL, which are likely to produce a quiescent endometrium. A definitive study combining progesterone cream administration, measurement of serum total progesterone levels, and endometrial biopsy has not been done. However, a summary of a 4-week trial of progesterone cream with serial endometrial biopsies on 58 women pretreated with conjugated estrogens has been published.³³ Twice-daily vaginal and topical progesterone creams of varying strengths were compared with placebo. All routes and concentrations of progesterone supplementation produced a significant decrease in the degree of endometrial proliferation induced by conjugated estrogens (0.625 mg/day) compared with placebo.

There are several additional lines of evidence that indicate that transdermal progesterone cream is delivered to tissue in

appreciable amounts. The first body of evidence comes from salivary hormone measurements. When a steroid hormone skin cream, such as progesterone, is rubbed on a relatively small area of skin, the salivary progesterone level increases dramatically within several hours and often by several orders of magnitude. For a given individual, this elevation is reproducible and dose dependent, although the degree of elevation varies between individuals for a given dose and site of application. A full explanation of the mechanism by which steroids enter saliva under these circumstances is beyond the scope of this article. Suffice it to say that transdermal application of steroids likely enriches the concentration of steroids in red blood cell (RBC) membranes. Due to the tight fit as the RBCs wedge their way through the capillaries, steroid hormones may be efficiently transferred directly to tissue by partitioning into the membranes of the capillary endothelial cells. Therefore, a salivary hormone level reflects delivery of hormone to cell membranes (tissue), unlike a blood level, which measures the amount of hormone that has not been delivered to tissue.

Chang examined the effect of topical progesterone and estradiol on breast tissue uptake and cell proliferation in women scheduled for biopsies or reduction mammoplasties.³⁴ Women were treated for 10 to 13 days with a placebo gel or gels that contained 1 mg estradiol, 25 mg progesterone, or a combination of estradiol and progesterone. Biopsy samples were taken, and half were analyzed for estradiol and progesterone content; the other half were analyzed by a pathologist for breast-cell proliferation. Estradiol and progesterone increased 200-fold and 100-fold with respective topical delivery, demonstrating tissue uptake. Estradiol increased breast-cell proliferation twofold, and progesterone decreased breast-cell proliferation from baseline but also suppressed proliferation activated by estradiol. Serum estradiol or progesterone did not increase significantly in any of the treatments, despite a remarkable tissue uptake and biological response. These results support the notion that tissue uptake and response can occur with topical hormone delivery without a noticeable effect on serum levels. A 25-mg dose of progesterone dramatically increases salivary progesterone to levels of 0.5 to 3 ng/mL at 12 to 24 hours after supplementation and peak levels (3 hours after application) above 20 ng/mL. Therefore, it is reasonable to conclude that salivary measurements are more meaningful than blood measurements in the context of transdermal hormone supplementation, since the former more closely reflects hormone delivery to tissue.

Optimum results with progesterone skin cream will likely be achieved with standardized products delivered in reproducible fashion with metered-dose delivery. Women who have not undergone a hysterectomy and use progesterone and estrogen(s) should be monitored with ultrasound and/or endometrial biopsy as indicated to evaluate the status of the endometrium. Practitioners cannot assume that, because progesterone is more natural, it is automatically protecting the endometrium over the long term.

Oral progestins exert a much stronger suppressant effect on the endometrium, which reduces our concerns about the endometrium. This is achieved at the expense of side effects; increased risk of cancer and cardiovascular and thromboembolic disease; and induction of an atrophic, degenerative tissue state, with increased risk of breakthrough bleeding. The published literature indicates that we cannot assume anything about the protection of the endometrium with transdermally administered progesterone, but we can have the expectation that it will do the job, although thought and attention are required. Certainly larger, more definitive trials of progesterone skin cream are needed; and at least one large, long-term study that compares progesterone skin cream/oral estrogen to oral progestin/oral estrogen is in progress. A protocol for a reasonable approach to combined HRT that employs progesterone skin cream, based on the foregoing discussion, has been included (see sidebar, p. 336).

Conclusion

We have spent 20 years researching both estrogen only and estrogen/progestin HRT. Estrogen replacement has been shown to relieve menopausal symptoms, improve bone and skin health and diminish long-term morbidity from

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Protocol for Combined HRT Using Progesterone Skin Cream

1. Compounded progesterone cream, 20 to 30 mg/twice daily or 25 days/month, applied anywhere but the abdomen (to avoid first-pass liver metabolism), with metered-dose delivery (eg, syringe or jar with détente delivery system);
2. Pre- and postapplication serum/salivary progesterone levels (post: 8 hours after cream application), after at least one cycle (25 to 30 days) of progesterone use, aiming for 1 to 3 ng/mL serum and 1 to 5 ng/mL salivary progesterone;
3. Estrogen replacement therapy 25 days/month concurrent with progesterone cream at a dose that does not result in withdrawal bleeding or spotting, such as:
0.5 to 1.0 mg estriol (oral or cream) twice daily, plus
0.05 to 0.1 mg estradiol (oral or cream) twice daily;
or 0.075 to 0.15 mg estradiol cream twice daily;
or estradiol slow-release patch 0.025 to 0.1 mg/24 hours;
4. Transvaginal ultrasound before institution of therapy and at 6-month intervals for the first 12 to 18 months, with endometrial biopsy as indicated for bleeding or spotting persisting after 3 months of initiation of therapy; and
5. Periodic monitoring of bone density, with adjustment of therapy as indicated.

cardiovascular disease. However, these benefits are accompanied by increased risks of breast cancer, venous thromboembolic disease, gallbladder disease, and endometrial hyperplasia/cancer. Addition of a progestin mitigates against endometrial problems but increases other risks, as demonstrated conclusively by the results of the WHI trial and other studies. Side effects from progestins seriously compromise compliance.

Patients have become increasingly aware of hormone replacement with bioidentical hormones and are coming to their physicians on a daily basis with questions about this more natural HRT option. We shouldn't hedge and turn our backs on patients suffering from hormonal deficiencies while we wait for large trials to be conducted. Moreover, we are not sure if large trials will be conducted or who will fund them, since bioidentical hormones are not patentable. We should go back to first principles, think for ourselves, incorporate what we have learned from more than 30 years of steroid hormone research, and make our best call. We have good indications from the literature about what types of estrogens we should use (estradiol and estriol), and we realize that transdermal delivery of hormones offers advantages over oral delivery. If oral delivery is used, we need to rethink dosing and be aware of the impact on other relevant parameters such as hormone-binding

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proteins and other hepatic proteins. There is evidence that we should avoid certain progestins, and there is strong evidence to support both the oral and transdermal use of bioidentical progesterone. Through testing modalities such as saliva, we are able to more closely monitor the delivery of hormone to tissue.

With good follow-up, good clinical judgment and good laboratory back-up, we have enough information about hormone replacement to offer BHRT as a viable option. It might take a little more thought on our part, but at least we will not be leaving the decision about HRT up to our patients (we know that many of them already vote with their feet). As time goes on, we need to analyze new information and modify our approach as indicated.

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