A Perspective on HRT for Women:

Picking Up the Pieces After the Women's Health Initiative Trial – *Part 1*

George R. Gillson, MD, PhD
Rocky Mountain Analytical, Calgary, Alberta, Canada
David T. Zava, PhD
ZRT Laboratory, Portland, Oregon

This article is the first of a two-part series discussing hormone replacement therapy (HRT). These articles discuss important concepts that shed light on the less-than-optimal results achieved thus far with conventional HRT, consider the possibility that some types of HRT are safer than others and discuss the reasons why they are safer. They suggest ways we can avoid repeating our mistakes.

In Part 1, bioidentical HRT is referred to as BHRT, and conventional HRT is referred to as CHRT. Progestins *is used to refer to synthetic compounds that exert an antiproliferative effect on uterine endometrium. Note that, by this definition, progesterone is not a progestin, since it is natural (not synthetic). Progesterone replacement will be discussed in Part 2. Testosterone replacement, although relevant, is beyond the scope of our discussion. This is not intended to be a "how-to" manual for HRT but, hopefully, to supply clinicians with additional information upon which to base decisions about bioidentical estrogen and progesterone replacement, now that the standard of care is in question.*

INTRODUCTION

Numerous articles that examine the practice of HRT have appeared in the popular press since the premature cancellation of the Women's Health Initiative (WHI) trial of oral conjugated estrogens and oral medroxyprogesterone acetate. Many articles have expressed surprise over the negative outcomes demonstrated (ie, increased cardiovascular and cerebrovascular disease, breast cancer, venous thromboembolic events) but have completely ignored or glossed over the reasons for these negative outcomes. As a result, physicians and patients have been presented with an overwhelming barrage of information about HRT, some of which is conflicting and alarming. Many physicians have responded by avoiding any form of HRT because they believe that there are no other options. This compromises the physician-patient relationship and drives patients to seek other alternatives that may be ineffective or even harmful.

BHRT/CHRT

Over the past 15 to 20 years, practitioners have quietly supplied natural forms of BHRT (ie, estrogen, progesterone, testosterone) to thousands of women. The treatments have included the use of various compounded hormone creams, capsules and sublingual drops, as well as off-the-shelf oral and patch-delivery hormones. The common theme is that BHRT is identical to hormones produced in the human body, and the doses are often individually tailored to the biochemical individuality of the patient. Anecdotally, BHRT has been well tolerated with concomitant good long-term compliance, although there are no large trials comparable to the WHI.

Fundamental Principles

When we analyze what we have been doing with HRT for the past 50 years in the light of what we have also learned

about steroid metabolism, it becomes apparent that we have overlooked the following fundamental principles:

- Oral delivery of hormones is suboptimal.
- Skin delivery of hormones has some important advantages.
- Synthetic progesteronelike molecules are not an acceptable substitute for progesterone.

Closer attention to these principles may help us find our way out of the current situation. Since every physician's goal for his/her patients is to alleviate bothersome symptoms and optimize long-term health outlook and function, with minimum risk, it is imperative that clinicians get a balanced view of the available HRT options.

Advocates of BHRT are now in a somewhat difficult position: a large controlled trial has shown that the most widely used CHRT combination carries unacceptable risks if used for more than 4 years.[1] However, there is no corresponding large trial of the less widely studied alternatives. Many authorities are now advocating that we freeze into immobility until more trials are conducted, or that we restrict hormone replacement to no more than 4 or 5 years.

It is the opinion of the authors that we already have enough information to consider other strategies. We are not starting from scratch as we were in the 1960s; we have amassed a tremendous amount of information on steroid hormones, their metabolism and their physiologic roles. Following natural physiology as closely as possible seems to be a reasonable approach in the face of uncertainty because, in a sense, bioidentical hormones have undergone safety trials as long as humans have walked the earth. If we pay attention to fundamentals, we should be able to go forward with minimum risk. We do not suggest that large trials of BHRT strategies are unnecessary, but we do emphasize that we already have a substantial knowledge base.

There has been a tendency to believe that menopause and its symptoms are problems that may be alleviated only by patentable pharmaceuticals; this is too narrow a focus. Also, hormone replacement is sometimes regarded as an anti-aging strategy; this, also, is inappropriate. The goal of HRT is not to reproduce the hormonal milieu of a 25-year-old in a 75-year-old; the goal is to optimize function and prevent morbidity as we age, without causing harm. Any hormone replacement strategy should be judged by these principles. In fact, the main caveat regarding any medical intervention, which, of course, applies to any form of HRT, is that if interventions are made, they should be done *cautiously*. Treatments should be modified or titrated in accordance with clinical and laboratory feedback.

Compliance

The first point to consider about the most common form of CHRT (oral estrogen/progestin therapy) is compliance. This type of therapy is simply not well tolerated. One of the main reasons why women discontinue therapy is because of side effects such as weight gain, breast tenderness and spotting; women do not discontinue therapy due to lack of efficacy.[2] One French-Canadian study indicated that 80% of women who start estrogen replacement therapy stop at the end of 4 years.[3]

Approximately 50% of women who start CHRT stop within 1 year.[2,4] For example, dropout rates in the WHI trial approached 30% at 4 years.[1] Side effects tell us that, for whatever reason, the body does not tolerate the treatment. Side effects are the "canaries in the coal mine" to inform us of perturbations to the liver with a general adverse effect on numerous biochemical processes. Trials with a substantial dropout rate, such as the WHI, have a built-in bias that is rarely discussed. The true extent of the potential harm inflicted by the therapy is masked because the people who stay with the therapy select themselves through lack of side effects. The women who finish these studies are not representative of the population at large. If we could somehow force all women who start these trials to finish them, we could gauge the full impact of some forms of HRT.

Compliance is also a function of mode of delivery; an HRT strategy is not worth pursuing if the patient will not stay on the regimen. Having the option to try different types and strengths of HRT has been shown to be a statistically significant factor in the decision to continue HRT.[5] BHRT provides that option, since it enables therapy to be tailored to accommodate biochemical individuality. BHRT with compounded, individually tailored regimens of bioidentical hormones should increase long-term compliance. Anecdotally, compliance with BHRT is more than 90%.

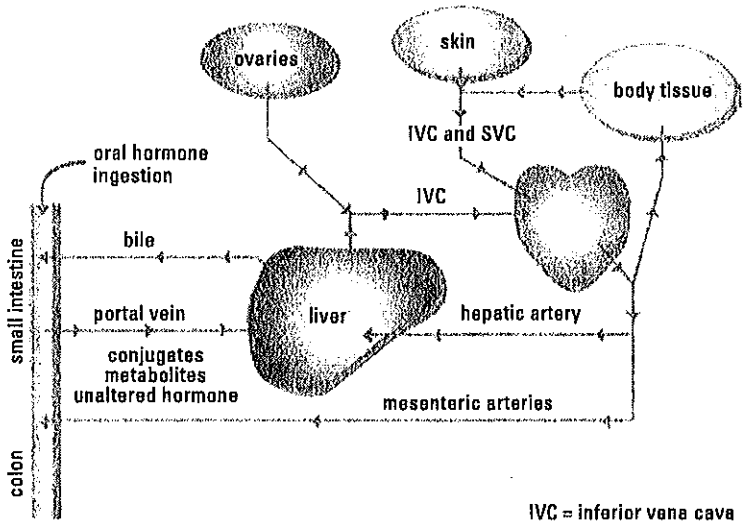
Estrogens

If we were to rethink estrogen replacement in the light of what we have learned about physiology/hormone metabolism over the last 20 to 30 years, one key issue to consider would be the metabolic ramifications of swallowing hormones. There are two aspects to this: consideration of (1) what the gut and liver do to the hormones and (2) what the hormones do to the liver.

An important concept is first-pass metabolism. It has long been recognized that orally ingested hormones go directly to the liver via the portal vein, where they undergo extensive processing by way of conversion into other hormones and by conjugation (addition of chemical groups to increase water solubility). However, significant hormone processing also takes place in the gut lumen and in the gut endothelial cells before ingested hormone ever reaches the portal circulation.[6,7] This preprocessing in the gut and liver is one aspect of oral hormone administration that sets it apart from other forms of hormone administration and from endogenous production of hormones; neglect of this preprocessing may confound our interpretation of the studies pertaining to oral estrogen/progestin CHRT.

Hormone originating from an endocrine gland (eg, estradiol from the ovaries) has a higher chance of going directly to other tissues without being transformed or conjugated. For example, estradiol of ovarian origin returns to the heart via the inferior vena cava, and only a fraction of that hormone is delivered to the liver via the hepatic arteries or mesenteric arteries (see Figure 1). Therefore, much of the estradiol produced endogenously does not reach the liver until after it has been processed through and exerted an effect upon other tissues

Figure 1. Circulation of Hormones.



such as breast, brain and bone.

The same is basically true of hormones applied to skin sites, with the exception of abdominal skin. Hormones applied to nonabdominal skin return straight to the heart and are then distributed to all the body tissues before going to the liver. There may be some metabolism of hormone in skin prior to absorption into the circulation; but, in general, this is not a significant effect. This brings up a point regarding transdermal hormones. Some authors have mistakenly identified lymphatic vessels as a means whereby transdermally applied hormones are delivered to tissue.[8] Lymphatics certainly represent an alternate means whereby hormones return to the central circulation, but lymphatics drain tissue – they do not deliver fluid to tissue.

Over the years, we have not paid enough attention to the mass balance of ingested hormones. It has been found that oral doses of estradiol and estrone in the range of 500 to 2000 µg/day are necessary for clinical response (ie, symptom relief). It is also widely accepted that only 10% of the oral dose is bioavailable, but many make the mistake of assuming that the other 90% of an oral estrogen dose is not absorbed. In reality, most or all ingested hormone is absorbed, but the key questions are what are the metabolites, are the metabolites bioactive and how rapidly are the metabolites cleared?

Composition of Metabolites Longcope looked at the metabolic fate of oral versus intravenous estradiol and found that in either case at least half of the dose was converted to estrone sulfate.[6] Estrone sulfate is the principal storage form of estrogen and, in estrogen-sensitive tissues, may be converted back to estrone and estradiol on an as-needed basis. Ingested estrogen is not wasted or destroyed; it simply turns up in other forms to which we have not been paying enough attention. We are now realizing that we need to look at estrogen metabolites such as 2-hydroxyestrone, 4-hydroxyestrone, estrone sulfate and estriol. These metabolites are important with respect to their effect on the risk of estrogen-sensitive cancers, and oral ingestion of estrogen may shift their

balance, with consequences we do not yet fully understand.

Oral Estrogen Replacement Therapy With oral ingestion, hormones are presented to the liver in a much more direct, concentrated way than is the case for endogenous production. For example, the average daily output of estradiol in a premenopausal woman is 100 to 200 µg, spread over 24 hours (4 to 8 µg/hour). A typical oral dose of estradiol, 1000 to 2000 µg of estrogens, is delivered to the liver and the body within a few hours of ingestion. This results in changes (increases and decreases) in the hepatic synthesis of various proteins, such as clotting factors, sex hormone-binding globulin and thyroid-binding globulin.[9] Orally administered estrogens have been shown to exert both prothrombotic effects (ie, increase in fibrinogen fractions 1 and 2, reduction in tissue factor pathway inhibitor, increase in C-reactive protein, increase in Factor VII) and antithrombotic effects (ie, increased D-Dimer, decreased plasminogen activator inhibitor Type 1).[10-13] The extent of these opposing effects varies with dose in a given individual,[14,15] from person to person with the same dose, and also varies with time in the same individual as the liver adapts to the stress of oral estrogen.

Consideration of this may help us understand what is going on with regard to cardiovascular disease and oral estrogen replacement therapy. In the doses used in the past, oral estrogen could both promote and discourage cardiovascular events, depending on individual circumstances such as genetic variation in liver enzyme expression, the duration of exposure to oral estrogens and other factors affecting the expression of liver enzymes such as alcohol intake, smoking, nutritional status and exercise.

As mentioned, perturbation of liver protein synthesis following oral ingestion of estrogens is dose dependent. There may be a trade-off dose at which effects on hepatic protein synthesis are minimized, but most benefits are retained. For example, Prestwood has recently demonstrated that 0.25 mg of oral micronized estradiol reduced bone turnover to a similar degree as higher doses (0.5 and 1.0 mg) with very few adverse effects.[16] However, we don't know the long-term effect of low-dose oral estrogens on cardiovascular disease risk, bone health and breast-cancer risk. At some point, we settled on the doses now in vogue, perhaps because lower oral doses did not alleviate symptoms of menopause. This, in turn, was probably because in the early days of CHRT no progesterone was given (progesterone is essential for the optimal expression and function of estradiol receptors and for optimal tissue response to estrogens). Initially, we mistakenly focused only on relief of vasomotor symptoms with CHRT, gave only estrogen and gave it in doses that were excessive. We traded relief from vasomotor symptoms for adverse effects including weight gain, water retention and fibrocystic breasts, not to mention cancers of the uterus and breast. Later, we added in medroxyprogesterone acetate, which is not well tolerated and has been shown to increase the risk of breast cancer, not mitigate it.

Transdermal Estrogen Over the years, many studies of transdermal delivery of estrogens (estradiol) have also been done; and much may be gained by reviewing some of these earlier studies. Some of the information obtained from these studies indicates that transdermally administered estradiol:

- Does not have the same impact on liver synthesis of proteins as orally administered doses (this is particularly true of estrogen);[17-19]
- Does not exert adverse effects on parameters that affect cardiovascular health;
- Does not negatively affect clotting parameters;[10,13,20]
- Enhances flow-mediated vasodilation of the brachial artery (as does estrogen);[21]
- Has resulted in a decrease in the number of hypertensive women with left ventricular hypertrophy after 18 months, compared to placebo;[22]
- Decreases triglycerides, a cardiovascular disease risk factor, whereas oral estrogen increases triglycerides[23] (except perhaps at doses less than 0.5 mg/day).

Most of these studies were done with slow-release estradiol patches. This delivery system provides estradiol to the body in a fashion that more closely mimics its production and delivery by the ovaries (ie, no first-pass liver metabolism, overall lower doses that approach physiological rates of delivery [2 to 3 µg/hour patch versus 4 to 8 µg/hour endogenous production], delivery to the body over 24 hours). Transdermal estradiol patches are efficient; a patch delivering just 50 µg of estradiol/24 hours is as effective as an oral dose 20 to 40 times higher, with less metabolic fallout.

Past studies have concluded that:

- The effects of oral ingestion of estrogens are unpredictable;
- The liver may be overburdened;
- Unwanted patterns of metabolites may be produced;
- The impact on cardiovascular function could vary with time and many other factors.

This is not to say that we should not use oral estrogens in our patients but that we should visit the issue of dosing. From a fundamental standpoint, transdermal estradiol delivery via patch or divided dose cream seems to be a more physiologic, controlled approach.

Estriol

Another important topic to consider if we are going to rethink estrogen replacement is the role of estriol. Estriol is an estrogen that is naturally present in the body. It is derived from estrone in nonpregnant women and from adrenal hormone precursors in pregnant women. It was studied in North America in the 1970s; and, although interest waned in North America, it is widely employed in Europe and Japan. Over the last 10 to 15 years, compounded mixtures of estriol and other estrogens such as triple estrogen (Tri-Est) (80% estriol, 10% estradiol, 10% estrone, total estrogen dose 1.25 to 2.5 mg/day) and double estrogen (Bi-Est) (90% estriol, 10% estradiol) have been used by thousands of women for both oral and transdermal hormone replacement. There are no large controlled trials of this therapy, but there have been many well-performed smaller trials of estriol alone. Many of these were summarized in a 1998 review[24] and

again more recently by Taylor.[25]

Composition of Metabolites One of the unique aspects of estriol is that it appears to have very little backward metabolism. It is an end metabolite that is not systemically back-converted to estrone or estradiol to any appreciable extent.[26] Estriol is also not subject to conversion to potentially carcinogenic catecholestrogen metabolites. Estriol is also an adaptogen. Given alone, it exerts definite estrogenic effects. Plasma concentrations of follicle-stimulating hormone and luteinizing hormone (LH) decreased significantly (by up to 50%) in women receiving 2 mg oral estriol for 8 weeks.[27] Various studies have demonstrated that oral estriol is effective for symptoms such as hot flashes [24,28] and urogenital complaints.[24,29] Intravaginal estriol reduced the incidence of urinary tract infection tenfold in a placebo-controlled trial of 93 women (estriol, n = 50; placebo, n = 43).[30] Of 27 women who received 2 mg oral estriol daily for 1 year, 4 (14%) experienced slight vaginal bleeding (but no atypical findings on endometrial biopsy).[28] A recent study by Lundstrom showed that 3 of 51 women (6%) who took 2 mg oral estriol daily for 2 years experienced a slight but stable increase in mammographic density.[31] Therefore, estriol does affect breast tissue in some women; and this may be related to differences in individual sensitivity to estriol. However, it should be noted that 40% of the women on conjugated estrogens/progestin experienced mammographic density increases in the same study.

Bioavailability of Metabolites Given in tenfold molar excess with estradiol, estriol antagonizes the effect of estradiol,[32] and this may be the basis for the approximate 10:1 weight ratio of estriol to estradiol commonly used in compounded Bi-Est formulations. Before birth, we were all immersed in what was effectively a sea of estriol *in utero*, and it has been postulated that this high estriol level served to protect us from adverse effects of maternal estradiol.[32] In the 1970s, estriol was administered to women with metastatic breast cancer in doses that ranged from 2.5 to 15 mg/day. Thirty-seven percent of these women had remission or arrest of metastatic lesions.[33] In a study by Lemon,[34] estriol also inhibited the formation of radiation and carcinogen-induced rat mammary carcinomas by 80%. These studies also support the observation that estriol may also exert anti-estrogenic effects in some tissues.

In a study by Takahashi,[28] oral estriol supplementation resulted in decreased excretion of calcium and decreased alkaline phosphatase levels, and there have been various studies that indicate that estriol supplementation exerts a positive effect on bone density.[24] It should be noted that most of these studies were done in Japan, and that dietary differences may be a confounding factor.

Oral Estriol No large trials that have assessed the effect of estriol on morbidity and mortality due to cardiac events have been performed. Nevertheless, various small trials indicate that oral estriol may be beneficial with regard to cardiac health. Oral estriol exerted no lasting effect on blood pressure in a 12-month study.[28] In an 8-week study, oral estriol (2 mg/day) lowered total cholesterol and low-density lipoprotein (LDL) cholesterol in 17 patients with familial hypercholesterolemia. In that same study, oral estriol also upregulated LDL receptor activity in those individuals with low activity at baseline.[35] In a 2-year study, oral estriol (2 mg/day) compared favorably with conjugated estrogen/medroxyprogesterone acetate; total cholesterol was lowered and high-density lipoprotein increased without the significant increase in triglycerides seen with conjugated estrogen/medroxyprogesterone acetate.[36]

Vaginal Estriol Both the vaginal and oral routes of administration of estriol have been studied extensively. Vaginally administered estriol does not appear to exert effects on liver protein synthesis.[37]

Schiff observed that vaginally administered estriol was 16 times as effective as oral estriol in lowering LH, and he also determined that vaginal administration resulted in a tenfold increase in unconjugated estriol.[38] Despite its wide use, estriol applied to external skin in cream form has not been widely studied.

Bioaccumulation In our personal experience, when our patients continued estriol use, the salivary estriol level in a given patient rose with time, which is consistent with bioaccumulation. Once again, this may be a dosing issue. In North America, estriol is typically dosed at 2 mg/day either orally or transdermally, whereas doses of 0.5 mg daily or every other day are common in other countries where estriol has been studied more extensively. For example, in Western Europe, estriol has been used successfully for over 60 years. Gradual accumulation of estriol with the higher doses in vogue in North America may reflect estriol's position as an end point in the metabolic chain.

There is a tendency by some to regard estriol as a completely benign estrogen. In light of the possible accumulation effect (as evidenced by a gradual increase in salivary estriol with continued estriol supplementation) and with the knowledge that estriol does exert a definite stimulatory effect on the endometrium and breasts, we should learn from the extensive Western European experience with estriol and be conservative with dosing.

CONCLUSION

Various bioidentical forms of both conjugated and unconjugated oral estrogens are available from pharmaceutical companies. At the doses that have been commonly employed, oral estradiol and estrone may be suboptimal due to individual variability in metabolism and impact on hepatic protein synthesis. As a general rule, untoward side effects with oral estrogens are a tip-off that the liver is under stress and that a dose reduction or a switch to a different delivery system should be entertained. In general, women have probably been overdosed with oral estrogens; and this has led to some confusion and contradiction in reported results.

Transdermal delivery of estrogens via slow-release patch is a sensible HRT strategy, since it more closely mimics the way the body produces estrogens, both from a metabolic standpoint and pharmacokinetic standpoint. The main drawback with patches is that they may not be well tolerated; the patch adhesive is irritating to some individuals.

The Tri-Est and Bi-Est estrogen skin creams have not been studied in controlled trials. In general, they are dosed to deliver intermediate amounts of estradiol and estrone (125 to 250 μg) and estriol (1000 to 2000 μg). We know that skin delivery can be efficient, since just 25 to 50 μg of estradiol usually works well if delivered over 24 hours. Just as we have probably overdosed with oral estrogens, we run the risk of doing the same with compounded creams.

The oral versions of Tri-Est and Bi-Est also have not been studied, although thousands of women have used these formulations in the last decade or so. The best we can say is that estriol has various studies supporting its systemic benefits at oral doses of 2 mg/day, and that the lower oral doses of estradiol and estrone in these formulations are associated with fewer side effects and adverse effects on blood parameters. An estriol dose of 2 mg/day may be too high. Also, the effect on estradiol receptors of combining a tenfold excess of estriol with estradiol and estrone has only been studied *in vitro*.

Clearly, there are a lot of unknowns surrounding the Tri-Est and Bi-Est formulations, but from a fundamental standpoint we may be less likely to do harm in the long term with these formulations. Once again, we come to the crux of the matter: there is a lot of evidence supporting BHRT, but no big trials. There are big trials examining some aspects of oral estrogen replacement, but the trials have uncovered some long-term risks. Regarding BHRT and CHRT (conjugated estrogens/progestin), each practitioner has to consider all of the evidence and decide whether the small trials that show benefits outweigh the large trials that conclusively demonstrate harm, since there is no longer any clear standard of care. Some may still opt to forgo any form of HRT.

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Address correspondence to: George R. Gillson, MD, PhD; Rocky Mountain Analytical, Unit A; 253147 Bearspaw Road, NW, Calgary, Alberta, T3L 2P5, Canada. E-mail: gillson@rmalab.com