Chapter 5 – Hormone Balancing

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In Defence of Estrogen

Phyllis J. Bronson, Ph.D.[1]

Introduction

The etiology of the aging female has taken on a life of its own in the western world, where the most basic academic aspects of how to contain the aging process are shunned, often in the quest driven by the "addiction to perfection." So women seek BOTOX® to numb their wrinkles and their faces, plastic surgery for every flaw.

The most important hormone of the female biology, 17-beta estradiol (E2) has recently been misinterpreted and vilified, leading women to believe that they are allergic to their own biology. As a result, many women have begun to seek answers from pharmaceuticals instead of working to replenish their own bio-identical chemistry. Estrogen is the critical molecule for the aging female and acts as a defence against depression and loss of cognitive function. A wealth of data suggest that if E2 is supplemented at the proper age it has profound, beneficial effects on all aspects of a woman's healthy biology, including moods and emotion, heart disease, memory, bone density, and cancer risk. Alzheimer's disease may be slowed or halted due to regulatory mechanisms on beta amyloid protein.[1]

Progesterone is a secondary female hormone, but also of great importance to a woman's health and moods. The introduction of synthetic "progestins" as analogues of true progesterone has lead to a great deal of confusion among women and their physicians. This is why birth control pills, given for the purpose of sustaining hormones, are the wrong choice for mid-life women; they contain synthetic progestins which cause many women to feel very bad, particularly emotionally.

1. Biochemical Consulting Company, 100 E. Main Street, Ste. 201, Aspen CO 81611

On the other hand since the original work with progesterone by Katarina Dalton, M.D., in England many years ago, physicians trying to establish the importance of progesterone have deemed it the molecule of most significance for women. This is simply untrue and misleading. Estrogen must be present in sufficient quantity in order to be properly "mediated" by progesterone. If this is not the case, and the woman uses progesterone to excess, those vulnerable to depression will become more so. Progesterone is anxyolitic while estradiol is a mood elevator, due to its impact on the catecholamine and indolamine families.

Estrogen in the human female is a composite of three molecules produced by our bodies: Estrone (E1); Estradiol (E2); and, Estriol (E3). For the purpose of this article estradiol is of primary interest and is identified as 17-beta estradiol, or E2. Estradiol is the most potent form of estrogen and makes up about 10% of the estrogen produced by the ovaries. Estrone is 12 times weaker in terms of biological impact and also makes up about 10% of a woman's normal estrogen levels, however it is a much more toxic estrogen.In fact it may be the principal culprit in estrogen toxicity as will be explained. Until recently it was assumed that there was a simple equilibrium reaction between estradiol and estrone, that estrone was produced via synthesis from estradiol, primarily in the liver. The current interpretation is that as women age, they produce a great deal of estrone in their fat cells (and many women gain weight and have bigger fat cells as they age) thus there is more estrone production.

Estriol is the weakest form of estrogen and though it is 80 times weaker than estradiol it makes up about 80% of a

woman's estrogen. Estriol is produced by conversion from estrone; this occurs through the down-regulation of estrone to the toxic 16-alpha hydroxy estrone and then to the relatively inactive estriol in the liver. Estriol appears to counterbalance estrone's toxicity. Asian women who eat a diet high in traditional fermented soy products, and have higher levels of estriol, appear to have less gender cancer. The inference is that estriol somehow plays a "protective role," possibly by creating fewer toxic metabolites. Epidemiological studies have linked soy to a decreased risk for breast cancer. Soy isoflavones, sometimes referred to as natural selective estrogen receptor modulators (SERMs) show interference with the binding of certain estrogens to SHBG.[2]

Estrogen 2/16 Metabolism

The important role played by estrogen oxidative metabolism in hormone-sensitive diseases has been elucidated by studies of estrogen-dependent neoplasms of reproductive organs. With respect to breast cell malignancies, estradiol is believed to act primarily as a promotional factor, causing increased growth rates in breast cells already transformed to a cancerous state. However, estradiol is not the only active estrogen in the human body: other metabolites formed from estradiol have the capacity to act as estrogens, and in some cases, as anti-estrogens.[3]

Considerable work has shown that the major metabolites of estradiol and estrone are those hydroxylated at either the C-2 or the C-16 alpha positions, although forms hydroxylated at the C-4 and C-15 alpha are present in relatively lesser amounts. There exists a complete divergence in the biological properties of the 2- and 16 alpha-hydroxylated metabolites of estradiol (2OHE1 and 16OHE1 respectively). The 2-hydroxy estrone metabolites inhibit cellular proliferation while the 16-alpha hydroxy estrone enhances proliferation.[4]

16OHE1 has several unique and potentially harmful properties: it is capable of binding covalently to the estrogen receptor,[5] to nuclear histone proteins,[6,7] and to DNA. Because of this covalent linkage to the receptor, 16OHE1 shows persistent biological responses[8] and the formation of 16OHE1 is elevated in women at high risk for breast cancer[9,10,11]

Estrogen plays a major role in the neurobiology of aging because all women experience a significant drop in this hormone at menopause. One hundred years ago women achieved menopause at about the same time as their life expectancy ran out. Over the last century life expectancy for women has almost doubled; women can now expect to spend about half their lives in menopause. There is no precedence for transition into the mid-life years, or indeed into older age. Concurrent with the increase in life expectancy, over the past 50 years menopause became a medical condition and has been treated as such by the pharmaceutical industry and the medical establishment. In response, the medical profession told most women approaching menopause to take estrogens. About 25 years ago, as a result of observed endometrial problems, doctors were told that women needed "progestins" to protect them. Thus began the introduction of the synthetic progestins to the pharmaceutical scene, which has been a catastrophe for women.

Progestins are synthetic analogs of progesterone but are not actual progesterone. In fact, their mechanism of action is quite distinct, and these drugs have harmed many women. For example, true progesterone is a very strong diuretic, while the synthetic progestins actually promote fluid retention due to the water holding effect driven by the acetate in the synthetic molecule. This shows clearly in the hydration peaks at 3400 on the Fourier Transform Infrared Spectra.[12]

For years the standard practice

in gynecology has been to put women on Hormone Replacement Therapy (HRT). Then in July 2002, the Women's Health Initiative Study (WHIMS) was abruptly halted. This was due to the inference that women on these drugs had various degrees of developing pathology. What was not noted at the time was that the demographic of the study was so flawed that a statistically relevant number of the women in the study had hypertension, diabetes or were obese. Further complicating matters was the fact that the majority of the women had started on HRT well past the onset of menopause, averaging 10 to 15 years. It is now suspected that major aspects of aging happen at the time of menopause and are much more difficult to rectify later, and may become worse with treatment, although this is certainly being challenged. The study had two components: Prempro for women with intact ovaries and uteruses (terminated in July 2002) and Premarin only for women who had had hysterectomies (terminated in March 2004).

The Prempro study showed an increase in breast cancer in approximately 2.5% of women: this is not statistically relevant. The study was stopped but not for the right reasons. The scientific community has known since 1997 that Provera has negative implications on the female cardiovascular system because it decreases vascular function.[13] The Premarin only study data showed no increased risk of breast cancer or heart attacks but an increased risk of stroke for women over 60.[14]

Impact of 17-Beta Estradiol on Mood and Emotion

Women are faced with a myriad of choices regarding menopause and confusion reigns. The assertion here is that the science is often being overlooked and other variables given precedence. Data from numerous laboratories indicate that Hormone Replacement can have multiple benefits on cognition and general brain function.

Over the past 20 years there has been a developing body of clinical work looking at neurological changes as correlated with declines in estrogen, particularly whether loss of primary estrogen (17-beta estradiol) is predictive to onset of clinical depression in the demographic of vulnerable women. In a study of women with treatment resistant depression conducted at MIT,[15] Edward Klaiber found a correlation between high monoamine oxidase levels and low levels of estradiol and testosterone. Monoamine oxidase is a potent catecholamine inactivator. It scavenges serotonin, norepinephrine and dopamine. Dr. Yutaka Kobayashi, a biochemist at the Worcester Foundation, and Don Broverman at MIT found a strong statistical relationship between low levels of MAO and high levels of serotonin and testosterone. Dr. Klaiber started giving the women higher than average amounts of testosterone and estrogen and the depressions lifted in a significant number of cases.

Far from being the cause of problems in the aging female human, the data strongly suggest that a lack of hormones, most significantly17-beta estradiol, precipitates a decline of well-being in mid-life women, and this pattern is acknowledged to exist as a precursor to many degenerative conditions, notably mood and sleep disorders. According to S.L. Berga, key systems mediated by estrogen are the basal forebrain, which regulates attention, and the forebrain cholinergic system, which regulates memory.[16]

The WHIMS showed that women using conjugated equine estrogens plus MPA (medroxy progesterone acetate) had an increase in dementia over a five-year period. Data from the physical

chemistry lab of the University Of Denver suggest that the difference in progestin versus progesterone molecules is extremely significant and is overshadowed by other aspects in these large randomized studies.[17]

In May 2007, The Food and Drug Administration asked makers of the SSRI drugs to expand its warning labels to include adults age 18-24. The labels already include similar warnings for children and adolescents. Eli Lilly and Co., the maker of Prozac, Zoloft manufacturer Pfizer Inc. and other pharmaceutical companies said they would comply with the FDA's request.

The seemingly limitless prescriptions for anti-depressants continue to be written. Physicians, primarily but not exclusively male, have been observed to lecture that "women don't need hormones, they need Prozac" (personal observation) despite the fact that the significant factor in mood regulation for women is allegedly hormonal. Women themselves are consistent in reporting that their major mood changes have occurred throughout their lifetimes in synergy with hormonal fluctuation. Bronson, Bruice and Whitcomb tracked women over 12 years looking at transition in serum estradiol levels correlating with flat affect depression.[18]

The data clearly shows correlation with E2 trends and mood. Two thirds of the women reporting long histories of flat affect, resignation depression stated that "the only time they were mentally up" was in the week after menses, so days 7-14; this correlates with the time of rising estradiol. As women age, the E1 levels rise naturally, due to increased density of fat cells, and the corresponding increase in E1 production from these cells. In order to overcome this, women need more E2 to drive the reaction the other way. As E2 levels rise with exogenous, transdermal application, and E1 levels diminish, the depression often lifts. Women report feeling this effect in as little as two hours after use.[19,20]

Progesterone and the Relationship to Neuroinhibition and the GABA-A Receptor

The data also show how the up-regulation of GABA at the GABA-A receptor is strongly connected to the down regulation of progesterone to allopopregnanolone and these processes can be modulated via exogenous administration of transdermal, compounded progesterone.[21]

GABA and Glycine are known to be the main inhibitory transmitters in the central nervous system acting through ionotropic receptors. This is documented in the work of Bohlen and Halbach on neuromodulators and we link the modulation of the chloride ionic channel to the alpha–4 subunit on the GABA-A receptor, and the impact of progesterone down regulation.[22]

According to Sheryl S. Smith at SUNY Medical Center, the critical interchange between the neurosteroid metabolite from progesterone, allopregnanolone, and the down regulation of the alpha-4 subunit of the GABA- A receptor is the critical link to achieving and maintaining neuroinhibition.[23] The binding of two GABA molecules between the alpha and beta subunits allows the chloride ionic channel to open, which increases inhibition. Therefore when the relationship does not occur, either due to a deficiency of GABA, or a lack of progesterone at crucial times, anxiety is manifested.

The assertion from our work at The University of Denver, correlates with the above: We have found that when there is enough GABA and transdermal progesterone is applied, anxiety reactions are halted. This has been replicated many times.

The author further suggests that if there are not enough GABA molecules present it is very easy to become addicted to benzodiazepine (BDZ) medication.

While these drugs can be helpful in the short term, they can create extreme dependency. Women (and men) who learn how to modulate their own biochemistry in response to a predilection to anxiety report that much less BDZ is needed and often are stopped, or used only at "extreme times."

Estradiol Impact on Memory and Cognition

Numerous laboratories have show that estrogen has a major impact in hippocampal neurons in rats and that rats perform significantly better after receiving estradiol than a placebo.[24] Woolley has shown that in young overiectomized rats two days of estradiol use resulted in a significant increase in the number of dendritic spines.[25] Estrogen increases NMDA (N-methyl-D-aspartate) responses.[26]

The neuroprotective action of E2 is well documented. Hippocampal neurons pre-treated with estrogen and then exposed to excitotoxic glutamate respond with an attenuated rise in Ca++, and increased survival capacity.[27] Protecting neurons from glutamate excitotoxicity enables them to perhaps resist neurological degeneration in diseases such as Alzheimer's.[28]

Implications on Cancer

The molecular structure has a great deal to do with the possible impact on cellular proliferation. Apparently, it is the unique orientation of 16 alpha-OH group with the keto group of estrone that leads to the potent effects of this estrogen metabolite.[29] We further suggest that the increased molecular stability induced by this format allows toxic metabolites to stay in the body for days instead of hours thus increasing the probability of proliferative action.[30]

There are references to the impact of DIM (di-indole methane) on limiting the HPV virus that is closely linked to cervical cancer. DIM is found in cruciferous vegetables.[31] Here the suggestion is that the actual type of estrogen used can have an even greater impact on limiting the aggressive estrogens and promoting the desired mood elevation.

Conclusion

The past four years have been a lonely battle for researchers in primary hormones. It is difficult, but absolutely necessary, to take a stand against the medical establishment for the future of science and man/womankind. Knowing the molecular aspects of hormone biology as we do, it would be wrong not to speak up. The unfortunate result of the interface of the pharmaceutical and medical worlds, as is dominant in today's medical culture, is that research is not unbiased and that science often gets pushed aside if the results are contradictory to the goals of the pharmaceutical industry. Pure, basic research remains a critical area and must confront the medical status quo. This is happening now with the hormone issues. For example, many doctors know, empirically, that many women thrive on estrogen, yet are dictated to by their peers to halt HRT until better drugs come out.

Our assertion, from the field of Orthomolecular Medicine, is that there are often no better 'drugs' than the human hormones and other chemicals that already exist in the body that simply need to be restored or enhanced with bio-identical chemicals. This is the ideal way to approach imbalances in hormone and other biochemical systems.

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WebMD

Article Link: http://women.webmd.com/estrogens?page=4

Women's Health

Estrogens

An estrogen test measures the level of the most important estrogen hormones (estradiol, estriol, and estrone) in a blood or urine sample.

- Estradiol is the most commonly measured type of estrogen for nonpregnant women. The amount of estradiol in a woman's blood varies throughout her menstrual cycle. After menopause, estradiol production drops to a very low but constant level.
- Estriol levels usually are only measured during pregnancy. Estriol is produced in large amounts by the placenta, the tissue that links the fetus to the mother. It can be detected as early as the 9th week of pregnancy, and its levels increase until delivery. Estriol can also be measured in urine.
- Estrone may be measured in women who have gone through menopause to determine their estrogen levels. It also may be measured in men or women who might have cancer of the ovaries, testicles, or adrenal glands.

Both men and women produce estrogen hormones. Estrogens are responsible for female sexual development and function, such as breast development and the menstrual cycle. In women, estrogens are produced mainly in the ovaries and in the placenta during pregnancy. Small amounts are also produced by the adrenal glands. In men, small amounts of estrogens are produced by the adrenal glands and testicles. Small amounts of estrone are made throughout the body in most tissues, especially fat and muscle. This is the major source of estrogen in women who have gone through menopause.

For pregnant women, the level of estriol in the blood is used in a maternal serum triple or quadruple screening test. Generally done between 15 and 20 weeks, these tests check the levels of three or four substances in a pregnant woman's blood. The triple screen checks alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and a type of estrogen (unconjugated estriol, or uE3). The quad screen checks these substances and the level of the hormone inhibin A. The levels of these substances-along with a woman's age and other factors-help the doctor estimate the chance that the baby may have certain problems or birth defects.

> Pregnancy: Should I Have the Maternal Serum Triple or Quadruple Test?

Health Tools

Health Tools help you make wise health decisions or take action to improve your health.

Decision Points focus on key medical care decisions that are important to many health problems.

Pregnancy: Should I Have the Maternal Serum Triple or Quadruple Test?

Why It Is Done

A test for estrogen is done to:

- Help detect fetal birth defects (especially Down syndrome) during pregnancy. When the test for estriol is combined with alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG), it is called a triple screen test. When the amount of a hormone called inhibin A is also measured along with estriol, AFP, and hCG, the test is called a quad marker screen. Other blood tests and fetal ultrasound may be done as well.
- Evaluate estrogen-producing tumors of the ovaries in girls before menstruation starts and in women after menopause.
- Explain abnormal sexual characteristics in men, such as enlarged breasts (gynecomastia). This test can also help detect the presence of estrogen-producing tumors growing in the testicles.
- Monitor therapy with fertility medicines.

How To Prepare

No special preparation is required before having an estrogen test.

Tell your doctor if you:

- Are menstruating. Note where you are in your menstrual cycle.
- Are using birth control pills, patches, or rings and other forms of hormonal birth control.
- Are or might be pregnant.

Talk to your doctor about any concerns you have regarding the need for the test, its risks, how it will be done, or what the results will mean. To help you understand the importance of this test, fill out the medical test information form.

How It Is Done

The health professional drawing blood will:

- Wrap an elastic band around your upper arm to stop the flow of blood. This makes the veins below the band larger so it is easier to put a needle into the vein.
- Clean the needle site with alcohol.
- Put the needle into the vein. More than one needle stick may be needed.
- Attach a tube to the needle to fill it with blood.
- Remove the band from your arm when enough blood is collected.
- Apply a gauze pad or cotton ball over the needle site as the needle is removed.
- Apply pressure to the site and then a bandage.

How It Feels

You may feel nothing at all from the needle puncture, or you may feel a brief sting or pinch as the needle goes through the skin. Some people feel a stinging pain while the needle is in the vein. But many people do not feel any pain or have only minor discomfort once the needle is positioned in the vein.

Risks

There is very little risk of complications from having blood drawn from a vein.

- You may develop a small bruise at the puncture site. You can reduce the risk of bruising by keeping pressure on the site for several minutes after the needle is withdrawn.
- In rare cases, the vein may become inflamed after the blood sample is taken. This condition is called phlebitis and is usually treated with a warm compress applied several times daily.
- Continued bleeding can be a problem for people with bleeding disorders. Aspirin, warfarin (Coumadin), and other blood-thinning medicines can also make bleeding more likely. If you have bleeding or clotting problems, or if you take blood-thinning medicine, tell your health professional before your blood is drawn.

Results

An estrogen test measures the level of the most important estrogen hormones (estradiol, estriol, and estrone) in a blood or urine sample.

Results are usually available within 24 hours.

Normal

For girls and women between puberty and menopause, estrogen levels vary throughout the menstrual cycle.

The normal values listed here-called a reference range-are just a guide. These ranges vary from lab to lab, and your lab may have a different range for what?s normal. Your lab report should contain the range your lab uses. Also, your doctor will evaluate your results based on your health and other factors. This means that a value that falls outside the normal values listed here may still be normal for you or your lab.

Estradiol levels in blood	
Women before menopause:	20-750 picograms per milliliter (pg/mL)
Women after menopause:	Less than or equal to 20 pg/mL
Men:	10-50 pg/mL
Children:	Less than 15 pg/mL

Results continued...

Estriol in pregnant women	
1st trimester:	Less than 38 nanograms per milliliter (ng/mL)
2nd trimester:	38-140 ng/mL
3rd trimester:	31-460 ng/mL

Many conditions can change estrogen levels. Your doctor will discuss any significant abnormal results with you in relation to your symptoms and past health.

High values

High values may be caused by:

- Ovarian stimulation used to treat infertility (for example, before in vitro fertilization).
- Cancer, such as cancer of the ovaries, testicles, or adrenal glands.
- Serious liver disease (cirrhosis).
- A pregnancy with more than one fetus, such as twins or triplets.
- Early (precocious) puberty.

Low values

Low values may be caused by:

- Problems with ovarian function, which can be caused by a failure of an ovary to develop properly (Turner's syndrome) or because of a drop in pituitary gland activity.
- Anorexia nervosa.
- Menopause.
- A problem with the fetus or placenta during pregnancy.

What Affects the Test

Reasons you may not be able to have the test or why the results may not be helpful include:

- Hormone replacement therapy after menopause.
- Birth control pills, patches, or rings and other forms of hormonal birth control.
- Having a test that uses a radioactive substance, such as a bone scan, within 1 week before the test.
- Medicines, such as clomiphene or steroids (for example, prednisone).
- High levels of sugar in the urine caused by diabetes.

What To Think About

- Blood estrogen levels are a more accurate indicator of how well the ovaries are working than urinary estrogen levels.
- Tests that measure blood levels of progesterone, luteinizing hormone, and follicle-stimulating hormone are often used to study the problems that can affect fertility and the menstrual cycle. For more information, see the topics Progesterone, Luteinizing Hormone, and Follicle-Stimulating Hormone.
- In some cases a combination of screening tests is done in the first trimester to look for Down syndrome. The first trimester screening often combines ultrasound measurement of the thickness of the fetus's neck (nuchal translucency) and measurements of hCG and a protein called pregnancy-associated plasma protein A to check for problems. For more information, see the topic Birth Defects Testing.
- The level of estriol in the blood is often used in a maternal serum triple or quadruple screening test. For more information, see the topic Triple or Quad Screening for Birth Defects.

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Estrogens

Breast

Obstet Gynecol. 2006; 108: 1354–60.

Breast Cancer Risk in Postmenopausal Women Using Estrogen-Only Therapy

Lyytinen, H., Pukkala, E., Ylikorkala, O.

Objective: To evaluate whether the risk of estrogen only therapy on breast cancer varies by dose, constituent, and route of administration.

Methods: All Finnish women older than age 50 years using oral or transdermal estradiol (n_84,729), oral estriol (n_7,941), or vaginal estrogens (n_18,314) for at least 6 months during 1994–2001 were identified from the national medical reimbursement register. They were followed for breast cancer with the aid of the Finnish Cancer Registry to the end of 2002.

Results: Altogether, 2,171 women with breast cancer were identified. The standardized incidence ratio of breast cancer with systemic estradiol for less than 5 years was 0.93 (95% confidence interval 0.80 – 1.04), and for estradiol use for 5 years or more, 1.44 (1.29 –1.59). Oral and transdermal estradiol was accompanied by a similar risk of breast cancer. The risk was most prominent with the dose greater than 1.9 mg/d orally; whereas the risk associated with transdermal route was not dose-dependent. The standardized incidence ratio for the lobular type of breast cancer (1.58) was slightly higher than that for the ductal type (1.36). The use of estradiol was associated with both localized breast cancer (1.45; 1.26–1.66) and cancer spread to regional nodes (1.35; 1.09– 1.65). The incidence of carcinoma in situ (n_32) was increased (2.43; 1.66 –3.42) among estradiol users.

Conclusion: Estradiol for 5 years or more, either orally or transdermally, means 2–3 extra cases of breast cancer per 1,000 women who are followed for 10 years. Oral estradiol use for

To Estriol or Not to Estriol? - The Role of Estriol in Hormone Balance

Jim Paoletti, RPh

So the doctor has succumbed to the cloud of confusion created by the FDA and Wyeth and now refuses to refill any prescriptions for estriol. What do you do for those patients that have been on bi-est or tri-est formulations? How much estradiol should you give to achieve similar therapeutic effects to those seen with bi-est? Understanding the underlying physiology and biochemistry will help when converting from bi-est or tri-est to estradiol only formulations, while maintaining control of symptoms.

The strength of a hormone is representative of how tightly it binds to its receptors. The tighter it binds the longer before it dissociates from the receptor and the ligand no longer exists. The commonly expressed comparison of estrogen strength is that estradiol is 12 times more potent than estrone, and 80 times more potent than estriol. These relative strengths of the three bio-identical estrogens were determined by measuring effects on the uterus lining, but do not necessarily apply to all tissues in the body. Estradiol has been estimated to be 1000 times more potent than estriol in stimulating proliferation of breast tissue. Estriol is the most potent of the three estrogens on the vaginal estrogen receptors. Estriol is the only estrogen that has been shown to reverse symptoms of vaginal atrophy at doses that do not raise blood levels or induce systemic effects in most women. However, estradiol appears to be the strongest estrogen in general for overall effects throughout the body, much stronger than estriol.

The result of any potential interaction of estrogens with the estrogen receptors depends not only on the relative strength of the estrogenic substances present, but their relative quantities as well. In most cases, estrogen receptors combine to form heterodimer receptors, so it takes two estrogenic molecules combined with the two receptors for formation of the ligand to begin translation of the message for genomic effects. If two stronger estrogenic molecules combine with the receptors, then they will produce the strongest genomic estrogenic effect. If a weaker estrogenic substance combines with one or both receptors, then the message will be comparatively short-lived, and a weaker estrogenic response will be effected. It therefore takes a greater quantity of a weaker estrogenic substance to produce similar results to a stronger estrogen because there has to be enough of the weaker substance to sustain the message over a longer period.

Estriol's role in the body has not been completely determined, but evidence points to the fact that it may protect against the proliferative effects of the stronger estrogens estradiol and estrone. Early studies by Lemmon demonstrated less risk of breast cancer in women with a greater proportion of estriol relative to their levels of estradiol and estrone[1]. Lemmon also showed that estriol limited the growth of breast tumors[2] (in rats). More recently, several studies have demonstrated that estriol administration causes no increase in the risk of breast cancer [3-6]. Being much weaker, estriol can block the interaction of the stronger estrogens with the receptors and reduce their genomic responses. The more estriol in the system, the greater the chance of blocking the effects of the stronger estrogens. In this sense, the estrogenic substance estriol could be considered an anti-estrogen when compared to estradiol and estrone. Similarly, tamoxifen, a substance that has been shown to increase the chance of reoccurrence of breast cancer if used more than 5 years, is classified as an anti-estrogen, even though tamoxifen is an estrogenic substance itself. The same receptor blocking effect occurs if too much of a phytoestrogen or xenoestrogen is introduced to the body. Although estrogenic in their effect, and much, much weaker than estradiol, sufficient quantities can decrease the effectiveness of estradiol.

Consider the effect of estriol by comparing two different formulations of bi-est, one containing 80% estriol and one containing 50% estriol. In 1.0 mg of an 80% estriol bi-est, the amount of estradiol contained in the formulation would be 0.2 mg. The same amount of estradiol would be

contained in 0.4mg of a bi-est containing 50% estriol and 50% estradiol. The "stronger" of the two bi-est formulas in my opinion is *not* the formulation with more total estrogen content, the 1.0 mg of the 80% estriol, but the 0.2 mg of the 50% estriol formula. Since estradiol is a much stronger estrogen than estriol, the formula with a greater amount of estriol will "interfere" more with the estradiol interacting with the receptors, and therefore decrease the response to estradiol. Consequently, the estradiol in the formula with less estriol should produce more estrogenic effect.

Estriol should be kept at normal physiological concentrations, consistent with one of the primary goals of bio-identical hormone restoration therapy, which is to restore all the hormones to a normal state of balance with each other. Even if we do not have full knowledge of the extent of the functions of estriol in the body, estriol has a role in balancing the effects of other estrogens and should therefore be included in the mix of hormones to best imitate normal physiology.

In switching a patient from a bi-est formulation to estradiol only, you should be able to theoretically reduce the amount of estradiol in the preparation and get a similar response. How much of a reduction should be made is unknown. An attempt to look at what doses of estradiol are typically used with manufactured products can be confusing. With any oral estradiol therapy, a dose necessary to produce normal pre-menopausal levels will result in estrone levels in the magnitude of 5 to 10 times the high normal levels of a pre-menopausal woman. A much greater estrogen burden to the body is produced than would be indicated by estradiol levels alone. Topical administration of estradiol with patches and cream can be even more confusing as the amount of hormone introduced into the body is often unknown. Manufacturers do not state doses for their products, but rather the amount of estradiol that is "delivered", "absorbed" or "bioavailable". These terms are defined by the amount of hormone measured in venous serum. Studies indicate that the venous serum levels will neither significantly change at physiological doses, nor represent the amount of hormone delivered to the tissues. The amount of estradiol contained in one commercial patch that claims delivery of 350 *mcg* over 7 days is actually 3.8 *mg*[7]. How much estradiol that comes out of the patch and goes into the body over 3.5 days has not been disclosed. Although some women have been found to achieve normal physiological levels as determined by saliva testing, as well as symptom management, when using estradiol patches, data indicating how many of these patients have normal physiological levels of estrone and estriol is lacking. Additionally, the constant release of estradiol from a patch may affect metabolism in ways not determined, and not applicable to the administration of compounded topical estradiol preparations.

In consideration of all the above, my suggestion is to switch to a dose of estradiol that is 75-80% of the estradiol contained in a bi-est formulation, and adjust according to individual patient response. Also provide nutritional guidelines on how to increase safe estrogen metabolism and elimination.

The switch to non-estriol preparations should not be made without providing the prescriber with the facts about estriol. Information can be found in the IACP website, www.iacprx.org. In the literature, estriol has been shown to be a safe and effective treatment for menopausal symptoms[8-17], especially urogenital and vaginal symptoms[9, 13, 18-21], and shown to improve bone density[22-25]. It has been marketed by several companies for many, many years outside the United States[26], and formerly in the U.S.[27, 28], with no reported problems concerning safety, including no increase in the risk for breast cancer. The FDA has responded to a citizen's petition filed by a major drug manufacturer, ignoring over 70,000 letters in opposition to the petition. The drug manufacturer claims that estriol is not safe to give women, yet sells two oral products containing estriol in Europe. The FDA has stated that compounding pharmacists must follow the guidelines established in FADMA 1997, but now wishes to ignore the section that allows pharmacies to compound with any ingredient listed in the USP, as estriol is. In addition, there is an oral estriol product, Trimesta™, which is currently in phase 3 clinical trials[29]. The FDA has acted in an unscientific and unethical way to suppress compounding, limit the choices that prescribers and

patients have, and support the bottom line of the manufacturers that produce estrogen replacement products. Clear up the confusion with the facts, and prescribers may agree that there is no valid reason to avoid using estriol.

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Labrix Clinical Services, Inc.
Provider News

Hair, Hair, It's Everywhere...some have little, some have lots...

Excess body hair growth (hirsutism), and an increase of hair loss on the scalp (androgenic alopecia) are often associated with Polycystic Ovarian Syndrome (PCOS). PCOS is one of the most common female endocrine disorders affecting approximately 5-10% of women of reproductive age. Both hirsutism and baldness in women with PCOS can be due to elevated levels of testosterone. Testosterone is converted to dihydrotestosterone (DHT) which directly stimulates the hair follicle to grow. Body hair grows in response to DHT much more so than does head hair. In the case of baldness, the head hairs are actually sensitive to too much DHT and male-pattern balding is the result.

If women have excess testosterone or other androgens such as DHEA, the very fine body hairs will turn into coarse, dark hairs on the abdomen growing toward the navel and on the face in a beard and mustache pattern. If they have a genetic predisposition to baldness and the androgens are high enough, balding results. Therefore in PCOS with elevated androgens, most women have increased body and facial hair growth and some of them also have balding if they are genetically predisposed.

Testosterone is converted to DHT by an enzyme called 5-alpha reductase. In order to affect hair growth then, the mechanisms to consider would be to:

- Decrease the amount of testosterone produced by the ovaries and/or adrenal glands
- Impair the action of the 5-alpha reductase enzyme.

Insulin resistance is widely considered to be the etiology of PCOS. As insulin levels rise and/or cells become less responsive to the insulin present in the blood stream, the female body raises testosterone levels in an attempt to move excess glucose and insulin into the cells. Thus, managing the body's metabolism of and response to insulin will help to decrease androgen levels. This can be accomplished by eating a low glycemic index diet and following a regular exercise program, as well as utilizing the help of glucose lowering supplements. Metformin is a commonly used pharmaceutical that can lower glucose and insulin levels, and thus testosterone levels.

A second approach to managing hirsutism and androgenic allopecia in women is to utilize a 5-alpha reductase inhibitor. Conventional drugs such as finasteride (Proscar, Propecia) are commonly used to slow the conversion of testosterone to DHT. However, there are alternatives to pharmaceuticals. Transdermal Progesterone can slow the conversion to DHT, as can the herbs Saw Palmetto, Nettles root or Green Tea.

It is important to note that insulin resistance in older women causes the same elevation in androgen levels that we see in younger women with PCOS. Elevated testosterone and/or DHT levels in women past reproductive age is simply called insulin resistance, or if multiple metabolic risk factors are present, Metabolic Syndrome.

If hirsutism or male pattern baldness are problems for your patients, consider salivary hormone testing to identify androgen levels.

For more information on treating PCOS/Insulin Resistance, check out the Labrix Handout entitled "Treating Insulin Resistance/ Metabolic Syndrome"...you can access the handout by emailing your request to education@labrix.com.

Testosterone: a Heart Healthy Hormone?

Article Written by Carol Petersen, RPh, CNP – Women's International Pharmacy

Link: http://www.womensinternational.com/newsletter/article_testosterone.html

In *Maximize Your Vitality and Potency*, Dr. Jonathan Wright calls testosterone "the healthy heart hormone." His book is well referenced and he has the clinical experience to back it up. The medical literature is also full of studies indicating the importance of testosterone to the heart.

For more information on testosterone and male hormones fill out this form to receive our free packet of information on male hormone therapies.

Yet, a paper entitled "Adverse Events Associated with Testosterone Administration" published in the June 2010 *New England Journal of Medicine* seems to tell a different story. In this study involving a group of 209 subjects, those that were treated with testosterone had a higher rate of cardiac events than the non-treated group, and they had also begun the study with a high prevalence of hypertension, diabetes, high cholesterol and obesity. Based on this, should we question the heart healthy benefits of testosterone?

Not so fast … in an article in *Life Extension* magazine, Dr. Steven Joyal, pointed out some of the study's flaws. For one, those that had already exhibited the worst cardiovascular indicators were placed in the treated group. Second, the testosterone treatment was twice the normal starting dose. And third, no attention was given to evaluate the estrogen status of these men before, during or after the study. No one monitored whether or not the testosterone converted directly to estrogen.

And why might that be a concern? Dr. Eugene Shippen, one of the earliest heralds of the dangers of excess estrogens in men and author of *The Testosterone Syndrome*, notes that elderly men may actually have more estrogen than their female counterparts of the same age. Dr. Shippen cited such factors as zinc deficiency and the use of diuretic drugs as contributing to increased estrogens in men as they age.

William Faloon, also writing in *Life Extension* magazine, points to a May 2009 study published in the *Journal of the American Medical Association* that the men in the study with chronic heart failure who also had balanced estradiol levels (not low, nor high) were the least likely to die during the three-year study. The estradiol levels in the successful group varied between 21.8 and 30.11 pg/ml, which gives us some guidelines for acceptable levels of estradiol in men.

Dr. Thierry Hertoghe points out in *The Hormone Handbook* that a weak heartbeat is a symptom of low testosterone, and that high estrogen levels have been associated with myocardial infarction. Excess estrogens also make a progesterone deficiency worse, further contributing to hormone imbalance, and translating into muscle tension, anxiety, nervousness and difficulty with sleep.

So, maintaining optimal testosterone levels remains at the center of heart health for men, recognizing that estrogens and progesterone also play their part.

When discussing testosterone therapy, our staff routinely suggests including either progesterone or chrysin, for example, to prevent excessive conversion of testosterone to estrogens. Our staff also recommends that men consult with their practitioners for careful monitoring of their hormone levels.

For more information on testosterone and men, follow this link to receive our Male Hormone Therapies Information Packet.

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Connections
An Educational Resource of Women's International Pharmacy

Testosterone - Not Just For Men Anymore!

To read the full article please click on link below:

http://www.womensinternational.com/connections/testosterone.html

Gynecol Endocrinol. 2012 Oct;28 Suppl 2:12-5. Epub 2012 Jul 27.

Percutaneous estradiol/oral micronized progesterone has less-adverse effects and different gene regulations than oral conjugated equine estrogens/medroxyprogesterone acetate in the breasts of healthy women in vivo.

Murkes D, Lalitkumar PG, Leifland K, Lundström E, Söderqvist G.

Source

Department of Obsterics and Gynecology, Södertälje Hospital, Södertälje, Sweden.

Abstract

Gene expression analysis of healthy postmenopausal women in a prospective clinical study indicated that genes encoding for epithelial proliferation markers Ki-67 and progesterone receptor B mRNA are differentially expressed in women using hormone therapy (HT) with natural versus synthetic estrogens. Two 28-day cycles of daily estradiol (E2) gel 1.5 mg and oral micronized progesterone (P) 200 mg/day for the last 14 days of each cycle did not significantly increase breast epithelial proliferation (Ki-67 MIB-1 positive cells) at the cell level nor at the mRNA level (MKI-67 gene). A borderline significant beneficial reduction in anti-apoptotic protein bcl-2, favouring apoptosis, was also seen followed by a slight numeric decrease of its mRNA. By contrast, two 28-day cycles of daily oral conjugated equine estrogens (CEE) 0.625 mg and oral medroxyprogesterone acetate (MPA) 5 mg for the last 14 days of each cycle significantly increased proliferation at both the cell level and at the mRNA level, and significantly enhanced mammographic breast density, an important risk factor for breast cancer. In addition, CEE/MPA affected around 2,500 genes compared with just 600 affected by E2/P. These results suggest that HT with natural estrogens affects a much smaller number of genes and has less-adverse effects on the normal breast in vivo than conventional, synthetic therapy.

PMID:
22834417
[PubMed - indexed for MEDLINE]

PATIENT HANDOUT

Bioidentical Hormones
The Basics

What are bioidentical hormones?

From a physiological perspective, bioidentical hormones derived from natural plant sources are identical to those that the body produces for itself, in the right proportions. When we are "replacing" the body's hormones, we feel it makes more sense to use entities which the body recognizes as its own, rather than hormones from horses, imbalanced versions or overly potent synthetic versions. The hormones we use are mainly Estradiol, Estriol, (E2, E3, respectively), progesterone, testosterone, and DHEA.

How can I get natural hormones?

With the exception of low potency progesterone creams (available over-the-counter), natural, bioidentical hormone therapy is generally obtained through a physician's prescription.

Once my doctor prescribes bioidentical hormones, can I get them at any pharmacy?

Because the ingredients are naturally derived, it is impossible for a manufacturer to obtain a patent on these substances. Without a patent, it is unlikely that any drug manufacturer will go to the expense of pursuing these products for marketing and sales. Consequently, these bio-identical hormones must be prepared for the patient from pure, plant derived chemicals by a pharmacist at a compounding pharmacy.

What is a compounding pharmacy?

Actually, it's the oldest type of pharmacy in the world: an apothecary with a pharmacist trained in formulating prescriptions and who prepares them from pure ingredients on the order of a physician. A caring and competent pharmacist works closely with the prescribing physician to create just the right dosage form and strength for you, the patient.

What dosage forms are available?

Compounded dosage forms are numerous and variable in nature. Each method has its advantages for use. Usage of specific dosage forms depend on patient compliance, type of response desired and medications involved. Oral capsules, vaginal suppositories, transdermal creams, gels and troches (a lozenge that dissolves between the gum and tongue) are among the variety of dosage forms available to be compounded. Ideally hormone supplementation should be tailored to individual treatment needs.

Where do bioidentical hormones come from?

Natural plant sterols are extracted from soybeans and/or Mexican yams. These are taken to a laboratory where they are converted chemically, or semi-synthesized to hormones that are identical and indistinguishable from the body's own.

If they are synthesized in a lab, doesn't that make them "synthetic"?

Since bioidenticals are derived from plant substances in soybeans and yams (diadzein and genistein), they are natural in the sense that they are formulated in the lab to be biologically identical in structure and function to hormones produced in the body. For that reason, we prefer to call these hormones "bioidentical, plant derived". We use the term "synthetic" to describe chemically altered hormones that are many times more potent than the "naturals."

Will my insurance company cover these treatments?

Although compounds such as these cannot be processed at the pharmacy like mass produced medications, most insurance companies will reimburse a percentage of the cost to the patient. Look closely at your benefit package. If you have a flexible spending account of HSA (Health Savings Account) you may use your account to pay for your consult and/or hormone prescription(s).

How will the doctor know what dose is right for me?

Every patient is different! Your physician will take many issues into account: age, weight, symptoms, gynecological history and prior or present use of hormones will all affect the choice of dose and dosage form. Saliva and/or blood spot testing to identify specific imbalances of one or more hormones eliminates physician guesswork when prescribing. Followup testing and regular monitoring when using hormones allows your doctor to adjust your dose as needed.

For a referral to a natural hormone friendly doctor, skilled in hormone testing, visit www.zrtlab.com.

PATIENT HANDOUT

Estrogen Dominance

Estrogen dominance refers to an excess of estrogen when progesterone levels are inadequate. This condition can occur in women during the reproductive years, but tends to be particularly symptomatic for women during perimenopause and in menopause. Estrogen dominance is worsened by women not ovulating, women being exposed to synthetic estrogens and/or women not metabolizing estrogens correctly. Estrogen dominance is a term coined by John Lee, M.D. in the book What Your Doctor May Not Tell You About Menopause.

The Problem

Scientific studies link high estrogen or estrogen imbalance with a wide range of symptoms and conditions, from hot flashes, night sweats, low libido, and foggy thinking to more serious conditions related to reproductive health (endometriosis and PCOS) as well as breast disease including cancer. Hormone imbalances triggered by medications like synthetic hormone combinations have also been found to contribute to estrogen dominance problems.

Symptoms of estrogen dominance include:

- Fibrocystic and tender breasts
- Heavy menstrual bleeding
- Irregular menstrual cycles
- Mood swings
- Vasomotor symptoms
- Weight gain
- Uterine fibroids

Causes

Premenopause: Lack of ovulation and/or reduction of ovarian production of progesterone.

Perimenopause (40s-mid-50s): Lack of ovulation or erratic cycles, when estrogen levels fluctuate rapidly from high to low in the absence of adequate progesterone.

Postmenopause: An imbalance of estrogen to progesterone ratio in waning reproductive years when ovarian production of estrogen can decline by as much as 60% and levels of progesterone can drop to nearly zero with the cessation of ovulation.

Balancing Estrogen

Women of all ages benefit from balanced hormones. With menstrual irregularities, PMS, endometriosis and infertility, testing can be helpful in understanding the underlying condition. Health care providers working with perimenopausal and menopausal women find hormone testing to be a key step in detecting and correcting imbalances. Testing hormone levels is also invaluable for monitoring women using hormone replacement therapy.

Why Test Hormones

Saliva and/or blood spot testing in a ZRT Comprehensive Hormone Profile is a simple, reliable means for determining estrogen dominance. The test measures bioavailable levels, those hormones actively working in the cells of the body. This "bioavailable" measurement can detect long-hidden hormone imbalances and more closely correlates with personal symptoms.

Because hormones work together to create a balanced internal milieu, it makes sense to test all of the following to help determine estrogen dominance:

- Estradiol (E2) the most potent of the estrogens
- Progesterone (Pg)
- Testosterone
- DHEAS
- Cortisol (stress hormones, for adrenal function)
- Thyroid Profile (TSH, T3, T4, TPO Antibodies for Hashimoto's Thyroiditis)

Benefits

At ZRT Laboratory, we compare symptoms with or without hormone usage and relate these back to tested hormone levels providing more information than is available with standard lab results. In this way, comprehensive hormone testing can assist detection of previously undiagnosed disorders, and serve as a rational basis for physician treatment to relieve symptoms and restore hormone balance.

For a referral to physician skilled in hormone testing and natural hormone balance, visit www.zrtlab.com.

Connections
An Educational Resource of Women's International Pharmacy

ESTROGENS: Friend of Foe?

To read the full article please click on link below:

http://www.womensinternational.com/connections/estrogens.html

LE Magazine October 2004

REPORT

What You Don't Know About Estrogen

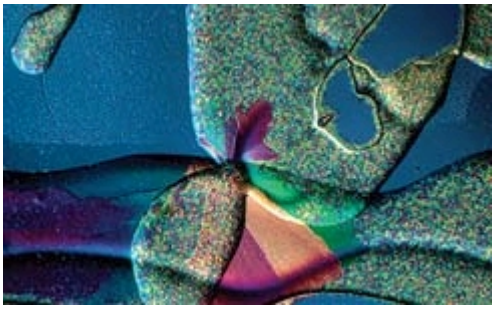
There are many misconceptions about what estrogen really is and how it works in the body. This widespread confusion exists in the minds of the lay public as well as the medical community. The result is poor choices being made about what women should be doing to maintain youthful hormone balance while also protecting against cancer.

This article uncovers the basic facts about estrogen that are so often overlooked by doctors today. It then reveals dietary modifications that women should consider if they are taking an estrogen drug. The science underlying this article is extremely complex. In order to make this information comprehensible to the lay reader, we have made a special effort to translate these new findings about estrogen metabolism into a version that most people will understand.

Nevertheless, some people may have difficulty understanding a few technical areas of this article. This information is so critically important, however, that we urge you to re-read paragraphs you do not understand in order to gain a full grasp of these crucial anticancer concepts.

The word estrogen strikes fear into the hearts of many. Women equate it with breast cancer, scientists equate it with "endocrine disruptors," and doctors equate it with hormone replacement. Are these perceptions accurate?

Estrogen is many things. It includes the body's natural estrogenic hormones and things that look like the body's natural hormones. As long as something behaves like an estrogen in the body, it is an estrogen, or is, quite simply, "estrogenic." The strongest natural estrogen in the human body is estradiol. Premarin® is an example of an unnatural estrogen—unnatural, at least, to the human body. It is made from estrogens excreted in the urine of pregnant horses. Chemical estrogens that behave badly once they are inside the body are known as "endocrine disruptors" for their adverse effects on development. All of these estrogens interact with the body's innate hormonal system. They do not, however, provoke the same responses.



Photomicrograph of estradiol crystals. Estradiol, the most potent of the natural estrogens, is used in its natural or semisynthetic form to treat menopausal symptoms.

What Makes Estrogen Tick

"Estrogen receptors" are rarely talked about unless a woman is diagnosed with breast cancer (or a man with prostate cancer), but they are critical to how an estrogen behaves. For example, tamoxifen is a "known human carcinogen" due to its estrogenic effects, yet it is marketed as an "estrogen blocker" because of its estrogen-blocking effects. It has beneficial effects on bone, but negative effects on the circulatory system.[1,2] It blocks estrogen-driven breast cancer growth temporarily, yet later becomes estrogenic in the same tissue, promoting new breast cancer. How can one "estrogen" do all these things?

The answer is, partly, estrogen receptors, which are proteins in the body that react to estrogen. Estrogen is like fuel, and estrogen receptors are like machines. When fuel meets machine, things happen.

Unfortunately, what happens depends on which area of the body is in question. The receptors of different parts of the body are different. In other words, although all the machinery runs on some type of estrogen, not all the machinery does the same thing. Estrogen does different things in different parts of the body. It does one thing in the brain and another in the breast. It might surprise you to learn, for example, that the pituitary gland is second after the uterus as the most estrogen-responsive area of the body.[3] So it is not accurate to think of estrogen as the thing that makes breast cancer cells grow.

Just a few years ago, researchers believed that there were two types of estrogen receptors: alpha and beta. That made things fairly simple. Estrogen hits receptor alpha and Y happens. Research focused mostly on the strong estrogen—estradiol—and it

seemed that progress could be made in understanding how estrogen affects at least breast tissue, though strange things continued to happen, such as the estrogen "blocker" tamoxifen causing the growth of tamoxifen-dependent cancers. With the discovery of a much larger picture, those days are over and a lot of research is now out the window. As a researcher at Columbia recently lamented, "where will it end?"[4] There is more to it than anyone ever imagined.

The Plot Thickens

It has now been discovered that there is an entire new class of estrogen receptors called estrogen-receptor-related receptors. These receptors do not respond to the body's natural estrogen.[5,6] They are instead activated by xenoestrogens (estrogens from the outside, or from the environment).[7] Pesticides and tamoxifen are two examples of xenoestrogens that activate estrogen-receptor-related receptors.[8,9] The extraordinary thing about these receptors is that they represent a whole new class of estrogen machinery, previously unknown. Not only can these receptors do everything the estrogen receptors that respond to "natural" estrogen can do, but they also have a major impact on how an estrogen—any kind of estrogen—behaves.[6] The discovery of this new class receptors will enable researchers to understand, for the first time, how environmental estrogens ("endocrine disruptors") interfere with the body's normal metabolism, and to better define the use of natural estrogen.

Estradiol Stops Cancer Cell Growth

How can this "strong" hormone—estradiol—stop hormonally responsive cancer cells from multiplying? The answer to that question first appeared in the *Journal of the National Cancer Institute*,[10] and has been known since at least 1977.[11] The cancer cells that estradiol stopped from growing had been treated with tamoxifen. Tamoxifen works two to five years after breast cancer treatment to block estrogen and prevent cancer recurrence, and then usually does the opposite.[12-14] When it starts doing the opposite of what it is supposed to do, so does estradiol. How can this puzzle be solved?

In 2001, researchers reported for the first time that tamoxifen breakdown products interact with one of the newly discovered estrogen-receptor-related receptors, and keeps it from activating certain genes normally activated by estrogen.[8,15] This opened a whole new vista for understanding how tamoxifen and other synthetic estrogens work. Important clues have already been found.

Estrogen Cofactors Discovered

In addition to interacting with estrogen-receptor-related receptors, tamoxifen and other xeno-estrogens interact with yet another new discovery.

In the laboratory, researchers can get estrogen, by itself, to activate estrogen receptors. In other words, in a laboratory setting, any estrogen fuel will activate the estrogen machinery and set things in motion. In real life, this does not happen. In real life, estrogen is only one of many factors that coordinate as a group to activate estrogen receptors.

The body makes proteins known as "coactivators" and "corepressors." These proteins attach themselves to estrogen and other hormones such as thyroid, creating big, complex "globs." It is these globs—not estrogen alone—that activate or suppress what was previously attributed to estrogen alone. In other words, studies showing what an estrogen does in the laboratory may have little to do with what actually occurs in the human body; in real life, other proteins run the show. This is bold new territory for hormone research.

Here is an example of just how important these coactivator and corepressor proteins are in determining how estrogen behaves. Corepressor SSN6 blocks estrogen's effects in cells. In other words, the SSN6 protein shuts the machinery down. The estrogen fuel can be available (estrogen could be floating all around), but the machinery will not start as long as corepressor SSN6 is working. It neutralizes the effects of estrogen. If something interferes with this protein, however, instead of dampening the effects of estrogen, it enhances them. In addition, estrogen blockers turn into estrogen enhancers.[16] Sound familiar? The importance of coactivators and corepressors cannot be overstated. They interact with both estrogen receptors and the newly discovered estrogen-receptor-related receptors. As you will soon read, there may be natural ways for women to regulate these "coactivators" in a manner that reduces breast cancer risk.

Estrogen Imposters

The three principal types of estrogen manufactured by the human body are estradiol (17 beta-estradiol), estriol, and estrone. Estradiol is the most feared because it is the strongest and is associated with the growth of cancer cells. Estrone is a metabolite of estradiol, and is less potent. Estriol is another metabolite, but is considered so mild mannered that it is recommended as a safe hormone replacement.[17-19] In addition, the human body contains 11 other estradiol metabolites that hardly anyone ever mentions.

Premarin® and Prempro™ are drugs made of 17 beta-estradiol and more than a dozen estrogen metabolites from horses.[20] These manmade drugs should not be confused with any estrogen manufactured by the human body, with other estrogen drugs, or with estrogen in general. The data from studies of women taking these drugs cannot, and should not, be extrapolated to other hormone replacement drugs or therapy. This is an important point: Premarin® is not estrogen, but instead is an estrogen—one of many

estrogens. Different estrogens produce different effects. The manufacturer of Premarin® and Prempro™ has argued that its horse estrogens have unique effects in humans, and undoubtedly they do.

Dozens of studies demonstrate important differences between the effects of Premarin® on the human body and the effects of other estrogen products. Transdermal estradiol, for example, may decrease triglycerides and LDL oxidation, whereas Premarin® may do the opposite.[21] Premarin® may increase C-reactive protein (a negative for the heart) while transdermal estradiol may not.[22] Changing from Premarin® to transdermal estradiol may reduce triglycerides significantly.[23] Estrogen patches may reduce blood pressure, whereas oral estrogen may not.[24] These and dozens of other studies show different effects depending on which estrogen drug is being evaluated. Not only are there differences between Premarin®/Prempro™ and other drugs, but there are differences between other drugs as well.

Neutralizing Estrogen: The Asian Advantage

Japanese women have been reported to have higher levels of estradiol in their blood than Americans, yet they have a much lower risk of breast cancer.[25,26] Why? Researchers believe it has more to do with environmental factors than genetics. When Japanese and other Asians adopt a Western lifestyle, risk increases.[27,28] The Asian diet may contain things that modulate the response to estrogen, and strong evidence indicates that how the body handles estrogen is far more important than how much estrogen it handles. Research indicates significant differences between Japanese and Western women in their number of estrogen receptors and in their response to xenoestrogens.[29-31] These differences suggest the involvement of the newly discovered estrogen coregulators. Dietary factors can activate or deactivate these factors, which means that every woman can regulate her own estrogen, to a certain extent.

Researchers have extensively investigated three aspects of the Asian advantage: soy, vegetables, and green tea. Each is associated with a dramatically lower risk of breast cancer.

Drinking 36 ounces of soy milk a day can reduce levels of estradiol by 20-27% within weeks.[32,33] Soy contains isoflavones that neutralize “strong” estrogens, converting them to estrogen metabolites that protect against breast cancer.[34] When mice implanted with human breast tumors were given soy concentrate and green tea, tumor size was reduced by 72%.[35] Estrogen receptor alpha was also reduced, an indication that the combination of soy and green tea was working at the genetic level, probably with estrogen cofactors. Forty milligrams of isoflavones a day significantly decreased “strong” estrogen levels in women, according to a study from the H. Lee Moffitt Cancer Center in Tampa, FL.[36] These are only a few of the many studies demonstrating the beneficial effects of soy.

In another experiment that shows the hormonal benefits of soy on the effects of chemical estrogens, when female monkeys were given birth control pills, their cortisol shot up, and their DHEA and testosterone plummeted. When they were given Premarin®, the same thing happened. When the monkeys were given soy protein with isoflavones, however, their hormones normalized.[37]

Several years ago, there was concern about genistein, an isoflavone in soy, when research showed that it activated estrogen-related genes. Some people took this to mean they should avoid consuming soy, which would be unfortunate given the overwhelmingly positive data about soy’s benefits to humans. Genistein has been called the “good estrogen” for its beneficial effects against estrogen-responsive breast cancer.[38] It subsequently emerged that most of the negative research on genistein was generated by one researcher, under conditions that would not exist in real life (such as extremely high levels of genistein put into cancer cells that were deprived of all other estrogen).

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The human body manufactures estrogen as a necessary component in many processes; estrogen is always in the body, even in postmenopausal women. Copper, too, is always in the body and is another example of something that can distort the way genistein behaves in a test tube.[39] Researchers at the University of California, Davis, recently did the same test tube study on genistein and produced the same negative results. They then put genistein in a test tube with the cancer cells and environmental estrogens. The result showed that genistein suppressed cancer cell growth.[40] These studies on pure genistein, however, do not accurately reflect what occurs in a complex environment such as the human body.

Fortunately, the safety of soy isoflavones (including genistein) for human consumption has been confirmed by experiments with monkeys, the experimental model closest to humans.[41] Monkeys treated for three years with soy or soy minus its isoflavones exhibited no abnormal cell growth; in fact, the result was just the opposite. The researchers concluded, “These findings suggest that high dietary levels of soy isoflavones do not stimulate breast or uterine proliferation in postmenopausal monkeys and may contribute to an estrogen profile associated with reduced breast cancer risk.” In addition, a new study clarifying the estrogenic effects of genistein on the uterus found that genistein may enhance cell growth for a few days, but then the effect stops. This is a new finding, and the results are different from those for estrogen drugs that perpetuate growth indefinitely.[42] With any luck, issues surrounding how genistein behaves will be soon resolved.

It is important to remember that genistein also blocks the growth of estrogen-receptor-negative breast cancer cells. By incorporating soy and isoflavones in her diet, a woman can potentially stop breast cancer before it develops.[43] The one caveat is that genistein may interfere with tamoxifen, and thus should not be taken by itself with that drug.[44]

One of the most exciting new findings is that genistein keeps amyloid from killing brain cells (without any negative effects on uterine cells), and has been suggested as an alternative to synthetic estrogens for the prevention ofAlzheimer’s disease.[45] Studies of the popular estrogen drugs Premarin® and Prempro™ show that they may actually increase the risk of dementia.[46]

Everybody knows that vegetables are good for you, and they are especially good for women who want to avoid breast cancer. Vegetables enable the body to rid itself of excess estrogens. Meat eaters have about 50% more estradiol and estrone in their blood than do vegetarians.[47] Women who eat the most vegetables, beans such as lentils, and fiber reduce their risk of breast cancer risk by 50%.[48] As you will read next, compounds found in vegetables favorably affect the way estrogen behaves in the body.

Other Ways To Tame Estrogen

The way estrogen is metabolized is critical to how it behaves. Fortunately, we can do more than cross our fingers and hope for the best. Certain compounds found in plants turn harmful estrogen into a more beneficial version. Chief among them is indole-3-carbinol (I3C), a phytochemical found in cruciferous vegetables such as broccoli. In China, where the risk of breast and prostate cancers is minuscule, consumption of cruciferous vegetables is more than three times that of the US.[49]

I3C helps convert “strong” estrogens into benign or even helpful estrogens such as 2-hydroxyestrone.[50,51] It also acts very much like tamoxifen in blocking undesirable estrogenic effects in breast cancer cells, and its antiestrogen effects are enhanced with genistein.[52]

When digested, I3C is converted to other substances, including diindolylmethane (DIM). Some earlier research suggested that I3C's beneficial effects were due to DIM. New research shows this is not the case, and that there are important differences in the effects of I3C and DIM on the metabolism of estrogen. Researchers recently stated, "This finding [of I3C's effects] is inconsistent with the claim that DIM is the biologically active metabolite of I3C with regard to its antiestrogenicity." DIM does not increase beneficial 2-hydroxylation of estrogen (at least in rats), but it does lower harmful 4- and 6-hydroxylations.[53] By contrast, I3C, which partially converts to DIM during digestion, affects all three in a positive way. Moreover, DIM does not have the anti-estrogen effects of I3C.[54]

Another potential supplement for breast cancer prevention that has drawn a lot of interest is melatonin. Melatonin is associated with sleep because it builds up during the night, but it may ultimately end up being more associated with estrogen than with sleep. Studies show that melatonin plays a major role in how estrogen behaves. In estrogen-receptor-positive breast cancer cells, melatonin can bring cell growth to a halt.[55] Research indicates that melatonin controls estrogen, and vice versa.[55-57] In studies of rodents, melatonin shows great promise with regard to its ability to prevent breast cancer when given continuously, before and after exposure to a carcinogen, and when given to mice with the HER2/neu genetic alteration.[58,59] Researchers have been unsuccessful in correlating blood levels of melatonin with breast cancer.[60] This reflects melatonin's complexity as a hormone that, like estrogen, comes in various forms and has several receptors. Without a doubt, melatonin plays a major role in breast cancer through its effects on estrogen and other cancer-related phenomena.

As an antioxidant, melatonin is not only powerful but also unique. Unlike vitamin E, which essentially has no further effects after it scavenges a radical, when melatonin gets a radical, it creates a new melatonin antioxidant; that is, it self-perpetuates. It also cooperates with other antioxidants like vitamins C and E.[61] Antioxidants are very important in preventing cancer, and it has been reported that free radicals can activate or deactivate genes that are involved in breast cancer.[62]

In addition, melatonin may suppress cortisol, which is a stress-related hormone.[63,64] It is interesting to note that the overwhelming majority of breast cancer patients say stress caused their disease.[65] In a study of older women, 2 mg of melatonin per day reduced estradiol levels, enhanced sleep, and improved levels of DHEA.66 Melatonin is very potent, and as little as 0.3 mg per day may be enough to produce beneficial effects.

Breast cancer is a serious concern for most women. Understanding that there are different types of estrogen, that different estrogens have different effects, and that women can, to a certain degree, control their own estrogen (through dietary modification and supplement use) will help women make informed choices about estrogen exposure and reduce their risk of breast cancer. Recent discoveries about estrogen receptors and how they interact may finally unlock the mysteries of how estrogens work, and provide the basis for nontoxic treatment and effective prevention.

What Causes Breast Cancer

According to the Breast Cancer Fund, a woman's risk of contracting breast cancer was 1 in 22 in the 1940s. Today, it is 1 in 7. There is no end to the theories as to why this risk has increased. "Endocrine disrupters" (chemicals that mimic hormones) are a likely suspect. They are wreaking havoc on wildlife and clearly affect brain cells in the developing embryo.[67] So far, however, studies have failed to show a link between breast cancer and blood levels of these chemicals. Still, they remain suspect—especially in combination with other factors.

Mainstream dogma is that exposure to estrogen causes breast cancer. By "estrogen," the mainstream means the body's own estrogens. This line of thinking always links variables (such as having/not having children or the age at which menopause occurs) to estrogen exposure and, hence, breast cancer risk. While this viewpoint appears to have some validity, a few things are wrong with it, including the thorny question of why, all of a sudden, exposure to something that has been a part of the human body for eons would cause cancer. It also skirts the question of why long-term use of birth control pills containing estrogens does not increase the risk of breast cancer.[68]

Genes are another possible explanation for breast cancer. This depressing theory implies that whether or not people get breast cancer is beyond their control and that nothing can be done about it, except having the breasts removed as a preventive measure.[69] New research may put an end to the notion that there is nothing a person can do about "bad genes."

"Bad genes" do not necessarily come from parents. Sometimes they come from the environment. Eighty-five percent of the "family risk" for breast cancer may come from something besides an inherited gene.[70] Moreover, it has now been discovered that there are genes that can modify "bad genes."[71,72] In other words, you may not have to live with "bad genes."

In addition, a new study shows that even if a person has a genetic predisposition toward breast cancer, the cancer does not

necessarily activate unless the person encounters something in the environment that activates it.[73] For some women, that "something" could be meat. For the first time, eating meat has been linked to genes and breast cancer.[73] Families tend to share not only genes but recipes as well, and it is becoming clear that what you eat may be more important than what you were born with.

In studies that search for the cause of breast cancer, certain things consistently emerge. One is that diets rich in vegetables, soy, and green tea reduce cancer risk, and diets rich in animal fats (especially from red meat) increase risk.[73-79] In a study from the Barbara Ann Karmanos Cancer Institute at Wayne State University in Detroit, beef, pork and vegetables accounted for 85% of the alterations to DNA in women, with meat causing damage and vegetables preventing it.[80] Damaged DNA lays the groundwork for cancer.

The case of red meat is interesting not only because cooking it creates carcinogens, but also because the use of hormone implants in cows (which dates back about 50 years) coincides with the beginning of a major increase in breast cancer in North America.[81] Countries with the highest rates of breast (and prostate) cancer also are the countries that allow such implants. North America's breast cancer rate is the world's highest—higher than all of South America and northern and southern Europe combined.[82] Australia and New Zealand, which allow hormones to be implanted in cattle, have similarly high rates of breast cancer. In Europe, such implants are banned.

It is not hard to figure out why. Cattle implants contain 17 beta-estradiol and other strong steroids, including synthetic estrogens. Cows are repeatedly implanted, and the implants are in the cows when they are slaughtered. Guidelines published by the US Department of Agriculture and the University of Nebraska advise implanting the strongest drug last, 70 days before slaughter.[83] The strongest implants last 90-120 days. Besides being in the cows at the time of slaughter, over time the hormones build up in fat.[84] Fifty percent of the hormones contained in a steak may be in the fat.[84] Neither the FDA nor the USDA monitors the use of hormone implants, or tests for residues in beef. Testing for the metabolites of estradiol alone would be a major undertaking, as there are more than a dozen such metabolites, and this is just one estrogen. Cows are given other hormones as well, including "male" hormones. Heifers are fed melengesterol acetate, a synthetic progesterone used for birth control and promoting rapid weight gain.

It has been demonstrated that a diet high in beef fat activates hormone-related genes.[85] Zeranol, a synthetic estrogen cow implant, causes breast cancer cells to grow in the test tube. The amount of Zeranol needed to cause this growth is 30 times less than the amount that the FDA deems to be safe.[86] A follow-up study being conducted at Ohio State University hopes to ascertain how much Zeranol ends up on the dinner plate and in the tissue of women with breast cancer.[87] The study, which began in 2002, is still in progress. Data from approximately 200 women have been collected and are being analyzed. This important study may shed some light on at least one hormone implant. Studies on the total amount of all hormones added to American beef have yet to be conducted.

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What Women May Consider After Breast Cancer

"Stop taking estrogen" are usually the first words out of a doctor's mouth after telling a woman that she has breast cancer. The estrogen that she is most likely to be taking is Premarin® or Prempro™drugs associated with a 300% increased risk of breast cancer.[88] Doctors equate Premarin® with estrogen, and estrogen with breast cancer. But hold on a minute—must a woman who has had breast cancer necessarily live the rest of her life in an estrogen-deficient state because one drug might have caused problems?

Not according to the research. In fact, a study from the Fred Hutchinson Cancer Research Center in Seattle showed a 50% reduction in the recurrence of breast cancer in women who used hormone replacement therapy, regardless of whether the therapy was oral, local, or both.[89] Doctors at Chicago's Rush-Presbyterian-St. Luke's Medical Center have argued for a change in viewpoint on the subject. Researchers at the MD Anderson Cancer Center in Houston have been examining the question for more than a decade,[90,91] and have found no compelling evidence against the use of hormone replacement therapy following breast cancer treatment.

In a study from the University of Texas Southwestern Medical Center in Dallas of 64 women with previous breast cancer—some of which was estrogen receptor positive—one case of recurrence and one case of new cancer in the other breast was reported after an average time on replacement therapy of 6 years and follow up of 12 years.[92] Researchers concluded that the use of hormone replacement therapy is not associated with increased breast cancer.

No large, long-term studies have been conducted, but two reports on all the smaller studies both state that there is no increased risk of recurrence or new cancer in the opposite breast—receptor positive or negative.[93,94]

Premarin® and Prempro™ do not appear to have the same propensity to promote breast cancer following treatment. A report from the University of California, Irvine, found 13 recurrences in 145 women taking Prempro™ for an average of 2.5 years after treatment for breast cancer.[95] Another report from South Africa had similar results. In 20 women taking Prempro™ and 4 taking tibolone (another hormone replacement drug), no recurrences were reported after three years of observation.[96] This contrasts sharply with the more than four times increased risk for breast cancer in women taking tibolone, and almost three times increased risk in women taking Prempro™, reported for women who have never been treated for breast cancer.[97]

At this time, no compelling published evidence exists to suggest that taking hormone replacement therapy after treatment for breast cancer increases the risk of recurrence or new cancer in the other breast. Some caveats should be noted, however. Large, long-term studies have not been conducted, and until they are, nothing is definite. Second, important differences exist between hormone replacement therapies. For example, in one study, the drug Prempro™ caused significant breast density in 40% of women; by contrast, oral low-dose estrogen caused it in 6%, and transdermal estrogen in 2%.98 Breast density increases the chance that a mammogram can be misread.

Another overlooked factor in these studies is that when women survive breast cancer, they change their habits. In one study, 77% reduced their consumption of meat, and 72% increased their intake of fruit and vegetables.[99] In another study, 64% started using dietary supplements, and almost all reported benefits.100 Women who have completed breast cancer treatment are seven times more likely to use alternative therapies, and if they are taking tamoxifen, they are even more likely to use alternative therapies to alleviate symptoms, with soy being a top choice.[101]

Might these changes in diet and lifestyle change a woman's risk/estrogen profile so that a xenoestrogen such as a hormone replacement drug might behave differently in her body? It is very likely, in view of scientific studies showing how various dietary factors modulate estrogen. In addition, breast cancer treatment may permanently alter the genes that respond to estrogen. Contradicting this, however, are short-term studies showing that breast cancer patients who take estrogen-suppressing drugs (aromatase inhibitors) have a reduced risk of cancer recurrence. None of these studies, however, looks at lifestyle modifications that could skew the findings. In other words, the women whose breast cancer did not recur when taking aromatase inhibitors could have made significant improvements in their diets that were not accounted for in these studies. These dietary changes, and not the estrogen-suppressing drug, could be responsible for the cancer not recurring.

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Labrix Clinical Services, Inc.

Provider News

Oct 6, 2010 5:34 AM

Hormonal Birth Control - The Big Picture

The previous two weeks newsletters covered the various forms of hormonal birth control and their mechanisms of action. This week the focus is on some of the impacts and outcomes that these forms of contraception may have on the health of your patients.

The prevention of unwanted pregnancy is very important for many women. Convenience and proven effectiveness mean hormonal birth control is used by millions of women in this country, often at the expense of optimal health. The synthetic progestins found in birth control pills, patches, and injections are very different from bio-identical progesterone that we often advocate using to oppose the proliferative effects of estrogen (treating estrogen dominance). Though these progestins bind to progesterone receptors, their actions in the body are remarkably different. Since the mechanism of action is to prevent ovulation (through inhibition of gonadotropins), there is no corpus luteum to produce progesterone. Women on hormonal birth control therefore have significantly reduced progesterone levels. Additionally, the progestin in the medication competes for receptors with progesterone, rendering what little progesterone that is present even less effective. The prevention of the luteinizing hormones and follicle stimulating hormones (LH/FSH) surge also lowers testosterone levels, which can affect metabolism, bone density and libido!

In addition to disruptions to the endocrine system, synthetic progestins increase the risk of several conditions including blood clots, migraines, cervical cancer, multiple vitamin and nutrient deficiencies and can alter the pH of the vagina which can increase susceptibility to infection. Oral contraceptives specifically deplete vitamin B6 and folic acid which can lead to depression and increase the risk of cancers. Zinc levels can be reduced while copper levels may rise which can also contribute to depression or symptoms of mood disorders. New research has also detected decreased levels of CoQ10, alpha tocopherol and overall antioxidant capacity in the serum of women using hormonal contraception compared to controls. These deficiencies may make women using these methods vulnerable to increased oxidative stress, and therefore, a host of degenerative and chronic diseases.

While we have had decades to study the effects of oral contraceptive hormones on the health of millions of women, the side effects of other delivery systems have only recently become available. The contraceptive patch delivers the estradiol and progestin transdermally and bypasses the liver. While this may decrease the overall liver strain (which is important for people with compromised liver function), it may result in an increase in the total amount of the hormone circulating in the body. For this reason, the contraceptive patch has implicated an increased risk of blood clots.

By knowing the risks and side effects associated with hormonal contraception, you can help your patients make informed, risk vs. benefit decisions about their reproductive health and support their bodies with the nutrients they may be missing!

Association between the Current Use of Low-Dose Oral Contraceptives and Cardiovascular Arterial Disease: A Meta-Analysis*. Jean-Patrice Baillargeon, Donna K. McClish, Paulina A. Essah, and John E. Nestler (2005). Journal of Clinical Endocrinology & Metabolism (The Endocrine Society) 90 (7):*

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Effects of oral, vaginal, and transdermal hormonal contraception on serum levels of coenzyme q(10), vitamin e, and total antioxidant activity*. Palan PR, Strube F, Letko J, Sadikovic A, Mikhail MS. Obstet Gynecol Int. 2010;2010. pii: 925635. Epub 2010 Aug 9.*

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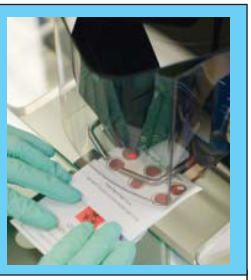
Looking to Learn More about the practicalities of saliva testing? Register for the next Labrix webinar on Wednesday October 6th at 10 a.m. PDT and hear detailed information about insurance billing, results interpretations, dosage windows and more.

PROVIDER DATA SHEET

About Blood Spot Testing

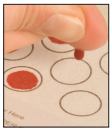


The Science of Blood Spot Testing

Blood spot and saliva are both now used for the minimally-invasive hormone testing that is the hallmark of ZRT Laboratory. Blood spot testing was originally developed in the 1960s out of a need to screen newborns for phenylketonuria (PKU), since a simple heelstick is more practical than a conventional blood draw in young infants. Later this was broadened to include tests for congenital hypothyroidism[1-4]. Today neonatal screening for PKU and thyroid deficiencies using blood spot tests is a routine procedure, and assays for a wide range of other analytes in blood spot have been successfully developed[5-15]. The simplicity of sample collection, stability of samples in storage and transport, and excellent correlation of blood spot assays with serum tests, have made it an ideal method for epidemiological and field research studies for a variety of health conditions in both children and adults[16].

The ability to measure accurately levels of steroid hormones in blood spots[17-21] has important implications for reproductive endocrinology, and also allows effective monitoring of hormone replacement therapy. This is of particular note for sublingual hormone users, for whom saliva testing is not optimal. Hormones held in the mouth as a troche or sublingual drops concentrate locally within the oral mucosa, which results in a higher local concentration in the saliva. This can result in "false high" salivary test results for up to 36 hours, depending on many factors responsible for clearing the locally concentrated hormone from the oral mucosa, including the ability to produce saliva, frequency and types of meals and beverages consumed, and toothbrushing. The blood spot assay circumvents this problem of "false-high" test results seen in saliva of sublingual hormone users because the capillary blood is taken from a site distal to the oral mucosa, the finger.

Blood spot testing has distinct advantages over conventional serum testing for monitoring topical hormone supplementation. Levels of steroid hormones produced endogenously are remarkably similar in venipuncture serum and finger stick capillary blood spots[21]. However, when hormones are delivered topically (transdermally, sublingually, or vaginally), capillary blood spot levels can be much higher than serum levels (ZRT internal data). Studies investigating tissue uptake of topically delivered hormones have also shown a striking discrepancy; high tissue hormone levels and much lower serum levels[22]. For example, topically delivered progesterone at a commonly used physiological dose results in high luteal phase levels of progesterone in capillary blood spots (20-40 ng/ml) and research shows that the same physiological dosing raises the tissue levels of progesterone to a very high luteal phase level (> 20 ng/g tissue)[22,23]. However, under these same conditions, venipuncture serum progesterone levels only increase marginally to sub-luteal levels (1-3 ng/ml). The same is seen with saliva versus serum levels, with much higher hormone levels seen in saliva[24]. This has led to the hypothesis that when hormones are delivered through the skin or oral or vaginal mucosa, conventional serum hormone tests grossly underestimate hormone delivery to tissues. In contrast, hormone levels in saliva or capillary blood spot better represent tissue hormone uptake. Using only serum test results to monitor topical progesterone supplementation has led to confusion and can result in over-dosing in an attempt to achieve physiological luteal levels of progesterone.



Blood Spot Collection

Collection of the blood spots is a relatively simple and nearly painless procedure that can be done at home or by the health care practitioner. A simple nick of the finger followed by placing blood drops on a filter card is all that is needed. The kit contains easy step-by-step instructions, skin cleansing wipes, two lancets, a filter paper on which the blood drops are collected, and a band-aid. The dry blood spot sample requires no special handling and is returned, together with a requisition form completed by the patient indicating any current hormone therapy and symptoms, to the laboratory for analysis in a pre-paid return package. Blood spot samples are collected in the morning before eating or drinking. Topical hormone users should use their hormones daily as usual but avoid applying the hormones with the hands for several days prior to collection.

Advantages

- Convenient for both patient and health care practitioner
- No phlebotomist, special preparation such as centrifugation of the blood, or special packaging and shipment required, therefore less expensive and more convenient than conventional blood draws
- Simple and convenient collection of blood at home allows for flexibility of testing at the right time of day or month or following hormone therapy
- Hormones and other analytes stable in dried blood spot at room temperature for weeks, allowing for greater latitude in collection and shipping
- Infectious agents such as HIV are inactivated by drying the blood thus allowing for safer transport and lab testing of the blood sample
- Familiarity of hormone test levels: ranges for hormones in blood spots nearly identical to ranges for conventional serum tests

Clinical Utility

Blood spot testing can help providers:

- Identify hormonal deficiencies or imbalances associated with aging and disease, thyroid dysfunction and symptoms of menopause and andropause
- Link clinical symptoms to specific hormone imbalances identified by the test
- Restore hormonal balance and patient quality of life using test results as a rational basis for treatment
- Monitor patient hormone levels for individualized, physiologic dosing of hormone supplementation
- Track patient progress with comparative history reports provided with follow-up testing

Customer Support

- ZRT's evaluation report includes test results, details of supplements and current symptoms reported by the patient, and ZRT analysis
- The report is returned to the patient or ordering healthcare provider in 5 – 7 business days and is also available via secure internet access
- ZRT staff physicians are available for enquiries without appointment, 8:00 a.m. to 5:00 p.m. weekdays

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PROVIDER DATA SHEET

About Saliva Testing

The Science of Saliva Testing

Estrogens (estrone, estradiol and estriol), progesterone, testosterone, DHEA-S and cortisol are routinely measured in saliva at ZRT. Why saliva? Steroid hormones in the bloodstream are mostly (95-99%) bound to carrier proteins (hormone-binding globulins, albumin), and in this form they are unavailable to target tissues. Only the unbound fraction freely diffuses into tissues, including the salivary gland. Hormone levels in saliva therefore represent the quantity of the hormone that is currently available to target tissues and actively exerting specific effects on the body. Because of this, salivary hormone levels often relate to specific symptoms of hormone excesses or deficiencies. Research at ZRT has demonstrated clear correlations between salivary hormone levels and reported symptoms. The rationale for and clinical utility of saliva testing is well documented[1-13].

The very small concentrations of salivary hormones (only 1 – 5% of the total hormone levels that include protein-bound hormone found in serum) necessitate extremely sensitive assay methods. This is a particular issue for estrogens, which are present in very minute quantities in saliva, especially in older populations such as postmenopausal women. ZRT is unique as the only commercial laboratory using extracted saliva testing for estrogens. Extraction removes contaminants that interfere with the assay and concentrates the sample, significantly improving assay sensitivity compared to the "direct" assay methods available commercially[14]. In fact, poor correlations between serum tests and non-extraction salivary estradiol assays have unfortunately led to some skepticism about saliva testing. Also, because of the extremely sensitive assays, it is important to avoid blood contamination of saliva as a result of oral injury, therefore toothbrushing must be avoided before collecting saliva for testing[15]. Saliva testing may also not be appropriate for sublingual hormone users unless samples are obtained at least 36 hours after the last dose. Blood spot testing is a preferred option for these patients.

Conversely, when some hormones, notably progesterone, are administered topically, saliva levels can rise higher than serum levels[16,17]. This is because progesterone is carried on the surface of red blood cells to target tissues including the salivary glands, where there is rapid uptake and release of the hormone into tissues and saliva, leaving very little hormone in the venous blood returning from the tissues[18]. Tissue levels of progesterone have been found to be very high after topical progesterone use[19-21], and a biological response can be demonstrated, e.g., the reduction of endometrial cell proliferation caused by estrogen therapy[22]. Serum testing for progesterone therefore grossly underestimates the amount of progesterone that is being delivered to tissues when progesterone is applied topically to the skin.

DHEA-S, the sulfated storage form of DHEA, is measured rather than DHEA because its levels are more stable (DHEA has a much shorter half life in blood) and at ZRT it has been found to correlate very well with reported clinical symptoms. However, as a conjugated hormone that does not diffuse into saliva as rapidly as the unconjugated hormones measured in ZRT's other hormone assays, its passage into saliva is flow rate dependent[12] and therefore flow stimulants such as gum chewing are not advised prior to saliva collection.

Research at ZRT shows good correlations between salivary hormone levels and dosages of hormones given exogenously. Saliva testing is therefore a good option for monitoring hormone therapy and adjusting dosages if necessary.

Advantages

- Saliva testing, unlike serum tests, measures the bioavailable ("free") levels of steroid hormones, correlating with symptomatology and potential deficiency
- Samples are collected by the patient at home, allowing convenient timing of collection especially for cortisol, which must be measured at specific times of the day or night
- Convenience of collection allows frequent sampling, e.g., during a menstrual cycle to determine fertility problems
- Hormone levels can be assessed during topical hormone supplementation
- Saliva collection avoids the stress of a blood draw, which can affect levels of cortisol
- Hormones are stable in saliva at room temperature for up to 2 weeks, allowing for worldwide shipment and convenient mailing of samples for testing
- Saliva testing is less expensive than conventional serum testing

Clinical Utility

Saliva Testing can help providers:

- Identify hormone imbalances prior to the appearance of symptoms or disease
- Identify specific hormone imbalances associated with symptoms
- Establish hormone baselines prior to surgery or beginning therapy
- Monitor hormone levels while supplementing, allowing for individualized hormone dosing
- Track patient symptoms and hormone levels using ZRT's comparative history reports provided with follow-up testing

Customer Support

- ZRT's Hormone Evaluation report includes hormone test results, details of hormone supplements and current symptoms reported by the patient, and ZRT analysis
- The report is returned to the patient or ordering healthcare provider in 5 – 7 business days and is also available via secure internet access
- ZRT staff physicians are available for enquiries without appointment, 8:00 a.m. to 5:00 p.m. weekdays

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PROVIDER DATA SHEET

Cortisol Testing for Adrenal Function

The Problem

People in today's society tend to lead frenetic, unbalanced lifestyles. Commonly, individuals experience continuous stress, not only from emotional stressors (e.g. marital, financial, and occupational) but also from physical stressors (e.g. sleep deprivation, caffeine consumption, pain, extreme exercise) without adequate recovery. Chronic exposure to these stressors often causes elevations in adrenal hormone levels, leading to disorders ranging from anxiety to infertility. While many individuals are able to cope, the adrenal glands may, over time, start to have an impaired response to stressors, which reduces adrenal hormone output. The resulting adrenal insufficiency, also known as "adrenal burnout" or "adrenal fatigue," may present with a constellation of symptoms from chronic fatigue to allergies. While everyone is potentially at risk, the problem is more prevalent among people with high-stress professions (e.g. medical professionals, police officers, executives and teachers).

Symptoms of Adrenal Dysfunction

- morning and/or evening fatigue
- allergies
- increased susceptibility to infection
- insomnia
- poor recovery from exercise
- apathy
- chemical sensitivity
- depressed mood
- unstable blood sugar
- low sex drive
- "burned out" feeling

Adrenal Function and Cortisol

The zona fasiculata of the adrenal cortex secretes approximately 15-20 mg of cortisol per day. Under the direction of the hypothalamus and pituitary and controlled by a negative feedback loop, the zona fasiculata is stimulated by adrenocorticotrophic hormone (ACTH) to produce cortisol in response to stressors. This feedback loop is commonly referred to as the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol has a wide range of effects on mind and body and interacts with the reproductive, thyroid and immunological systems. As part of the response to stress, it prepares the body for "fight or flight" and in doing so it can suppress the production of other hormones. This temporarily shuts down processes that would otherwise divert the body's resources away from its more immediate requirement to respond to the stressor, including processes involved with reproduction and some immune functions. Because of these effects, when cortisol levels remain chronically high, this suppression of other processes is maintained for longer than normal and this can result in susceptibility to infection, hypothyroidism, bone loss, and low libido. On the other hand, lower than normal cortisol levels are associated with decreasing attention span, fatigue, and blood sugar imbalances. Since both high and low cortisol levels are associated with multiple symptoms, cortisol testing often provides the answers to complicated health situations, which have led patients to visit multiple physicians without success. Successful diagnosis and treatment of the underlying problem improves patient symptoms, and cortisol testing provides an objective measurement of response to treatment. There are several good books and websites that discuss the relationship between adrenal function, cortisol levels and overall health, and some of these are listed under Useful Resources at the end of this sheet.

Blood Spot and Saliva Cortisol Testing

Salivary cortisol testing is an established method for the diagnosis of Cushing's Disease (hypercortisolism) and preferred over serum or urine testing because of its reliability, non-invasiveness and convenience of sampling[1]. In research on HPA axis function, salivary cortisol is also preferred to serum measurements as a reliable indicator of adrenal status because it represents the free, bioavailable hormone levels, excluding the cortisol-binding globulin (CBG)-bound hormone that circulates in the blood but does not pass into saliva[2-6]. The convenience of saliva collection and the avoidance of an anticipatory rise in cortisol levels caused by the stress of venipuncture has also been an advantage in research on adrenal function and depression in infants and children[7,8]. Saliva collection is ideal for multiple sampling over the course of a day and it is therefore the medium most commonly used in clinical studies of adrenal function, for example the study of job-related stress in professionals such as teachers[9,10].

Blood spot testing is also minimally-invasive, involving just a momentary finger-stick and collection of a few drops of blood on a filter paper. Blood spot cortisol levels have been found to correlate well with serum levels[11] and the blood spot test for morning cortisol gives an excellent snapshot of adrenal function without the stress and inconvenience of venipuncture serum collection.

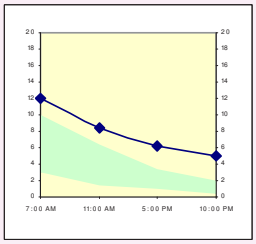
ZRT offers a single morning cortisol test in either saliva or blood spot, and this is included in all our multi-hormone profiles because of the interconnection of adrenal function with other hormone systems.

Because of the additional information to be gained by observing a patient's diurnal pattern, saliva tests are offered for twice a day sampling (morning and bedtime), or four times during a day (within one hour of waking, mid-day, evening and bedtime).

Diurnal Patterns of Cortisol Production

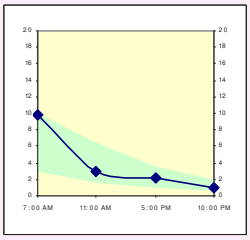
Cortisol production is normally at its highest upon waking and declines steadily during the day, reaching its lowest point at bedtime. Examples of some patterns that can be seen in various types of adrenal dysfunction are shown below, against a shaded area showing the normal range at each point during the day.

Chronically Elevated Cortisol



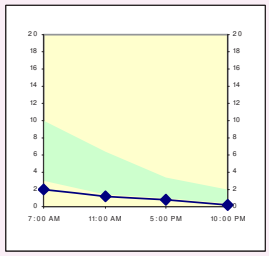
Chronic adrenal stress pattern – overall higher than normal cortisol production throughout the day

Steep Drop in Cortisol



Stress/fatigued pattern – morning cortisol in the high normal range or elevated, but levels drop off rapidly, indicating adrenal dysfunction

Adrenal Exhaustion



Adrenal fatigue/burnout pattern – morning cortisol surge is suppressed and overall diurnal pattern is flattened

(Examples courtesy of Rocky Mountain Analytical)

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Useful Resources:

James L. Wilson. Adrenal Fatigue: The 21st Century Stress Syndrome. Smart Publications; 2001.
www.adrenalfatigue.org

Shawn M. Talbott. The Cortisol Connection: Why Stress Makes You Fat And Ruins Your Health – And What You Can Do About It. Hunter House Inc.; 2002.

Cherie Carter-Scott. If Life Is A Game, These Are The Rules. Broadway Books; 1998.

Richard Shames, Karilee Shames. Feeling Fat, Fuzzy or Frazzled? A 3-Step Program to: Beat Hormone Havoc, Restore Thyroid, Adrenal, and Reproductive Balance, and Feel Better Fast! Hudson Street Press; 2005.
www.feelingfff.com

FEMALE Symptom Checklist

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ZRT Laboratory

Use each of the following checklists to determine your symptoms of hormone imbalance and to help you choose the appropriate hormone test profile.

Category 1: Basic Hormone Imbalance

Mark which of the following symptoms are troublesome and/or persist over time.

_____ Hot flashes
_____ Heart palpitations
_____ Heavy menses
_____ Fibrocystic breasts
_____ Thinning skin
_____ Mood swings (PMS)
_____ Cystic ovaries
_____ Foggy thinking
_____ Irritability
_____ Uterine fibroids
_____ Urinary incontinence
_____ Vaginal dryness
_____ Weight gain
_____ Increased body/facial hair
_____ Night sweats
_____ Acne
_____ Depressed mood
_____ Headaches
_____ Bone loss

Category 2: Adrenal Hormone Imbalance

Mark which of the following symptoms are troublesome and/or persist over time.

_____ Aches and pains
_____ Sleep disturbances
_____ Infertility
_____ Chronic illness
_____ Elevated triglycerides
_____ Depression
_____ Nervousness
_____ Evening fatigue
_____ Morning fatigue
_____ Anxiety
_____ Allergic conditions
_____ Susceptibility to infections
_____ Bone loss
_____ Blood sugar imbalance
_____ Autoimmune illness

Category 3: Thyroid Hormone Imbalance

Mark which of the following symptoms are troublesome and/or persist over time.

_____ Aches and pains
_____ Dry skin
_____ Fatigue
_____ Heart palpitations
_____ Constipation
_____ Anxiety
_____ Cold hands and feet
_____ Foggy thinking
_____ Low libido
_____ Thinning hair
_____ Brittle nails
_____ Headaches
_____ Weight gain
_____ Inability to lose weight
_____ Menstrual irregularities
_____ Depression
_____ Infertility
_____ Feeling cold all the time
_____ Sleep disturbances
_____ Elevated cholesterol

Category 4: Cardiometabolic Risk

Mark which of the following symptoms are troublesome and/or persist over time.

_____ Smoker
_____ High blood sugar
_____ High blood pressure
_____ Overweight or obese
_____ Weight gain
_____ Sugar cravings
_____ Fatigue
_____ Low physical activity
_____ Heart disease or family history of heart disease
_____ Diabetes or family history of diabetes
_____ Waist size greater than 35 inches

If you checked symptoms in <u>All four categories</u>, the suggested test profiles are:
GOOD: Female Blood Profile I (Blood Spot) or Female/Male Saliva Profile I (Saliva)
BEST: Comprehensive Female Profile I or II (Saliva/Blood Spot) and CardioMetabolic Profile I (Blood)

If you checked symptoms <u>ONLY in Category 1</u>, the suggested test profiles are:
GOOD: Female Blood Profile I (Blood Spot) or Female/Male Saliva Profile I (Saliva)
BEST: Comprehensive Female Profile I or II (Saliva/Blood Spot)

If you checked symptoms <u>ONLY in Category 2</u>, the suggested test profiles are:
GOOD: Diurnal Cortisol (Saliva)
BEST: Comprehensive Female Profile I or II (Saliva/Blood Spot)

If you checked symptoms <u>ONLY in Category 3</u>, the suggested test profiles are:
GOOD: Complete Thyroid Profile (Blood Spot)
BEST: Comprehensive Female Profile I or II (Saliva/Blood Spot)

If you checked symptoms <u>ONLY in Category 4</u>, the suggested test profiles are:
GOOD: CardioMetabolic Profile I (Blood) plus Diurnal Cortisol (Saliva)
BEST: CardioMetabolic Profile I (Blood) plus Female/Male Saliva Profile III (Saliva)

PATIENT HANDOUT

Vitamin D in Blood Spot

Vitamin D Deficiency – A Real Problem

Most people are familiar with vitamin D's role in preventing rickets in children and in helping the body absorb calcium from the diet. Recently, research has shown that vitamin D is important in protecting the body from a wide range of diseases. Disorders linked with vitamin D deficiency include stroke, cardiovascular disease, osteoporosis, osteomalacia, several forms of cancer, some autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, type I diabetes, type II diabetes, depression and even schizophrenia.

Vitamin D is actually a prohormone and not technically a vitamin: a vitamin is defined as a substance that is not made naturally by the body but must be supplied in the diet to maintain life processes. But in fact, we make most of our vitamin D by the action of ultraviolet light (sunlight) on the vitamin D originator that is found in our skin. We only get very small amounts of vitamin D from our diet, although increasingly it is added to foods eaten by children, in an attempt to prevent rickets in the population.

A major cause of deficiency is not getting enough sun. This is very common in northern climates where people don't spend much time outdoors, but even in countries near the equator, women in particular often have much of their skin area covered for cultural reasons, and the use of sunscreen also blocks the formation of vitamin D in the skin.

Vitamin D is metabolized by the liver to a storage form of the vitamin, which circulates in the blood until needed. Enzymes in the kidneys metabolize it further to form the highly active hormone that is involved in essential biochemical processes throughout the body.

Testing for vitamin D is therefore an important screening test, especially if you spend much of your time indoors, or live in a colder climate. The ZRT blood spot test measures both the natural form of Vitamin D (D3) as well as D2, the form that is used in many supplements. So testing can be used to monitor vitamin D supplementation to ensure you are getting the right amount for optimum health.

A useful website for more information about vitamin D is www.vitamindcouncil.org.

Who is at Risk?

The Elderly

Amounts of the vitamin D originator in the skin decrease with age, therefore elderly people are particularly prone to deficiency, and living in rest homes or becoming home-bound can limit exposure to sunshine. Muscle weakness and osteoporosis associated with vitamin D deficiency make the elderly more susceptible to falling and fracture risk and studies show that vitamin D supplementation may decrease the risk of fractures.

Dark-Skinned People

Because people with darker skin have higher levels of melanin which can block the action of sunlight on vitamin D originators, they may require much longer sunlight exposure than people who are fair skinned.

People with Limited Sunlight Exposure

People living at northern latitudes or who have limited sunlight exposure because of their working environment or cultural dress rules may have low vitamin D levels.

Musculoskeletal Pain Sufferers

People with symptoms of hypothyroidism, non-specific musculoskeletal pain, chronic low back pain, or fibromyalgia are frequently found to have low vitamin D levels and show clinical improvement after supplementation. Vitamin D screening is strongly recommended in people with muscle and joint pain.

Overweight or Obese People

Vitamin D can be locked up in the fat stores of obese people, who have been found to have lower levels of circulating vitamin D and are at risk of deficiency.

Breast-Fed Infants, and Children with Limited Sunlight Exposure

All children require adequate circulating vitamin D to prevent rickets. Dark-skinned children and those who spend much of the day inside daycare centers are at risk of deficiency, and breast-fed children often receive inadequate amounts of vitamin D, particularly when their mothers are deficient. Giving vitamin D supplements to the nursing mother or the use of cod liver oil or other vitamin D supplements in infants and children can reduce the risk of developing type I diabetes in childhood.

Vitamin D screening has been recommended as a routine part of the annual physical examination. **Deficiency does not have obvious symptoms, but increases your risk for more serious diseases.**

Advantages of a Simple Blood Spot Test

Whole blood is collected with a simple nick of the finger using the lancet provided in the collection kit. Blood drops are dropped on the filter card provided and allowed to dry. The lab measures the vitamin D in the dried blood spots, which correlate closely with conventional blood tests done in serum.

Your doctor has chosen this blood spot test because:

- It is less expensive and more convenient than going to a phlebotomist or clinic for a blood draw, and samples are simply mailed in for analysis requiring no special storage conditions
- It is suitable for babies and children, since heelstick is already used in routine neonatal screening and it's easy to collect a few extra drops of blood at the same time
- Collection is minimally-invasive and nearly painless

Clinical Utility

Blood spot testing of Vitamin D can help your doctor:

- Identify vitamin D deficiency as a potential cause of health problems – levels below 20 ng/mL indicate deficiency, while levels below 32 ng/mL are "low"; optimal levels are 32-100 ng/mL (research is ongoing to establish definitive recommendations)
- Recommend the right dose of vitamin D as a supplement and monitor your D levels during supplementation to ensure you have adequate levels without overdosing – toxicity may be expected at levels >150 ng/mL
- Recommend appropriate ways to safely increase sunlight exposure and modify your diet to include more vitamin D-containing foods and/or supplements
- Track treatment progress with follow-up testing

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Consumption of animal products, their nutrient components and postmenopausal circulating steroid hormone concentrations.

Brinkman MT, Baglietto L, Krishnan K, English DR, Severi G, Morris HA, Hopper JL, Giles GG.

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Abstract

BACKGROUND/OBJECTIVES: Little is known about nutritional factors that influence circulating concentrations of steroid hormones, which are consistently associated with risk of breast cancer for postmenopausal women. We aimed to investigate the association between consumption of animal products and the plasma concentrations of steroid hormones and sex hormone-binding globulin (SHBG).

SUBJECTS/METHODS: Cross-sectional analysis was conducted on plasma from 766 naturally postmenopausal women. We measured plasma concentrations of steroid hormones and SHBG, and estimated dietary intakes using a 121-item food frequency questionnaire. Log-transformed values of hormone concentrations were regressed on quartiles of intake of meat and dairy products among food items, and fats, proteins and cholesterol among nutrient intake.

RESULTS: Total red and fresh red meat consumption was negatively associated with SHBG levels (P for trend=0.04 and <0.01, respectively). Mean SHBG concentrations were approximately 8% and 13% lower for women in the highest quartile compared with the lowest quartile of total red and fresh red meat consumption, respectively. Positive associations were observed between dairy product consumption and total and free estradiol concentrations (P for trend=0.02 and 0.03, respectively). Mean concentrations of total and free estradiol were 15 and 14% higher for women in the highest quartile of dairy product consumption than for those in the lowest quartile, respectively. No associations were observed with consumption of processed meat, chicken, fish, eggs, cholesterol, fats or protein.

CONCLUSIONS: Our study suggests that greater consumption of total red and fresh red meat and dairy products might influence circulating concentrations of SHBG and estradiol, respectively. Confirmation and further investigation is required.

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Publication Types, MeSH Terms, Substances

Publication Types:

- Research Support, Non-U.S. Gov't

Full Text Sources:

- Nature Publishing Group
- EBSCO
- Ovid Technologies, Inc.
- Swets Information Services

Medical:

- Dietary Fats - MedlinePlus Health Information
- Dietary Proteins - MedlinePlus Health Information

Molecular Biology Databases:

- ESTRADIOL - HSDB

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Provider News

HPA Dysregulation by Dr Jay Mead at Labrix

Like many of the homeostatic systems in the body, cortisol levels and stress response are regulated by a region of the brain called the hypothalamus with a negative feedback loop. The hypothalamus acts as the "thermostat" of the body, regulating not only body temperature, but many other systems including blood pressure, metabolic rate, and hormone levels. Most of the actions of the hypothalamus are done through the pituitary, a "master gland" that sits just below the hypothalamus deep in our heads.

When the hypothalamus detects a fluctuation in an otherwise stable system, such as an increased demand on the body, it sets about a chain of events to increase the body's production of cortisol, a hormone that helps to deal with stress. The hypothalamus provokes the pituitary to produce a stimulating hormone ACTH (adrenocorticotropic hormone) that travels to the adrenal glands to encourage an increase in cortisol production. Once the cortisol levels have increased, there is a feedback loop that lets the hypothalamus and pituitary know to decrease their stimulation signal. The hypothalamus has cortisol receptors that when activated, decrease the ACTH signal and therefore lessen the cortisol levels.

We have previously discussed how chronic stress can result in elevated cortisol levels due to overstimulation of production, and also how prolonged stress can cause adrenal fatigue and depressed cortisol levels. Adrenal fatigue can occur when the adrenal glands are no longer able to respond to the increased demands of the pituitary and hypothalamus. But this isn't the only effect of prolonged stress. Chronic stress can also wreak havoc on the rest of the hypothalamic pituitary axis. Excess cortisol production can cause a down regulation of the cortisol receptors in the hypothalamus which blunts the negative feedback loop and handicaps the ability of the hypothalamus to detect sufficient cortisol levels. This results in continued and uncontrolled production of cortisol and leads invariably to hypoadrenia.

PATIENT HANDOUT

Facts On Hormone Balance Issues for Women

Menopause and Hormonal Imbalance

In the years leading up to menopause (perimenopause), menstrual cycles that may once have been like clockwork start to become erratic. Bleeding may be heavier or lighter than usual-although we are not officially in menopause until we have had 12 consecutive months without a period. Erratic cycles are a sign of erratic ovulation leading to highs and lows in estrogen and progesterone, an effect many women describe as an emotional roller coaster.

And don't let anyone tell you it's all in your head. When the ovaries begin to sputter, hormone production sputters and so do we…forgetfulness and foggy thinking, mental confusion and mood swings are hallmark symptoms for many women; as are hot flashes and night sweats, tearfulness, unwanted weight gain, thyroid problems and declining interest in sex, no matter how much we love our partner. Of course not all women experience these symptoms-as individuals we each have our very own biochemistry-but it is common to experience some degree of discomfort during the menopausal years. And the degree to which we experience discomfort is likely to be associated with the degree to which our hormones are out of balance.

If you are a woman experiencing menopausal symptoms, you will want to test at least two hormones: estradiol and progesterone. If you would like a more comprehensive picture, our five panel test measures estradiol, progesterone, testosterone, DHEAs and morning cortisol.

The Anatomy of a Hot Flash

Is it hot in here or is it just me? – is a common refrain among the estimated 50 to 75 percent of women in the U.S. who experience hot flashes during menopause. Hot flashes can be very mild, or bad enough to have you opening every window in the house, even in the dead of winter. Also known as "vasomotor flushing," the hot flash occurs when the blood vessels in the skin of the head and neck open more widely than usual, allowing more blood to shift into the area, creating the heat and redness. Perspiration is also common to the phenomena and in some women the hot flash takes the form of a night sweat, followed by a chill that has one groping for the covers kicked to the floor just minutes earlier. It's usually over in seconds, and there's no telling when it will recur-maybe minutes, maybe hours-but it will be back. Triggered by falling estrogen and rising levels of follicle stimulating hormone, hot flashes arrive unannounced, and usually at a most inconvenient time-in the middle of a job interview, in the middle of an important speech, in the middle of the night. Besides hormonal changes, anxiety and tension magnify hot flashes and many women find that hot drinks and wine do the same.

Saliva testing identifies the degree to which the specific hormones linked to hot flashes are out-of-whack. Using test results as a guideline, natural hormone supplements can be prescribed to restore balance and cool the hot flashes. Many women also use phyto(plant)estrogens, such as Dong Quai and Black Cohosh; optimal nutrition and relaxation exercises for added relief. In most cases, hot flashes usually go away a year or two after actual menopause and the cessation of menses.

"Tired but Wired" - Fatigue, Stress and Hormone Imbalance

Many people experience high levels of mental and emotional stress on a regular basis, which puts a significant strain on adrenal function. When stress is not well-managed, the ability of the adrenal glands to do their job becomes compromised. The adrenals normally secrete cortisol in response to stress, with exercise and excitement, and in reaction to low blood sugar. The body normally secretes the highest amount of cortisol in the morning to get us going, with levels decreasing throughout the day. People with adrenal imbalance will often have normal cortisol levels in the morning with below normal levels at other times during the day. If stress remains too high for a prolonged period, the adrenals can't keep up with demand and total cortisol output plummets, leading to adrenal exhaustion.

The hallmark symptoms of adrenal imbalance are stress and fatigue that is not alleviated with sleep-that "tired all the time" feeling. Other common symptoms include sleep disturbances, anxiety, depression, increased susceptibility to infections, reduced tolerance for stress, craving for sweets, allergies, chemical sensitivities and a tendency to feel cold.

Saliva testing charts the extent to which cortisol levels are out of balance, and can be used as part of a strategy that looks at the **whole** person and his or her lifestyle. It is helpful to work with a doctor who can design a complete program of hormone balance and then monitor your progress.

You can begin to support adrenal function on your own by avoiding hydrogenated fats, excess caffeine, refined carbohydrates, alcohol, and sugar. Get plenty of quality protein and eat regular meals of high nutritional value. Key to success is to discover and practice stress management in whatever form works for you personally. Take time out, evaluate the stressors in your life, and find ways of expressing yourself creatively. Get enough rest and sleep, and last but not least, keep a sense of humor!

Low Sex Drive (Libido) and Hormone Imbalance

Estrogen, progesterone and testosterone are key players in the maintenance of circulation, nerve transmission and cell division, so an imbalance of these hormones can easily lead to changes in sexual response. Declining estrogen levels common to the menopausal years can dampen nerve impulses during sex, making us less sensitive to vibration and touch. And since estrogens increase blood flow to sexually sensitive areas, decreased levels can slow or diminish the arousal response. Imbalances of estrogen and testosterone can cause dryness and thinning of vaginal tissue making intercourse uncomfortable or downright painful-an effect that does absolutely nothing for libido.

Key to a normal sex drive is the right balance of estrogen to progesterone. An excess blocks thyroid function which inhibits libido. A balance stabilizes mood and supports thyroid function which enhances libido. Significantly, progesterone is also a precursor to estrogen and testosterone so we need it in steady supply for optimal sexual pleasure.

Testosterone and DHEA also have a major impact on sex drive. Levels gradually decline in the years leading to menopause and can drop dramatically with hysterectomy, chemotherapy, surgery and radiation. If you have a low libido and have lost interest in sex, saliva testing to measure levels of estradiol, progesterone, testosterone and DHEA-s can establish probable cause and a rationale for correcting the imbalance.

Hormone Imbalance and PMS

PMS differs from all other disorders because the diagnosis does not depend on the type of symptoms you suffer from, but on the time when your symptoms appear and disappear. Dr. Katharina Dalton of the U.K., a leading specialist who first used the term "premenstrual syndrome" defines it as the presence of recurrent symptoms before menstruation with the complete absence of symptoms after menstruation. Doctors have identified at least 150 symptoms that occur in PMS but fortunately, because all of us are different, no one has all of them! Among the most common are bloating, headache, backaches, severe grouchiness, depression, breast tenderness, loss of libido and fatigue. Do these symptoms sound familiar? They are also the symptoms of estrogen dominance!

Katherine Dalton knew this back in the late 50s when she successfully pioneered the use of natural progesterone to balance estrogen in PMS patients. Over the years other U.S. physicians, like Dr. John Lee joined her in treating women this way. The great majority of patients report remarkable improvement in their PMS symptoms, including the elimination of premenstrual water retention and weight gain. Dr. Joel T. Hargrove of Vanderbilt University Medical Center published results indicating a 90 percent success rate in treating PMS with oral doses of natural progesterone. We know too, that topical progesterone creams are equally effective. This has to do with progesterone's potent balancing effect upon estrogen. Saliva testing can determine if your PMS is associated with estrogen dominance. Measure your saliva levels of estradiol and progesterone during days 19-21 of your cycle. A low progesterone/estradiol ratio on your test report indicates estrogen dominance and the likelihood of PMS symptoms. If this is the case, it is worthwhile to talk to your doctor about supplementing with natural progesterone to keep estrogen levels in check. To learn more read, PMS: The Essential Guide to Treatment Options by Dr. Katharina Dalton and What Your Doctor May Not Tell You About Menopause, by Dr. John Lee.

All About Natural (Bio-identical) Hormones

Natural or "bio-identical" hormones (BHRT) are synthesized from natural plant substances to be identical in structure and function to those our bodies produced naturally before menopause. When hormone production starts to drop below normal levels in the years leading up to menopause, natural hormones are the best and safest way for women to supplement. They are available through your doctor by prescription and tailormade to meet individual need by a compounding pharmacist. Some

natural hormones are available over-the-counter but it is always wise to do research first. Consult Dr. John Lee's books on pre-menopause and menopause for an approved list of creams.

Please note: Progesterone, **not progestin**, is the natural bio-identical form of the hormone as opposed to progestin, the synthetic version (the "pro" in Prempro). Natural progesterone is just like the progesterone your ovaries make; it is available in a topical cream, over-the counter, and by prescription when compounded with natural estrogens and other hormones by compounding pharmacists.

When hormone balance is restored and maintained using natural bio-identical hormones, there are far fewer side effects, symptoms and cancers as observed with synthetic HRT. Following natural physiology as closely as possible makes sense, because in a sense, natural hormones have undergone safety trials as long as humans have walked the earth.

What is Progesterone and Why Do We Need It?

Progesterone can be thought of as a hormonal balancer, particularly when it comes to the estrogens. Progesterone is a steroid hormone made by the corpus luteum of the ovary at ovulation, and in smaller amounts by the adrenal glands. It is the precursor, or substance from which most of the other steroid hormones are derived, including cortisol, androstenedione, the estrogens and testosterone. Progesterone has a remarkable repertoire of important jobs from normalizing blood sugar levels and facilitating thyroid hormone action to regulating menstrual cycles and maintaining a healthy pregnancy. The survival of the embryo in the womb absolutely depends on this vital hormone. Progesterone also has natural calming and diuretic properties, and it enhances the positive effects of estrogen, while preventing the problems associated with estrogen dominance.

Unopposed estrogen can build to unsafe tissue levels that can lead to a strong risk for breast cancer and reproductive cancers. While estrogen levels drop only 40-60%, at menopause progesterone levels may drop to near zero in some women, resulting in estrogen dominance and the array of symptoms that go with it. Supplementation of natural bio-identical progesterone has been shown to restore hormonal balance, especially during perimenopause and menopause.

Hormone Balance and Osteoporosis

Saliva testing can easily test for imbalances in each of the major hormones that have an impact upon bone health-particularly, testosterone, DHEA, cortisol, estrogen and progesterone. Bone is a hormonally sensitive tissue that is affected by age-related decline in production of these hormones. Many studies show as they age, both men and women begin to lose bone as the androgens-testosterone and DHEA-s in particular-start to fall off. And when these hormones are low and cortisol is high, bone loss increases at an even more rapid pace. We know that too much stress raises cortisol output, interfering with calcium absorption and bone-building activity, while at the same time stepping up the activity of bone destroying cells. We also know that cigarette smoking, alcohol intake and a lack of physical activity are associated with bone loss. In a typical case study from our files, a 63 year-old woman, who had never taken hormones since her menopause at age 51, had a bone density scan which revealed osteoporosis in her hip and spine. Saliva testing identified an imbalance of androgens, as well as low estrogen and progesterone levels. Supplementing with natural hormones brought noticeable improvement, but to gain full relief, a program of stress reduction, optimal nutrition and weight-bearing exercise was introduced.

Estrogen Dominance and Low Thyroid: Weight Gain and Depression

More than 10 million Americans have been diagnosed with thyroid disease, but interestingly, women are at greatest risk, developing thyroid problems seven times more often than men. Thyroid hormone regulates metabolic rate, so low levels tend to cause unwanted weight gain, depression, low energy and cold intolerance. Excess thyroid causes higher energy levels, a feeling of being too warm all the time and weight loss. But it's hypothyroidism or low thyroid that is most common in women during the perimenopausal and postmenopausal years; in fact, some 26% of women in or near menopause are diagnosed with hypothyroidism. In his book, What Your Doctor May Not Tell You About Menopause, Dr. John Lee discusses how, as he learned more about the condition of estrogen dominance, it became apparent that the taking of thyroid supplements among his women patients was especially common in those with estrogen dominance. This is because when estrogen is not counterbalanced with progesterone, the estrogen buildup blocks thyroid hormone creating hypothyroidism. Saliva hormone tests show that women who are estrogen dominant often have menopausal symptoms intertwined with low thyroid symptoms. The most common are weight gain or being unable to lose weight and depression. Cold intolerance, thinning hair, sleep disturbance, fatigue, mood swings and low sex drive are also associated with low thyroid. If you are suffering from these symptoms, estrogen dominance may be a factor that can be identified through saliva testing. Blood spot testing of the full Thyroid Panel (TSH, fT3, fT4, TPO) is recommended as a follow-up to estrogen dominance with low thyroid symptoms.

Depression and Mood Swings

Many women experience mood swings and depression as their hormones begin to fluctuate erratically in the perimenopausal years and then decline to even lower levels at menopause. Unfortunately, far too many women are put on anti-depressants when in fact, natural hormone supplementation to smooth out the roller coaster of waxing and waning hormones during these years may be all they need. All of the sex hormones, especially progesterone, estrogens and androgens have a potent effect upon state of mind, mood, and memory. So when they are out of balance (too high, too low, or up and down) as is not uncommon in mid-life, the effects can range from less than desirable to devastating.

Estrogen, the hormone that surges to highest levels in the first half of the menstrual cycle, has been shown to increase mood-enhancing beta-endorphins in menopausal women as well as in women who are still cycling. It is also known to boost serotonin and acetylcholine-the neurohormones associated with positive mood and memory. So a lack of estrogen can bring on tearfulness and anxiety. But an excess can also affect our mental state by holding sway over progesterone in the waning reproductive years. That's because as we age, we ovulate less frequently and when we do not ovulate, we do not produce progesterone. In this way we lose the inherent calming and mood-stabilizing effects of progesterone. We also lose its balancing power upon estrogen which then builds up, blocks thyroid action leading to low thyroid, and with it, depression.

The androgens, testosterone and DHEA also play an important role in mental outlook and vitality. So it's not surprising that many women find they are in much better spirits once they are put on natural hormone therapy. Hormone balancing is vital after a hysterectomy, as the removal of the ovaries shuts down all hormone production, forcing a woman into menopause overnight. One of the immediate consequences of the surgery is depression, which can be more safely alleviated by restoring hormone balance than by taking Prozac. Saliva testing to identify hormone imbalances linked to depression can serve as a basis for restoring balance, and with it a positive outlook on life.

Hormone Imbalance and Hysterectomy

A hysterectomy, with surgical removal of the uterus and/or the ovaries, results in a dramatic drop in hormone production. Overnight the main source of estrogen, progesterone and testosterone dries up, with dramatic short and long-term consequences. Among these: decreased bone and muscle mass, heart palpitations, vaginal dryness, reduced sex drive and depression. Most women go into instant, surgically-induced menopause following a hysterectomy and are usually placed on estrogen, unbalanced by adequate progesterone. In this case it doesn't take long for supplemented estrogen levels to lead to "estrogen dominance" the term coined by Dr. John Lee in his popular book, What Your Doctor May Not Tell You About Menopause. Symptoms of estrogen dominance in women (with or without hysterectomy) range from mood swings and irritability to heavy periods, tender breasts and weight gain. Long-term, too much estrogen can lead to low thyroid, fibroids and endometriosis, the latter two, ironically, constituting common cause for hysterectomy! Identifying estrogen dominance through saliva hormone testing and taking steps to correct the imbalance can prevent conditions leading to hysterectomy in the first place. Saliva testing is also important post- hysterectomy to pinpoint the extent of resulting hormonal deficiencies and monitor physician treatment to restore balance naturally.

Hormone Imbalance and Insulin Resistance

Insulin is a hormone produced in the pancreas that is responsible for carrying glucose (blood sugar) from the bloodstream into the cells where it is converted into fuel for body functions. Good health and energy depends upon the body's ability to make and use just the right amount of insulin to keep our blood sugar at optimal levels and our metabolism working normally. Every cell of the body has receptor sites that allow insulin to open the door of the cell so that glucose can enter and go to work. If the body builds up a surplus of glucose, usually from high caloric intake of sugar and carbohydrates that are not burned up through regular exercise, the cells become overloaded and cannot accept more blood sugar. The door is closed. The cells have in effect become resistant to insulin's attempt to provide them with more glucose. In this scenario, blood levels of insulin and glucose reach and remain at unnaturally high levels, leading to obesity, high blood fats and a heightened risk for diabetes. Blood spot testing of Fasting Insulin levels (using a nearly painless finger stick) to collect a few drops of blood which are then dried and mailed in to ZRT Lab, can detect excess insulin in the blood stream to provide an early warning system for prevention of insulin resistance and diabetes. Candidates for Fasting Insulin testing in blood spot include: individuals with known/suspected hypoglycemia, insulin resistance, pre-diabetes, family history of diabetes, overweight or obese, women with irregular menses, scalp hair loss, increased facial/body hair, polycystic ovary syndrome, individuals with symptoms of anxiety, palpitations, fatigue, profuse sweating, irritability, weakness, shakiness, dizziness, food and sugar cravings and central obesity. Early detection of insulin resistance through blood spot testing is the key to prevention of harmful changes in the body, leading to diabetes.

Labrix Clinical Services, Inc.

Provider News

A Must for the Bust!

Breasts are one of the most recognizable symbols of womanhood. Though their primary biological purpose may be for breastfeeding, they play a large role as a symbol of sexuality and for some even a source of power. Many women will empty their savings account and risk their lives to have "bigger and better" breasts, and breast augmentation has now surpassed liposuction to become the #1 cosmetic surgery in the country!

At the same time, breast cancer is now **the most common cancer affecting women**. In addition to the hundreds of thousands of women diagnosed with breast cancer each year, an estimated 1 million may be undiagnosed, due to lack of medical coverage and false negative or insufficient screening tests. The current likelihood of a woman developing breast cancer in her lifetime is approximately 1 in 8, yet our typical approach is only a defensive one...i.e. wait until the cancer occurs.

So what is the best way to protect our breasts? Recent discussion about recommended screening guidelines and confusion about hormone replacement therapies have left many practitioners and patients puzzled about the best approach to take. Sufficient screening is important, but we don't have to wait for cancer to show itself before we take action!

A simple breast health plan should incorporate the following three items at the very least:

D- **Vitamin D** deficiency is literally an epidemic, as an estimated 75-90% of the population has insufficient levels. Vitamin D binds to specific receptors in just about every cell in the body and modulates transcription of genetic material. The effects of vitamin D include the promotion of cellular differentiation and apoptosis (programmed cell death) as well as the down regulation of cellular proliferation.

I- Breast tissue is the second most concentrated place we should find iodine in the body. **Iodine** can regulate hormone metabolism as well induce apoptosis, disrupt proliferation and regulate differentiation. The average dietary intake of iodine in Japan is approximately 13.8 mg/day (compared with less than 1000 **micro**grams in this country)

and the Japanese have one of the lowest breast cancer rates in the world! Furthermore, iodine is one of the most effective treatments for breast pain and fibrocystic breast changes.

P- **Progesterone** is needed to balance the proliferative effects of estrogen and has been shown repeatedly in studies to decrease cellular proliferation of breast cells when given alone or in conjunction with estradiol. And yes, this effect is especially true in women with a history of "progesterone receptor positive" breast cancer!

Don't miss the DIP! Ensuring that your patients have adequate vitamin D, iodine and progesterone levels is imperative to the health of their breasts and can significantly reduce their risk of breast cancer. Progesterone levels, and more importantly the ratio of estradiol to progesterone (Pg/E2 ratio) are easily evaluated with salivary hormone testing. An iodine spot and 24 hour challenge test can assess whole body sufficiency for iodine and vitamin D is most effectively monitored in serum with a 25-OH Vitamin D3 assay.

PATIENT HANDOUT

Iodine Deficiency
The Basics

The Problem - Iodine Deficiency

Iodine deficiency is a worldwide health problem today. Some important current research indicates:

- Urinary iodine levels in the US today are about half what they were in the 1970s
- Some individuals are within the ranges considered by the World Health Organization (WHO) and the Centers for Disease Control (CDC) as mild and moderately deficient
- In 2004, the New England Journal of Medicine defined our iodine status in the US as "marginal," based on data acquired from the International Council for the Control of Iodine Deficiency Disorder and the World Health Organization (WHO)

Geographically, one-third of the world's population lives in iodine-deficient areas. The fact is that very little of the earth's iodine is found in top soils, and even where this mineral is present, it may remain tightly bound up in soil particles. This is the main reason why land vegetable crops are generally not good dietary sources of Iodine. Due to this, much of the world has addressed iodine deficiency by fortifying foods with iodine and providing iodized salt – but iodine deficiency clearly persists in populations, including in the US.

Iodine Impact

Because iodine is an essential element in the formation of thyroid hormones, low iodine levels are associated with low thyroid hormone production and enlargement of the thyroid gland (goiter) – as it attempts to maintain production of normal levels of thyroid hormones. The inverse side of the problem is that iodine is an essential nutrient that you can get in excess. So both excess iodine and iodine deficiency can impair thyroid function and lead to elevated thyroid-stimulating hormone (TSH) levels.

From Intake to Uptake - Who is at Risk?

Iodine deficiency may often be overlooked because the symptoms overlap with those of other illnesses, sometimes masking the problem. Women, in particular, may be at even greater risk. The 2004 National Health and Nutrition Survey helped dispel the assumption that iodine deficiency in women is a myth. Although there was some leveling off of the drop in overall intake, more than a third of women of childbearing age had insufficient iodine levels. From thyroid issues to breast concerns to cognitive function, this could have serious implications for women's short- and long-term health, as well as that of their children.

More and more researchers are saying that increasing the RDA would greatly benefit breast, thyroid, and nervous system health in women and infants. In the US, the recommended daily allowance (RDA) for iodine for adults is 150 mcg/day and 290 mcg/day for lactating women This RDA is well below the US Food and Nutrition Board's "upper limit of safety" for iodine (UL = 1,100 mcg).

Clinical Utility

In summary, iodine intake has decreased significantly over the past thirty years and consequently clinical symptoms have become apparent. Iodine is an essential element that is pivotal to normal function of the thyroid gland and the health and integrity of breast tissue.

Adequate iodine status is essential for the production of normal levels of thyroid hormones and the integrity of thyroid and mammary glands. Thyroid hormones regulate growth, metabolic rate, body heat, energy production, and neuronal and sexual development. Iodine is concentrated in the breasts where it is associated with protection against fibrocystic breast disease and cancer. Sub-clinical iodine/iodide deficiency has been associated with impaired mental function and loss of energy due to hypothyroidism.

Detecting Iodine Deficiency in Urine - Accuracy of the ZRT Iodine Test

A convenient way to test for iodine deficiency is to measure it in urine since more than 90 % is excreted. However, a problem with urinary iodine measurements has always been in the procedure for collecting it. With most tests, urine produced over 24-hours must be collected, which is logistically very difficult. Upwards of 40% of people who collect urine over 24-hours do not do it correctly and either miss collections or estimate the volume incorrectly.

ZRT has developed a new and simplified test for measuring iodine in urine. This method allows for testing relatively small amounts of urine that have that have been dried on FDA approved filter paper. This innovative and accurate method for detecting Iodine levels is easy to perform, and can be done at home.

With iodine playing so many different roles optimizing health and preventing disease, it is essential that adequate iodine intake is maintained and problems associated with excessive iodine intake are identified.

Progesterone Summaries

Progesterone Information | Progesterone Supplementation
Dosage of Progesterone

PROGESTERONE INFORMATION

Sixty years ago, progesterone was found to be the main hormone produced by the ovaries. Since it was necessary for fertility and for maintaining a healthy pregnancy, it was called the "pro-gestational hormone," and its name sometimes leads people to think that it isn't needed when you don't want to get pregnant. In fact, it is the most protective hormone the body produces, and the large amounts that are produced during pregnancy result from the developing baby's need for protection from the stressful environment. Normally, the brain contains a very high concentration of progesterone, reflecting its protective function for that most important organ. The thymus gland, the key organ of our immune system, is also profoundly dependent of progesterone.

In experiments, progesterone was found to be the basic hormone of adaptation and of resistance to stress. The adrenal glands use it to produce their antistress hormones, and when there is enough progesterone, they don't have to produce the potentially harmful cortisol. In a progesterone deficiency, we produce too much cortisol, and excessive cortisol causes osteoporosis, aging of the skin, damage to brain cells, and the accumulation of fat, especially on the back and abdomen.

Experiments have shown that progesterone relieves anxiety, improves memory, protects brain cells, and even prevents epileptic seizures. It promotes respiration, and has been used to correct emphysema. In the circulatory system, it prevents bulging veins by increasing the tone of blood vessels, and improves the efficiency of the heart. It reverses many of the signs of aging in the skin, and promotes healthy bone growth. It can relieve many types of arthritis, and helps a variety of immunological problems.

If progesterone is taken dissolved in vitamin E, it is absorbed very efficiently, and distributed quickly to all of the tissues. If a woman has ovaries, progesterone helps them to regulate themselves and their hormone production. It helps to restore normal functioning of the thyroid and other glands. If her ovaries have been removed, progesterone should be taken consistently to replace the lost supply. A progesterone deficiency has often been associated with increased susceptibility to cancer, and progesterone has been used to treat some types of cancer.

It is important to emphasize that progesterone is not just the hormone of pregnancy. To use it only "to protect the uterus" would be like telling a man he doesn't need testosterone if he doesn't plan to father children, except that progesterone is of far greater and more basic physiological significance than testosterone. While men do naturally produce progesterone, and can sometimes benefit from using it, it is not a male hormone. Some people get that impression, because some physicians recommend combining estrogen with either testosterone or progesterone, to protect against some of estrogen's side effects, but progesterone is the body's natural complement to estrogen.

Used alone, progesterone often makes it unnecessary to use estrogen for hot flashes or insomnia, or other symptoms of menopause.

When dissolved in vitamin E, progesterone begins entering the blood stream almost as soon as it contacts any membrane, such as the lips, tongue, gums, or palate, but when it is swallowed, it continues to be absorbed as part of the digestive process. When taken with food, its absorption occurs at the same rate as the digestion and absorption of the food.

PROGESTERONE SUPPLEMENTATION

SYMPTOMATIC: For tendonitis, bursitis, arthritis, sunburn, etc., progesterone in vitamin E can be applied locally after a little olive oil has been put on the skin to make it easier to spread the progesterone solution. For migraines, it has been taken orally just as the symptoms begin.

FOR PMS: The normal pattern of progesterone secretion during the month is for the ovaries to produce a large amount in the 2nd two weeks of the menstrual cycle, (i.e., day 14 through day 28) beginning at ovulation and ending around the beginning of menstruation, and then to produce little for the following two weeks. An average person produces about 30 milligrams daily during the 2nd two weeks. The solution I have used contains approximately 3 or 4 milligrams of progesterone per small drop. Three to four drops, or about 10 to 15 milligrams of progesterone, is often enough to bring the progesterone level up to normal. That amount can be taken days 14 through 28 of the menstrual cycle; this amount may be repeated once or twice during the day as needed to alleviate symptoms. Since an essential mechanism of progesterone's action involves its opposition to estrogen, smaller amounts are effective when estrogen production is low, and if estrogen is extremely high, even large supplements of progesterone will have no clear effect; in that case, it is essential to regulate estrogen metabolism, by improving the diet, correcting a thyroid deficiency, etc. (Unsaturated fat is antithyroid and synergizes with estrogen.)

PERIMENOPAUSAL: The symptoms and body changes leading up to menopause are associated with decreasing production of progesterone, at a time when estrogen may be at a lifetime high. The cyclic use of progesterone, two weeks on, two weeks off, will often keep the normal menstrual cycle going. Three to our drops, providing ten or twelve milligrams of progesterone, is typical for a day, but some women prefer to repeat that amount. Progesterone is always more effective when the diet contains adequate protein, and when thee isn't an excessive amount of unsaturated fat in the diet..

POSTMENOPAUSAL: Some women continue the cyclic use of progesterone ater menopause, because the pituitary gland and brain may continue to cycle long after menstruation has stopped, and progesterone is an important regulator of pituitary and brain function. The cycling pituitary affects the adrenal glands and other organs, and progesterone tends to protect against the unopposed actions of prolactin, cortisol, and adrenal androgenic hormones. Progesterone's effects on the pituitary apparently

contribute to its protective effect against osteoporosis, hypertension, hirsutism, etc. But some women prefer to use progesterone without interruption after the menopause, for its protective antistress effects. Slender people usually find that two or three drops are enough, but this amount may be repeated once or twice as needed to relieve symptoms. Adequate protein in the diet and good thyroid function help the body to produce its own progesterone; even if the ovaries have been removed, the adrenal glands and brain continue to produce progesterone.

DOSAGE OF PROGESTERONE

Since progesterone has none of the harmful side effects of other hormones (except for alteration of the menstrual cycle if it is taken at the wrong time of month), the basic procedure should be to use it in sufficient quantity to make the symptoms disappear, and to time its use so that menstrual cycles are not disrupted. This normally means using it only between ovulation and menstruation unless symptoms are sufficiently serious that a missed period is not important. The basic idea of giving enough to stop the symptoms can be refined by some information on a few of the factors that condition the need for progesterone.

If a person has an enlarged thyroid gland, progesterone promotes secretion and unloading of the stored “colloid,” and can bring on a temporary hyperthyroid state. This is a corrective process, and in itself isn't harmful. A thyroid supplement should be used to shrink the goiter before progesterone is given. Normal amounts of progesterone facilitate thyroid secretion, while a deficiency, with unopposed estrogen, causes the thyroid to enlarge. The production of euphoria has been mentioned as a side effect, but I think euphoria is simply an indication of a good physiological state. (The history of official medical attitudes toward euphoria is a subject that deserves more attention.) Very large doses that are given in vitamin E solution, allowing complete absorption, can reach the level that is sometimes achieved late in pregnancy, producing both euphoria and a degree of anesthesis. To avoid unexpected anesthesia, the correct dose should be determined by taking about 10 mg. at a time allowing it to spread into the membranes of the mouth, and repeating the dose after 10 minutes until the symptoms are controlled.

An excessive estrogen/progesterone ratio is more generally involved in producing or aggravating symptoms than either a simple excess of estrogen or a deficiency of progesterone, but even this ratio is conditioned by other factors, including age, diet, other steroids, thyroid, and other hormones. The relative estrogen excess seems to act by producing tissue hypoxia (as reported in my dissertation, University of Oregon, 1972), and this is the result of changes induced by estrogen in alveolar diffusion, peripheral vascular changes, and intracellular oxygen wastage.

Hypoxia in turn produces edema (as can be observed in the cornea when it is deprived of oxygen, as by a contact lens) and hypoglycemia (e.g., diminished ATP acts like insulin), because glycolysis must increase greatly for even a small deficiency of oxygen. Elevated blood lactic acid is one sign of tissue hypoxia. Edema, hypoglycemia, and lactic academia can also be produced by other “respiratory” defects, including

hypothyroidism, in which the tissue does not use enough oxygen. In hypoxia, the skin will be bluer (in thin places, such as around the eyes), than when low oxygen consumption is the main problem. Low thyroid is one cause of excess estrogen, and when high estrogen is combined with low thyroid, the skin looks relatively bloodless.

Symptoms in cycling women are most common around ovulation and in the premenstrual week, when the estrogen/progesterone ratio is normally highest. At puberty, in the early twenties and in the late thirties and menopause are the ages when the ratio is most often disturbed--and these are also the ages when thyroid disorders are commonest in women.

The individual who suffers from one aspect of the progesterone (and/or thyroid) deficiency will tend to develop other problems at different times. With cyclic depressions or migraine headaches at age 22, there will possibly be breast disease later, and often there will be problems with pregnancy. These people with a history of sever symptoms are the ones most likely to have severe problems around menopause. Prenatal exposure to poorly balanced hormones seems to predispose the child to later hormone problems.

Excess stress (which can block progesterone synthesis and elevate estrogen) may bring on symptoms in someone who never had them. Spending a summer in Alaska, with an unusually long day, may relieve the symptoms of a chronic sufferer. Dark cloudy winters in England or the Pacific Northwest are powerful stressors, and cause lower production of progesterone in women, and testosterone in men. Toxins can produce similar symptoms, as can nutritional deficiencies. A very common cause of an estrogen excess is a dietary protein deficiency--the liver simply cannot detoxify estrogen when it is under-nourished.

With a diet high in protein (e.g., at least 70-100 grams per day, including eggs) and vitamin A (not carotene), I have found that the dose of progesterone can be reduced each month. Using thyroid will usually reduce the amount of progesterone needed. Occasionally, a woman won't feel any effect even from 100 mg. of progesterone; I think this indicates that they need to use thyroid and diet, to normalize their estrogen, prolactin, and cortisol.

Progesterone stimulates the ovaries and adrenals to produce progesterone, and it also activates the thyroid, so one dose can sometimes have prolonged effects. It shouldn't be necessary to keep using progesterone indefinitely, unless the ovaries have been removed. In slender post-menopausal women, 10 mg. per day is usually enough to prevent progesterone deficiency symptoms.

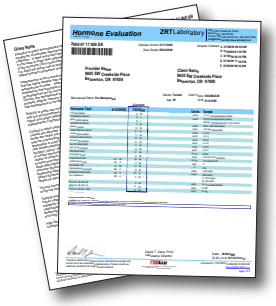
In a 10% solution of progesterone in vitamin E, one drop contains about three milligrams of progesterone. Normally, the body produces 10 to 20 milligrams per day. A dose of 3 or 4 drops usually brings the blood levels up to the normal range, but this dose can be repeated several times during the day if it is needed to control symptoms.

For general purposes, it is most economical and effective to take progesterone dissolved in vitamin E orally, for example taking a few drops on the lips and tongue, or rubbing it into the gums. (It is good for the general health of the gums.) These membranes are very thin, and the progesterone quickly enters the blood. When it is swallowed, the vitamin E allows it to be absorbed through the walls of the stomach and intestine, and it can be assimilated along with food, in the chylomicrons, permitting it to circulate in the blood to all of the organs before being processed by the liver. These droplets are smaller than red blood cells, and some physicians seem to forget that red blood cells pass freely through the liver.

For the topical treatment of sun damaged skin, or acne, wrinkles, etc. the oil can be applied directly to the affected area.

PATIENT HANDOUT

Understanding Hormone Highs and Lows



ESTROGENS (Estradiol, Estrone, Estriol) Estradiol is the most potent of the three natural estrogens, which also include estrone and estriol. Estrogens play important roles in stimulating growth of the reproductive tissues, maintaining healthy bones, increasing the levels of neurotransmitters in the brain, and helping keep the cardiovascular system healthy.

LOW ESTRADIOL in **premenopausal women** is unusual unless they experience an anovulatory cycle (no ovulation) or are supplementing with birth control pills, which can suppress endogenous (made in the body) production of estrogens by the ovaries. A low estradiol level is much more common in **postmenopausal women** or in women of any age who have had their ovaries surgically removed (oophorectomy) and/or those who have not been treated with hormone replacement. Symptoms and conditions commonly associated with estrogen deficiency include hot flashes, night sweats, sleep disturbances, foggy thinking, vaginal dryness, incontinence, thinning skin, bone loss, and heart palpitations.

HIGH ESTRADIOL in **premenopausal women** is usually caused by excessive production of androgens (testosterone and DHEA) by the ovaries and adrenal glands, which are converted to estrogens by the 'aromatase' enzyme found in adipose (fat) tissue, or, by estrogen replacement therapy (ERT). When estrogen levels are high in **postmenopausal women**, this is usually due to estrogen supplementation or slow clearance from the body (sluggish liver function). Excess estrogen levels, especially in combination with low progesterone, may lead to the symptoms of "estrogen dominance," including: mood swings, irritability, anxiety, water retention, fibrocystic breasts, weight gain in the hips, bleeding changes (due to overgrowth of the uterine lining and uterine fibroids) and thyroid deficiency. Estradiol, even at normal, premenopausal levels, can cause estrogen dominance symptoms if not balanced by adequate progesterone. Diet, exercise, nutritional supplements, cruciferous vegetable extracts, herbs and foods that are natural aromatase inhibitors and bioidentical progesterone can help to reduce the estrogen burden and symptoms, naturally.

PROGESTERONE is manufactured in the ovaries at about 10-30 mg of progesterone each day during the latter half of the menstrual cycle (luteal phase). Younger women with regular cycles generally make adequate progesterone, consistent with their having fewer symptoms of estrogen excess. Progesterone is important in normal menstrual cycles, breast development, maintaining pregnancy, relaxing blood vessels and influencing neurotransmitters in the brain.

LOW PROGESTERONE in **premenopausal women** is more commonly seen with anovulatory cycles, (no ovulation), luteal insufficiency (ovulation with low progesterone production), or use of contraceptives containing synthetic progestins. A lower level of progesterone is more common in **postmenopausal women** who no longer ovulate, who have had their ovaries removed, or use synthetic progestins in contraceptives or HRT (Provera). Synthetic progestins are not detected by the highly specific immunoassays used to quantify progesterone .

HIGH PROGESTERONE in normal **premenopausal and postmenopausal women** can occur with supplementation, exposure (e.g. anti-aging creams, transference from someone using progesterone), and/or sluggish metabolism. Transdermal (through the skin) progesterone is very well absorbed at physiological levels (10-30 mg/day). Progesterone results higher than the reference range can occur with topical doses greater than 30 mg. Note: a significant number of individuals in this range are without adverse symptoms, indicating that a high progesterone level is associated with few side effects. Symptoms of high progesterone are relatively benign and include excessive sleepiness, dizziness, bloating, susceptibility to yeast infections, and functional estrogen deficiency (more problematic when estradiol levels are low-low normal).

RATIO OF PROGESTERONE/ESTRADIOL - The ideal ratio of progesterone/estradiol ranges from 100-500 in **premenopausal and postmenopausal women** supplementing with progesterone. The ideal ratio is not useful in postmenopausal women with low estrogen levels and women on synthetic hormones; e.g. oral contraceptives or conventional hormone replacement therapy-HRT.

TESTOSTERONE is an anabolic hormone produced predominately by the ovaries in women and the testes in men, and to a lesser extent in the adrenal glands. It is essential for

creating energy, maintaining optimal brain function (memory), regulating the immune system, and building and maintaining the integrity of structural tissues such as skin, muscles, and bone. **Premenopausal** testosterone levels usually fall within the high-normal range and **postmenopausal** levels at low-normal range. In **men** testosterone levels peak in the teens and then fall throughout adulthood.

LOW TESTOSTERONE is most commonly caused by aging, removal of the ovaries or testes, suppression of ovarian and testicular production by stress hormones (cortisol), use of contraceptives and synthetic HRT, and/or damage to the ovaries, testes and adrenal glands by trauma, medications, or radiation therapies. Chronically low testosterone can cause loss of bone and/or muscle mass, erectile dysfunction, thinning skin, vaginal dryness, low libido, incontinence, fatigue, aches and pains, depression, and memory lapses.

HIGH TESTOSTERONE is usually the result of excessive production by the ovaries, testes and adrenal glands or supplementation with androgens (testosterone, DHEA). Slightly elevated testosterone (range 50-60 pg/ml) is often seen in **postmenopausal women** as they transition into menopause. High testosterone in **premenopausal women** is associated with polycystic ovarian syndrome (PCOS), which in turn is caused by insulin resistance/metabolic syndrome. Symptoms include loss of scalp hair, increased body and facial hair, acne, and oily skin. Supplementation with topical testosterone at doses in excess of levels produced by the ovaries (0.3-1 mg) or testes (5-10 mg) can raise testosterone to levels beyond physiological range.

DHEA is a testosterone precursor shown to have direct effects on the immune system independent of testosterone. DHEA and its sulfated form, DHEAS, are produced predominately by the adrenal glands. Youthful levels are at the high end of the range; levels decrease with age and are usually at the lower end of normal in healthy middle-aged individuals. Athletes tend to have higher than normal DHEAS levels. **Low DHEAS** can be caused by adrenal exhaustion and is commonly seen in accelerated aging and diseases such as cancer. **High DHEAS** is associated with insulin resistance/PCOS (polycystic ovaries) or DHEA supplementation.

CORTISOL is produced by the adrenal glands in response to stressors, both daily (e.g. waking up, low blood sugar) and unusual (e.g. emotional upset, infections, injury, surgery). Cortisol levels are highest in the morning, and then drop steadily throughout the day to their lowest point during sleep. Cortisol is essential in regulating and mobilizing the immune system against infections, and reducing inflammation. It helps to mobilize glucose, the primary energy source for the brain and maintain normal blood sugar levels. While normal levels of cortisol are essential for life and optimal functioning of other hormones, particularly thyroid hormone, chronically elevated levels can be detrimental to health. Stress and persistently elevated cortisol levels can contribute to premature aging and chronic illness.

LOW CORTISOL, particularly if low throughout the day indicates adrenal exhaustion, caused by some form of stressor, e.g. emotional stress, sleep deprivation, poor diet, nutrient deficiencies (particularly low vitamins C and B5), physical or chemical insults (chemo, radiation) or synthetic glucocorticoid medications that suppress cortisol production. Chronic stress depletes cortisol and is associated with symptoms of fatigue, allergies (immune dysfunction), chemical sensitivity, cold body temp, and sugar craving. Symptoms of thyroid deficiency can also stem from low cortisol. Adequate sleep, gentle exercise, meditation, proper diet (adequate protein), 'bioidentical' progesterone, adrenal extracts, herbal, and nutritional supplements are often helpful in correcting low cortisol (hypoadrenia).

HIGH CORTISOL suggests some form of adrenal stress (see above), supplementation with topical hydrocortisone or use of corticosteriod medication. Heightened cortisol production by the adrenal glands is a normal response to routine stress and essential for health; when stress is chronic and cortisol output remains high over a prolonged period (months/years), breakdown of normal tissues (muscle wasting, thinning of skin, bone loss) and immune suppression can result. Common symptoms of chronic high cortisol include sleep disturbances, fatigue, depression, weight gain in the waist, anxiety.

For more information and recommended reading please visit www.zrtlab.com.

Resources – Hormone Balance

Websites:

- Women's International Pharmacy - http://www.womensinternational.com/hormones.html
- ZRT Laboratories – www.zrtlab.com