

Functional Medicine University's Functional Diagnostic Medicine Training Program

INSIDER'S GUIDE

Interpretation and treatment: Female Hormonal Assessment

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<http://www.FunctionalMedicineUniversity.com>

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The Thinking Process

One of the primary differences between health professionals who practice functional diagnostic medicine and traditional global disease suppression medicine is the *reacquaintance* of the first two years of medical training as it relates to functional physiology and applied biochemistry.

As I share today's lesson on female hormone dysfunction, please be observant of the subtle yet critical underlying physiological and biochemical components of common symptom manifestation and disease entities.

The health professional who masters functional diagnostic medicine and its focus on biochemical and physiological function and dysfunction will be a unique position to unmask and uncover the key causes of most female disease entities.

No more having to depend on some cook-book approach to female health disorders but instead you will have the confidence to understand the hormonal physiology and biochemistry as it relates to a host of female health conditions and come up with a sound and scientifically grounded solution.

With that being said, let's begin with a quick review of the steroidal hormone profile and discuss the delicate yet intricate details of how hormones, androgens, biochemical precursors, enzymes and metabolites deviate from optimal to create hormonal dysfunction and eventually symptom expression and disease entities.

Sex steroids affect a wide array of functions in the body. All of these hormones are inter-dependent rather than functioning in isolation; hence a comprehensive evaluation is crucial toward an understanding of hormonal imbalance.

Furthermore, hormonal imbalances are not always clinically apparent, yet may be associated with a variety of clinically significant disorders.

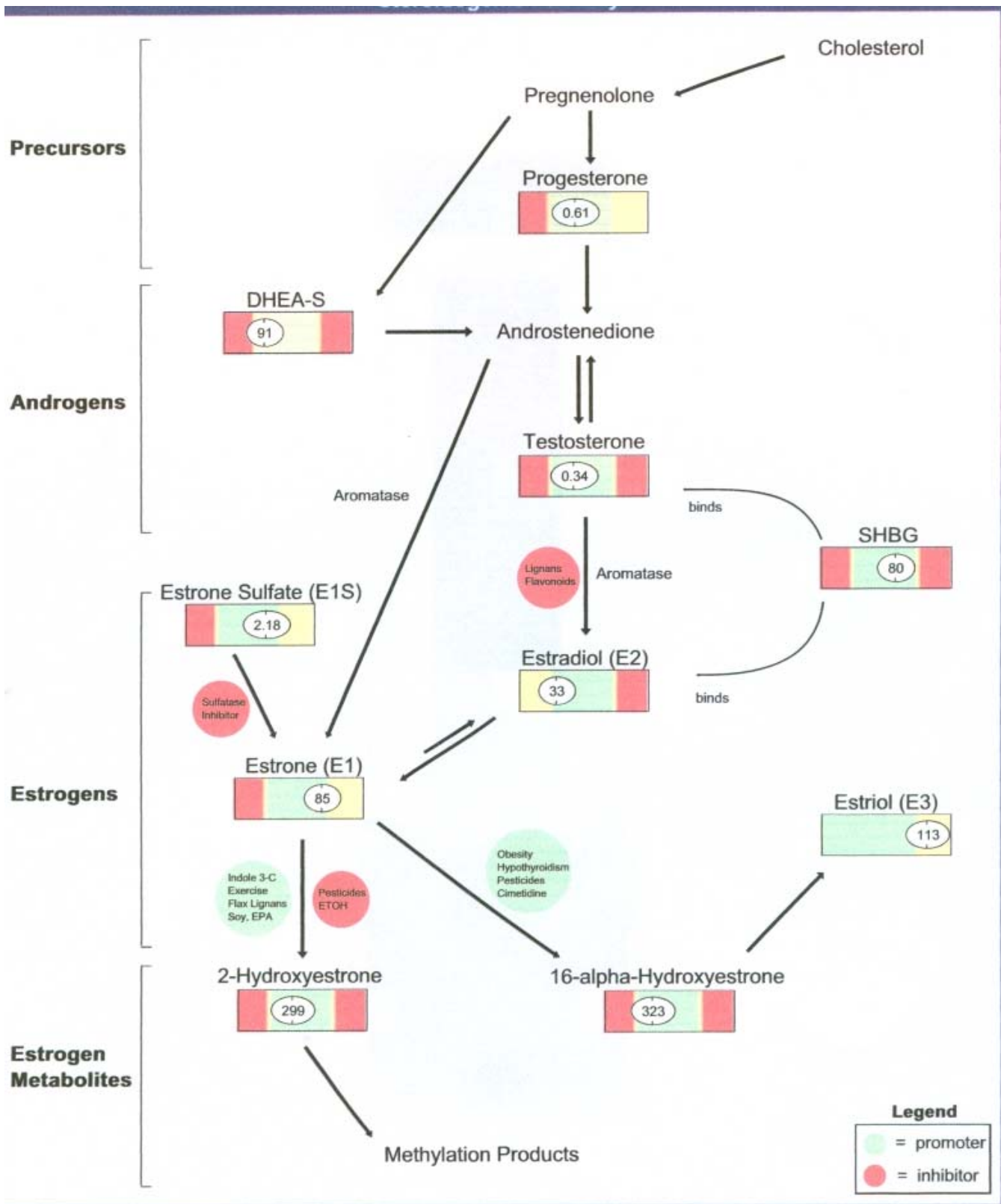
The Objective of the Female Hormone Profile

Sex steroids affect a wide array of functions in the body. All of these hormones are inter-dependent rather than functioning in isolation; hence a comprehensive evaluation is crucial toward an understanding of hormonal imbalance.

Furthermore, hormonal imbalances are not always clinically apparent, yet may be associated with a variety of clinically significant disorders.

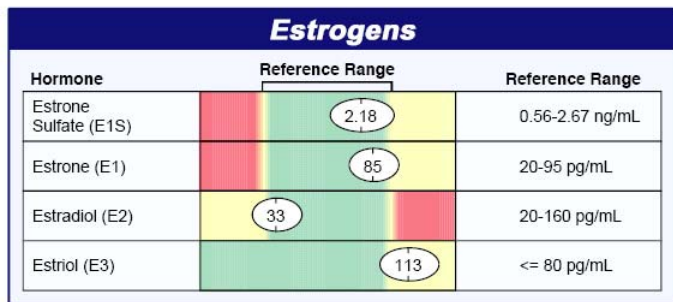
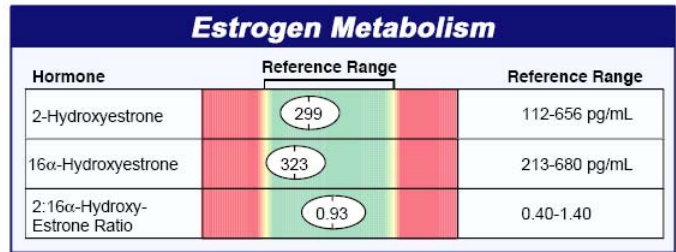
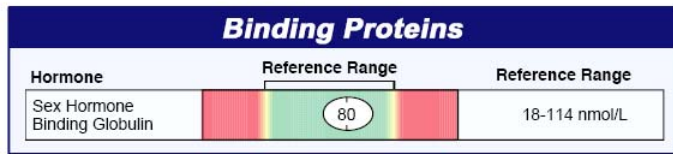
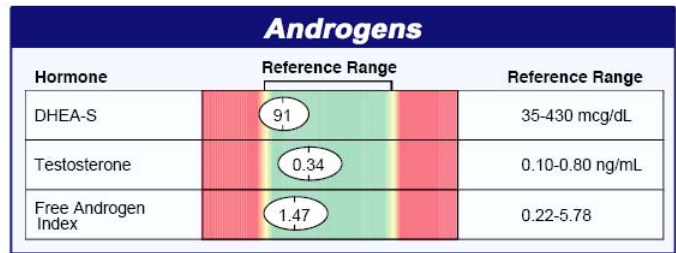
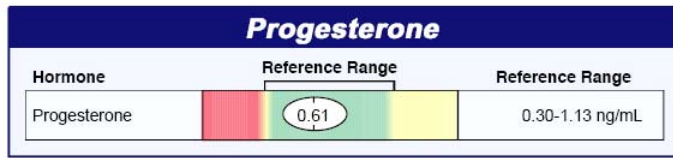
- Amenorrhea
- Galactorrhea
- Osteoporosis
- Menstrual irregularities
- Infertility / Miscarriage
- Cardiovascular Disease
- Ovarian cysts
- Breast Cancer

- Uterine fibroids
- Post-menopause Autoimmune Disease
- Endometrial Cancer
- Sexual dysfunction
- Hypo- or Hyperthyroidism
- Polycystic Ovarian Syndrome
- Vaginal Dryness
- Fibrocystic Breast Disease
- Incontinence



Genova- www.gdx.net

Serum Female Hormone Testing

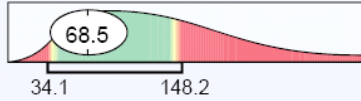


Salivary Female Hormone Testing

Sample #	Estrone (E1) (pmol/L)	Estradiol (E2) (pmol/L)	Estriol (E3) (pmol/L)	Progesterone (pmol/L)
1	8.6	6.30	112.0	722
2	12.2	4.80	109.0	588
3	6.1	9.32	89.0	618
Reference Range	4.7-18.9	3.66-9.38	<=132.9	163-669

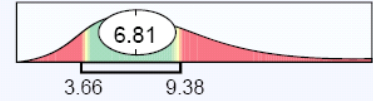
Testosterone

Ref Range
pmol/L



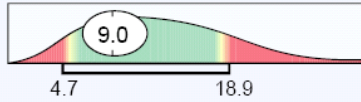
Average Estradiol

Ref Range
pmol/L



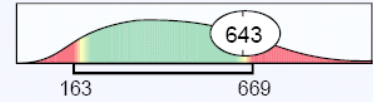
Average Estrone

Ref Range
pmol/L



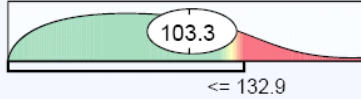
Average Progesterone

Ref Range
pmol/L



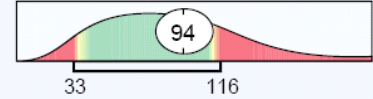
Average Estriol

Ref Range
pmol/L

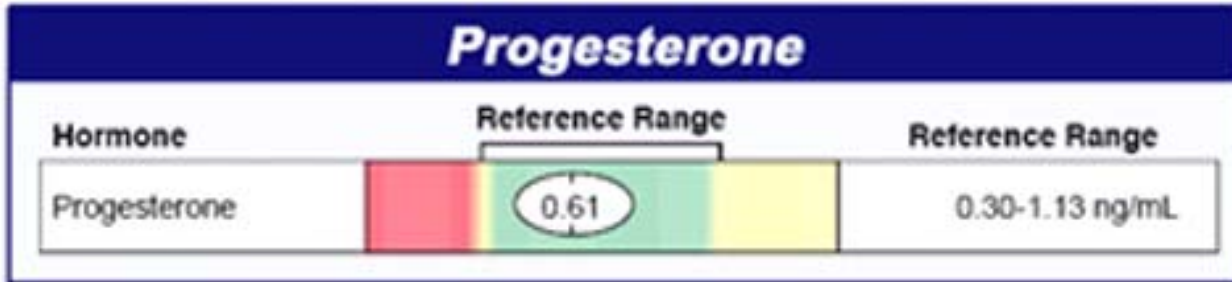


P/E2 Ratio

Ref Range
Ratio



Progesterone



Progesterone, like all other steroid hormones, is synthesized from pregnenolone, a derivative of cholesterol.

Progesterone is the precursor of the mineralocorticoid aldosterone, and after conversion to 17-hydroxyprogesterone (another natural progestogen) of cortisol and androstenedione. Androstenedione can be converted to testosterone, estrone and estradiol.

In women, progesterone levels are relatively low during the preovulatory phase of the menstrual cycle, rise after ovulation, and are elevated during the luteal phase.

The Functions of Progesterone

Besides its critical role in the physiology of reproduction, progesterone has other roles that play a major part in experiencing optimal health.

- ❑ Progesterone, like pregnenolone and dehydroepiandrosterone, belongs to the group of neurosteroids that are found in high concentrations in certain areas in the brain and are synthesized there. Neurosteroids affect synaptic functioning, are neuroprotective, and affect myelination. They are investigated for their potential to **improve memory and cognitive ability**.
- ❑ It raises epidermal growth factor-1 levels, a factor often used to induce proliferation, and used **to sustain cultures, of stem cells**.
- ❑ It increases core temperature (thermogenic function) during ovulation.
- ❑ It reduces spasm and relaxes smooth muscle. Bronchi are widened and mucus regulated. (Progesterone receptors are widely present in submucosal tissue.)

Smooth muscle is a type of non-striated muscle, found within the tunica media layer of large and small arteries and veins, the bladder, uterus, male and female reproductive tracts, gastrointestinal tract, respiratory tract, the ciliary muscle, and iris of the eye.

- ❑ It acts as an anti-inflammatory agent
- ❑ Regulates the immune response.
- ❑ It reduces gall-bladder activity.
- ❑ It normalizes blood clotting and vascular tone,
- ❑ It normalizes zinc and copper levels

- ❑ It normalizes cell oxygen levels
- ❑ It normalizes use of fat stores for energy.
- ❑ It assists in thyroid function, in bone building by osteoblasts, in bone, teeth, gums, joint, tendon, ligament and skin resilience and in some cases healing by regulating various types of collagen, and in nerve function and healing by regulating myelin.
- ❑ It appears to prevent endometrial cancer (involving the uterine lining) by regulating the effects of estrogen.

Since most progesterone in females is created the ovaries, the shutting down (whether by natural or chemical means), or removal, of those inevitably causes a considerable **reduction in progesterone levels.**

Low Progesterone

Underlying Cause

This is what you should be thinking about when you see low (depressed) levels of progesterone

1. Chronic stress, infection and inflammation causing steroid precursors to be **shunted toward cortisol/cortisone production.**
2. Natural aging process of decreased production via aging ovaries
3. Luteal insufficiency
4. Complete hysterectomy: no ovarian output of progesterone
5. Medication side effects causing depressed progesterone: ampicillin

Clinical Treatment Protocol

- Stress management, adrenal support
- Glandular hypothalamus, pituitary, adrenal and ovarian tissue
- Address infection or inflammatory condition
- Insufficient dosing for HRT management
- Use of synthetic progestins, e.g., Provera®.
- Chaste tree berries (*Vitex agnus-castus*) considered to help stimulate synthesis of
- Progesterone (may decrease androgen and estrogen synthesis)

Hormones Therapy

Progesterone

- Continuous therapy: 50 to 200 mg/day –oral, topical, or transdermal, customized to patient
- Cycling therapy: 200 to 400 mg for 10 to 14 days of cycle, if still cycling

Pregnenolone (as a precursor):

- 5 to 10 mg/day: oral capsule or percutaneous gel

Will Statins Compromise the Steroidal Pathway?

As we already know, cholesterol is the precursor of glucocorticoids, mineralocorticoids and sex steroids, besides being a structural component of the cell membrane. Both adrenal and non-adrenal (ovarian+testicular) all steroid hormones are primarily synthesized using the LDL-

cholesterol in the circulation. In addition to this, there is 'de novo' cholesterol synthesis in both the adrenals and gonads controlled by the HMG-CoA reductase enzyme. A third pathway, which under normal circumstances has little contribution as compared to the first two, is the use of circulatory HDL-cholesterol by the adrenal and gonadal tissues for the synthesis of steroids. Our knowledge on extremely lowered LDL levels is quite limited. However, since statins both decrease circulatory LDL and inhibit de novo cholesterol synthesis, they are likely to affect the synthesis of steroid hormones.

Abant Izzet Baysal Unuversity: Clinical Study

High Progesterone

Underlying Cause

This is what you should you be thinking about when you see high (elevated) levels of progesterone

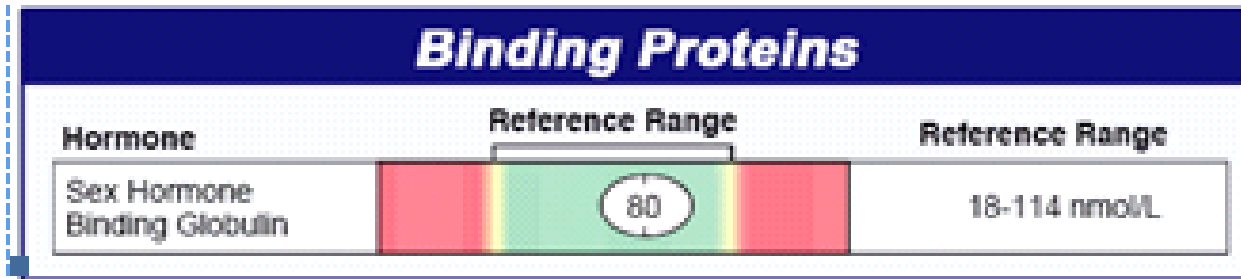
- Menopause
- Ovulatory/Luteal cycle (patient may still be in a peri-menopausal state)
- Adrenal hyperactivity
- Exogenous progesterone or pregnenolone supplementation
- Inhibitors of progesterone metabolism (e.g., ketoconazole, cimetidine, cigarette smoke, or glucocorticoids)

Clinical Treatment Protocol

Stress management, adrenal support, relaxant herbs, if relevant.

- Remove metabolic inhibitors
- Consider decreasing dosage of progesterone only if clinical picture and/or patient history warrants.
- Diindolylmethane (DIM) supplementation: By promoting 2-hydroxy production, diindolylmethane supplementation can help support progesterone production

Sex-Hormone Binding Globulin (SHBG)



Sex hormone-binding globulin (SHBG) is a glycoprotein that binds to sex hormones, specifically testosterone and estradiol. Other steroid hormones such as progesterone, cortisol, and other corticosteroids are bound by transcortin.

SHBG is produced by the liver cells and is released into the bloodstream. Other sites that produce SHBG are the **brain, uterus, and placenta and vagina**. In addition SHBG is produced by the **testes**; testes-produced SHBG is also called androgen-binding protein.

The SHBG inhibits the function of these hormones. Thus bioavailability of sex hormones is influenced by the level of SHBG.

SHBG levels appear to be controlled by a delicate balance of enhancing and inhibiting factors. Its level is decreased by high levels of insulin and insulin-like growth factor 1 (IGF-1). Also, **high androgen levels** (testosterone, dehydroepiandrosterone (DHEA), androstenedione, androstenediol, androsterone, dihydrotestosterone) decrease SHBG, while **high estrogen and thyroxine levels increase it**.

However, recent evidence suggests that it is the liver's production of fats that reduces SHBG levels.

Low SHBG Levels

Underlying Cause

This is what you should be thinking about when you see low (depressed) levels of SHBG

- Polycystic ovary syndrome
- Diabetes
- High body mass index
- Western-type diet
- Low estradiol
- Alcohol intake
- Hyperprolactinemia
- Oral testosterone or high levels of endogenous androgens
- Corticosteroids

- ❑ Meds: Danazol, glucocorticoids, insulin, Norplant®, norethindrone acetate (androgenic progestin)
- ❑ Hyperinsulinemia
- ❑ Hypothyroidism

Clinical Treatment Protocol

- ❑ Attention to relevant underlying disorders (e.g., normalize thyroid function, improve insulin sensitivity, reduce body mass index)
- ❑ SHBG may be increased with isoflavones, dietary fiber, flaxseed
- ❑ Switching from transdermal to oral estrogen generally raises SHBG level
- ❑ Be observant of medications noted for decreasing SHBG

Elevated SHBG Levels

Underlying Cause

This is what you should you be thinking about when you see high (elevated) levels of SHBG?

- Hypert thyroidism
- Thyroxine (T4) therapy
- Significant weight loss
- Smoking
- Caffeine
- Pregnancy
- Anorexia nervosa.
- Breast and testicular cancer
- High fiber diet
- Oral estrogens or high levels of endogenous estrogens
- Oral contraceptives
- Meds: tamoxifen, carbamazepine, clomiphene, anti-convulsants, phenytoin, and rifampin

Clinical Treatment Protocol

- Normalize thyroid function, if relevant.
- DHEA supplementation may reduce SHBG, at least in postmenopausal women
- Switching from oral to transdermal estrogen may reduce SHBG
- Conjugated equine estrogens are more potent stimulators of SHBG than bio-identical estrogen
- Oral androgens generally lower SHBG
- Be observant of medications noted for decreasing SHBG

Dehydroepiandrosterone sulfate (DHEA-S)

Dehydroepiandrosterone (DHEA) is a natural steroid hormone precursor (prohormone) produced from cholesterol by the adrenal glands, the gonads, adipose tissue, brain and in the skin. DHEA is the precursor of androstenedione, which can undergo further conversion to testosterone and the estrogens estrone and estradiol.

Low DHEA

Underlying Cause

This is what you should be thinking about when you see low (depressed) levels of DHEA

- Inflammation (TNF α activity)
- Smoking
- Meds: ketoconazole and anti-epileptics
- Depression
- High body mass index
- Impaired immunity
- Dyslipidemia
- Reduced insulin sensitivity
- Reduced bone mass
- Rheumatoid arthritis
- Lupus
- Chronic fatigue
- Cardiovascular disease

Clinical Treatment Protocol

- Stress management
- Adrenal support:
- Nutrition (e.g., vitamin C, pantothenic acid, B6, zinc, magnesium)
- Herbal adrenal adaptogens (Siberian or Panax ginseng, ashwaganda, etc. Avoid licorice when cortisol is high)
- Adrenal glandular
- Anti-inflammatory measures, if relevant
- DHEA supplementation

Elevated DHEA

Underlying Cause

This is what you should be thinking about when you see high (elevated) levels of DHEA

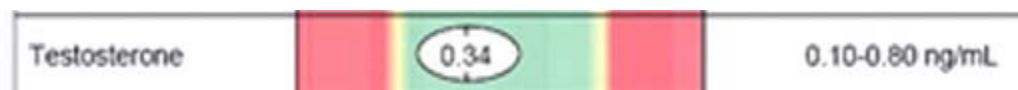
- Observed in PCOS (polycystic ovary syndrome)
- Insulin resistance with hirsutism
- Acute stress
- Adrenal hyperplasia or Cushing's syndrome
- Hyperprolactinemia
- DHEA supplementation
- Meds: clomiphene

High DHEAS may result in **testosterone excess in women.

Clinical Treatment Protocol

- Stress management, if relevant
- Address PCOS and/or hyperinsulinism (e.g., weight reduction, exercise, reduce carbohydrates and hydrogenated fats, chromium, zinc, magnesium, alpha lipoic acid, fish oils, meds such as metformin or pioglitazone)

Testosterone



In both men and women, testosterone plays a key role in health and well-being as well as in sexual functioning. Examples include enhanced libido, increased energy, increased lean muscle mass, increased production of red blood cells and protection against osteoporosis.

Low Testosterone

Underlying Cause

This is what you should be thinking about when you see low (depressed) levels of testosterone

- ❑ Ovarian or adrenal insufficiency (check DHEAS level)/pregenolone steal. (adrenal glands should compensate for reduced ovarian function by providing precursors for the sex hormones)
- ❑ The enzyme aromatase converts testosterone into estradiol. With high aromatase activity you will likely see higher estradiol (E2) levels. The following have been found to increase aromatase activity: alcohol; glucocorticoids, inflammation, glycerhiza; hypothalamic or pituitary insufficiency, inflammatory conditions (**TNF α inhibits production of its precursor, DHEA**).
- ❑ Meds: ketoconazole, fluconazole, digoxin, danazol, glucocorticoids, nafarelin, spironolactone, thioridazine, phenothiazines, troglitazone, oral contraceptives, THC, or licorice (suppressed production).
- ❑ High sex hormone-binding globulin (SHBG), resulting in reduced “free” estradiol (common causes may include hyperthyroidism, low insulin, smoking, high amounts of caffeine or flaxseed).

Clinical Treatment Protocol

- ❑ Glandular supplementation (e.g., hypothalamus, pituitary, ovarian, adrenal)
- ❑ Address infection or inflammatory condition (tumor necrosis factor alpha /TNF α reduced by fish oils, nettle leaf, green tea, ginkgo biloba, N-acetyl cysteine, and Eleuthrococcus, abdominal fat reduction)
- ❑ Rule out aromatase stimulation
- ❑ Consider aromatase inhibitors if E2 and E1 are high (e.g., chrysin, flavonoids, phytoestrogens, flaxseed, procyanidins in grape seed and red wine, progesterone (inhibits cortisol-induced aromatase induction), non-steroidal aromatase inhibitors, e.g., anastrozole (Arimidex)
- ❑ Testosterone or DHEA supplementation (also reduces SHBG, thus increasing bioavailable testosterone)

- ❑ Testosterone-enhancing herbs (e.g., Stinging nettle, Siberian or Korean ginseng, ashwaganda, Tribulus terrestris, horny goat weed)

Elevated Testosterone

Underlying cause

This is what you should be thinking when you see high (elevated) levels of testosterone

- ❑ Ovarian (primarily) or adrenal hyperactivity (refer to DHEAS)
- ❑ May be related to PCOS and/or insulin resistance
- ❑ Abdominal obesity
- ❑ DHEA supplementation
- ❑ Aromatase inhibition (e.g., smoking, chrysin, flavonoids, ketoconazole, oxidative stress)
- ❑ Meds: barbiturates, cimetidine, clomiphene, estrogens, rifampin, phenytoin
- ❑ Gonadotropin stimulation of ovary in perimenopause (may lead to spikes in testosterone)
- ❑ Low sex hormone-binding globulin (SHBG), resulting in high amounts of “free” estradiol. (common causes may include hypothyroidism, high BMI, excessive insulin)

Clinical Treatment Protocol

- ❑ Rule out testosterone-raising drugs or aromatase inhibition
- ❑ Aromatase may be enhanced by boron, vitamin D3, diindolylmethane (DIM), licorice
- ❑ Consider reducing dietary protein or fat, increasing exercise
- ❑ Increase SHBG to reduce bioavailable testosterone (e.g., isoflavones, dietary fiber, flaxseed, oral estrogens)

Estrogens

Hormone	Reference Range	Reference Range
Estrone Sulfate (E1S)	2.18	0.56-2.67 ng/mL
Estrone (E1)	85	20-95 pg/mL
Estradiol (E2)	33	20-160 pg/mL
Estriol (E3)	113	<= 80 pg/mL

Estradiol, like other steroids, is derived from cholesterol. The androgen, androstenedione, is the key intermediary. A fraction of the [androstenedione](#) is converted to testosterone, which in turn undergoes conversion to estradiol by an enzyme called aromatase. Alternatively, androstenedione is "aromatized" to estrone, which is subsequently converted to estradiol.

Functions of Estradiol

- Supports the lining of the vagina, the cervical glands, the endometrium and the lining of the fallopian tubes
- Has a profound effect on bone. Estrogen deficient women have been found to experience an accelerated loss of bone mass.
- Has intricate effect on the liver and can lead to cholestasis.
- Affects the production of multiple proteins including lipoproteins, binding proteins, and proteins responsible for blood clotting.
- Have been found to have neuroprotective function.
- Considered to play a significant role in women's mental health.
- Improves arterial blood flow (coronary arteries)

Low Estradiol

Underlying Cause

This is what you should be thinking when you see low (depressed) levels of estradiol

- Adrenal insufficiency (adrenal glands should compensate for reduced ovarian function by providing precursors for the sex hormones)

- ❑ Low BMI (less conversion from androgens)
- ❑ Chronic stress (precursors shunted to production of stress hormone or inhibitory HPA feedback loops)
- ❑ Hypothalamic or pituitary insufficiency
- ❑ Chronic inflammation/Pregnenolone steal
- ❑ Decreased conversion from androgens (check for high testosterone) (e.g., smoking, chrysin, flavonoids, ketoconazole)
- ❑ High sex hormone-binding globulin (SHBG), resulting in reduced “free” estradiol. (common causes may include hyperthyroidism, low insulin, smoking, high amounts of caffeine or flaxseed).
- ❑ Meds: ketoconazole, oral contraceptives (including recent use), megestrol, cimetidine

Clinical Treatment Protocol

- ❑ If testosterone is elevated, rule out aromatase inhibition (e.g., smoking, chrysin, flavonoids, ketoconazole). Aromatase activity enhanced with boron, vitamin D3, licorice.
- ❑ Consider estrogen replacement Note: Oral ERT (less so with transdermal) usually increases SHBG, thus reducing bioavailable testosterone
- ❑ Common herbs with estrogen-like activity include red clover, pomegranate, fennel, sage, hops, black cohosh, licorice, panax ginseng, fennel, anise
- ❑ A high-grade multiple vitamin/mineral formula to support steroidogenesis
- ❑ Boron supplementation, to help activate estrogen
- ❑ Glandulars: (Ovarian, pituitary and adrenal tissue)
- ❑ DHEA: As a precursor, DHEA supplementation may result in an increase in any of the androgens or estrogens.
- ❑ Pregnenolone: As a precursor, pregnenolone supplementation may result in increases in any of the adrenal or gonadal steroids, including estradiol, so individual results must be monitored

Elevated Estradio

Underlying Cause

This is what you should be thinking when you see high (elevated) levels of estradiol

- Ovarian and/or adrenal dysfunction
- Excessive aromatization
- Excessive estrogen affects PMS, ovarian cysts, fibroids, menstrual irregularities, and breast cancer.
- Perimenopause (estrogen may still be at premenopausal levels)
- Estrogen (E2 or E1) or androgen supplementation
- Low sex hormone-binding globulin (SHBG), resulting in high amounts of “free” estradiol. (common causes include hypothyroidism, high BMI, excessive insulin).
- Decreased hepatic clearance of estrogen.
- High intestinal beta-glucuronidase activity (increased reuptake of estrogen)
- Hypothyroidism
- Smoking (higher E2 levels)
- Meds: clomiphene, tamoxifen
- Inflammation (cytokines increase conversion of E1 to E2)

Clinical Treatment Protocol

- Promote hepatic clearance (e.g., lipotropic factors, dandelion, milk thistle, picrorrhiza broad-spectrum nutrition)
- Calcium D-Glucarate: To decrease beta-glucuronidase activity in the bowel and promote estradiol detoxification
- Reduce excess weight
- Increase exercise
- Increase dietary fiber (reduces enterohepatic reuptake of estrogen)
- Stress management, adrenal support
- If testosterone is low, aromatase activity can be reduced with chrysin, flavonoids, phytoestrogens (esp. genestein), flaxseed (enterolactone), procyanidins in grape seed and red wine, progesterone (inhibits cortisol-induced aromatase induction)
- Stimulate SHBG, if low (Note: will lower bioavailable testosterone)
- Phytoestrogens (e.g., soy isoflavones) act as weak antagonists to estrogen when levels are high
- Consider progesterone supplementation
- Cruciferous vegetables: constituents such as indole 3-carbinol or diindolylmethane help with metabolism and detoxification of steroids

Estrone

Estrone is one of the three estrogens, which also include estriol and estradiol. **Estrone** is the least abundant of the three hormones, estradiol is present almost always in the reproductive female body, and estriol is abundant primarily during pregnancy.

Estrone is relevant to health and disease states because of its conversion to estrone sulfate, a long-lived derivative. Estrone sulfate acts as a **reservoir of estrone** which can be converted as needed to the more active estradiol.

Estrone is the only one of the three estrogens which is present in any quantity in post-menopausal women.

Estrone is synthesized via aromatase from androstenedione, a derivative of progesterone.

Low Estrone

Underlying Cause

This is what you should be thinking when you see low (depressed) levels of estrone

- Low ovarian and/or adrenal function
- Inhibition of aromatase enzymes

Clinical Treatment Protocol

- Support ovarian function with botanicals, glandulars
- Check for adrenal hypofunction
- Check for use of medications/supplements affecting aromatase activity

Elevated Estrone

Underlying Cause

This is what you should be thinking when you see high (elevated) levels of estrone

- ❑ Increased conversion from estradiol or exogenous supplementation
- ❑ Excessive aromatization, due to increased Body Mass Index (BMI)
- ❑ Impaired detoxication of estradiol

Clinical Treatment

- ❑ Support with indole-3-carbinol or diindolylmethane
 - Sources include cruciferous vegetables (eg. broccoli, Brussels sprouts, cabbage) and dietary supplements
- ❑ Support with flavonoids and lignans
 - •Sources include flaxseed, whole grains, beans, and seeds. These substances may decrease conversion of androstenedione to estrone

Estriol

Low Estriol

Underlying Cause

This is what you should be thinking when you see low (depressed) levels of estriol

- ❑ Reduced conversion from 16 α -hydroxyestrone (check level)
- ❑ Meds: ampicillin, penicillin, aspirin, probenecid, thyroxine, albuterol (although most effects seen only in pregnancy)
- ❑ Low E3 results in higher net estrogen activity in body (if E1 and/or E2 are higher)

Clinical Treatment Protocol

- ❑ Any intervention should be based on levels of 16 α -hydroxyestrone and the other estrogens

Elevated Estriol

Underlying Cause

This is what you should be thinking when you see high (elevated) levels of estriol

- ❑ Generally results in lower net estrogen activity in body (competitive antagonist to E1 and E2)
- ❑ Enhanced conversion from 16 α -OHE1 (protective effect on breast CA risk); OR associated with high level of 16 α -OHE1 (increased breast CA risk)—

The Significance of Estrogen Metabolism

A growing body of research reveals that it is not simply the amount of total estrogen circulating in a woman's body that is critical to her health. How estrogen is broken down, or metabolized, in the body may also play an important role in the pathogenesis of a wide variety of estrogen-dependent conditions—including osteoporosis, autoimmune disorders, and certain cancers.

Two competing pathways represent a critical "fork in the road" in estrogen metabolism.

In the dominant pathway, estrogen is metabolized into 2-hydroxyestrone, an inactive, possibly anti-estrogenic metabolite. 2-hydroxyestrone (or 2OHE1, for short) is sometimes called the "good" estrogen.

This is because 2OHE1 is not likely to stimulate cell division in target tissues; thus, it is not likely to promote the proliferation of cells in the breast or endometrium, a process linked to DNA damage and tumor growth.

Moreover, by latching onto available estrogen cell receptors, 2OHE1 may exert a blocking action that prevents more potent estrogen metabolites from gaining a foothold into the cell.

Along a competing pathway, estrogen is metabolized into 16 α -hydroxyestrone (16 α -OHE1). This metabolite is much more active and powerful, with a potent stimulatory effect. 16 α -OHE1 binds strongly to special receptors inside cells that can accelerate the rate of DNA synthesis and cell multiplication.

In this way, higher levels of 16 α -OHE1 may increase the risk of estrogen-dependent conditions, such as lupus and breast cancer.

The levels of 2OHE1 and 16 α -OHE1, as well as the balance between these metabolites (measured in a 2/16 OHE1 ratio), provide important clinical information about estrogen metabolism. The ultimate goal is to promote proper balance, interpreted in light of each woman's unique health risks.

For example, a woman may have "normal" total levels of estrogen, but if her 2/16 OHE1 ratio is low, indicating dominance of the active metabolite, she may feel symptoms of, or be at increased risk for, conditions linked to estrogen excess.

Alternately, if her 2/16 OHE1 ratio is high, pointing to a surplus of the inactive metabolite, her body may lack the stimulatory estrogenic "fuel" it requires to adequately maintain bone tissue—thus increasing her risk of osteoporosis.

The 2/16 OHE1 ratio is very useful for tracking the clinical effects of therapies designed to optimize estrogen metabolism.

Studies indicate that the balance between these two unique metabolites can be modulated through a variety of lifestyle, dietary, and supplement interventions.

Substances such as plant lignans (flaxseed, grains, legumes), indole-3-carbinol (cruciferous vegetables)²¹, omega-3 fatty acids (coldwater fish)²², and isoflavones (soy)²³ have been shown to increase the 2/16 OHE1 ratio very significantly, reducing the risk of estrogen-dependent health disorders by shifting estrogen metabolism toward the inactive 2OHE1. Follow-up testing is able to assess the clinical impact of these interventions after just a few weeks.

Low 2:16 α -Hydroxyestrone Ratio?

Underlying Cause

This is what you should be thinking when you see a Low 2:16 α -Hydroxyestrone Ratio

Low 2:16 α -OHE1 ratio suggests shunting of estrogen metabolism to the more potent 16 α -OHE1 and/or 4-OHE1 (check level of 16 α -OHE1)

- Increased net estrogen activity in body
- Increased risk of breast cancer
- Rheumatoid arthritis
- Lupus (Systematic lupus erythmatosus [SLE])
- Greater bone mass, although possibly less likely to show increases in BMD with HRT
- Note: The above risks are modified when E1 and E2 trend low
- Pesticide exposure
- Hypothyroidism
- Obesity
- High fat, low fiber diet
- Omega-6 fatty acids
- Alcohol consumption
- Meds: oral contraceptives

Clinical Treatment Protocol

Note: Decision to modify ratio should be based on patient's respective risks for breast cancer (high estrogen) and osteoporosis (low estrogen).

To increase ratio

Nutritional Intervention

- Cruciferous vegetables (e.g., broccoli, cabbage, cauliflower)
- Indole 3-carbinol (I3C) or diindolylmethane (DIM)
- Flaxseed (lignans)
- Soy isoflavones (genestein, daidzein)
- Fish oils (omega-3 fatty acids)

Reduce dietary fat

- Rosemary, kudzu, turmeric

High 2:16 α -OHE1 ratio

Underlying Cause

This is what you should be thinking when you see a High 2:16 α -OHE1 ratio

High 2:16 α -OHE1 ratio suggests shunting of estrogen metabolism away from the more potent 16 α -OHE1 and/or 4-OHE1 (check level of 16 α -OHE1)

- Decreased net estrogen activity in body
- Decreased risk of breast cancer
- Studies on bone density are mixed: High ratio (along with low estrogens) may correlate with increased risk of osteoporosis. However, 2OHE1 stimulates osteoblasts, and women with higher 2:16 ratio appear to gain more bone with HRT.

Note: The above risks are modified when E1 and E2 trend high

- High intake of cruciferous vegetables, soy, flax
- High coffee consumption
- Regular alcohol consumption
- Smoking
- Meds: Prozac®, thyroxine

Clinical Treatment Protocol

To reduce ratio

- Apiaceous vegetables (e.g., carrots, parsnips, celery, dill, parsley)
- Reduce intake of cruciferous vegetables, soy, flax

Other Hormonal Testing to Consider

Low Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

Underlying cause

- Hypogonadism
- Peri-menopause
- Excess estrogen or testosterone (provides negative feedback to anterior pituitary)
- Deficient progesterone (pre-menopausally)
- Glucocorticoid excess
- Excessive exercise
- Hyperprolactinemia (may suppress GnRH via a dopamine-related mechanism)
- Hypothyroidism (TRH-induced prolactin secretion)
- Possible PCOS (if low FSH along with high LH)
- Deficient hypothalamic secretion of GnRH (including anorexia nervosa or genetic disorders)
- Pituitary insufficiency
- Congenital adrenal hyperplasia
- Radiation or trauma to pituitary
- Critical illness (transitory suppression)
- Prolonged administration of anabolic steroids
- Autoimmune damage to hypothalamus or pituitary
- Meds: Oral contraceptives, estrogens, phenothiazines

Clinical Treatment Protocol

Identify and correct underlying cause

- Refer to estrogen levels and suggested interventions
- Refer to prolactin level and suggested interventions
- Evaluate thyroid function

High Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

Underlying Cause

- ❑ **Elevated FSH and LH serve as a gauge of declining ovarian function**
- ❑ **Low estrogen or testosterone**
- ❑ Primary ovarian insufficiency (premature ovarian failure or onset of menopause)
- ❑ Hyperinsulinemia (increases LH); may cause hyperandrogenism
- ❑ Congenital disorders (e.g., Turner Syndrome)
- ❑ Pituitary adenoma (FSH high, LH normal)
- ❑ Meds: L-dopa, clomiphene, ketoconazole

Clinical Treatment Protocol

Identify and correct underlying cause

- ❑ Refer to estrogen level and suggested intervention
- ❑ Rule out hyperinsulinemia (high LH)

Low Androstenedione

- ❑ Ovarian or adrenal insufficiency (check DHEAS level)
- ❑ Hypothalamic or pituitary insufficiency (also expect low estrogens, thyroid, and adrenals)
- ❑ High aromatase activity (expect higher estrone); e.g., alcohol, glucocorticoids
- ❑ Inflammatory conditions (TNF α inhibits production of its precursor, DHEA)
- ❑ Hyperprolactinemia (stimulates adrenal androgen production)
- ❑ Meds: carbamazepine, ketoconazole, Norplant®

Clinical Treatment Protocol

- ❑ Identify and correct underlying cause (see column to left)

High Androstenedione

Underlying cause

- ❑ Ovarian or adrenal hyperactivity (see DHEAS level)
- ❑ DHEA supplementation
- ❑ Aromatase inhibition (e.g., smoking, chrysin, flavonoids, ketoconazole, oxidative stress)
- ❑ Licorice (inhibits conversion of androstenedione to testosterone)
- ❑ Meds: clomiphene, metyrapone, cimetidine, DHEA

Clinical Treatment Protocol

Identify and correct underlying cause

- ❑ Evaluate for PCOS (refer to levels of testosterone, LH, and DHEA; if levels high, check insulin)

Low Prolactin

Underlying Cause

Prolactin has been implicated in hyperandrogenism, visceral fat accumulation, breast cancer risk, and autoimmunity, including celiac disease.

- Hypothyroidism (prolactin inhibited by T3)
- Prolonged dopamine infusion
- Sheehan syndrome (post-partum pituitary necrosis)
- Pituitary tumor, or treatment of tumor
- Head injury
- Infection (e.g., histoplasmosis, TB)
- Infiltrative diseases (e.g., hemochromatosis, sarcoidosis)
- Bulimia
- Inborn error
- Meds: ergot derivatives, L-dopa, bromocriptine, calcinonin, rifampin, valproic acid, tamoxifen

Clinical Treatment Protocol

Identify and correct underlying cause

- Normalize thyroid, if high
- Remove prolactin-suppressing medications

High Prolactin

Underlying Cause

Excess estrogen

- Pregnancy or post-partum
- Primary hypothyroidism
- Alcoholic cirrhosis
- Celiac disease (active)
- Hypoglycemia
- PCOS
- Insulin resistance
- Chest trauma or surgery
- Pituitary tumor (micro- or macroadenoma)
- Anti-prolactin antibodies (prolactin/IgG complex; symptoms may be minimal)
- Intracranial tumors
- Meds: cimetidine, cocaine, estrogens, oral contraceptives, haloperidol, methadone, phenothiazines, tricyclic antidepressants, MAO inhibitors, metoclopramide, reserpine, danazol, phenytoin, verapamil, opiates

Clinical Treatment Protocol

Identify and correct underlying cause

- Pregnancy test, if relevant
- Refer to estrogen levels and suggested interventions
- Normalize thyroid, if low
- Evaluate adrenal function
- Rule out celiac disease, remove gluten if positive
- Improve insulin sensitivity
- Remove prolactin-inducing medications
- IgG Anti-prolactin antibodies
- MRI, if suspect tumor
- L-tyrosine? (dopamine inhibits prolactin)
- Vitamin B6
- Progesterone (inhibits prolactin in vitro)
- Dopamine agonists (e.g., bromocriptine, pergolide, quinagolide)
- Ergoline derivatives (e.g., cabergoline)

- ❑ Surgery (large tumors causing visual field deficit)

Credit is contributed to the following labs for their advancement in the field of functional medicine:

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