Functional Medicine University's Functional Diagnostic Medicine Training Program

Module 7 * FMDT 565A

Functional Physiology of the Reproductive Hormones
(Part 2 of 2)

By Wayne L. Sodano, D.C., D.A.B.C.I. & Ron Grisanti, D.C., D.A.B.C.O., M.S.
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Functional Medicine University; Functional Diagnostic Medicine Training Program/Insider's Guide
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Required Reading: Located on www.FunctionalMedicineUniversity.com download library:

Inhibins in female and male reproductive physiology: role in gametogenesis, conception, implantation and early pregnancy, Stefano Luisi, Pasquale Florio, Fernando M.Reis and Felice Petraglia. Human Reproduction Update, Vol.11, No.2 pp. 123–135, 2005

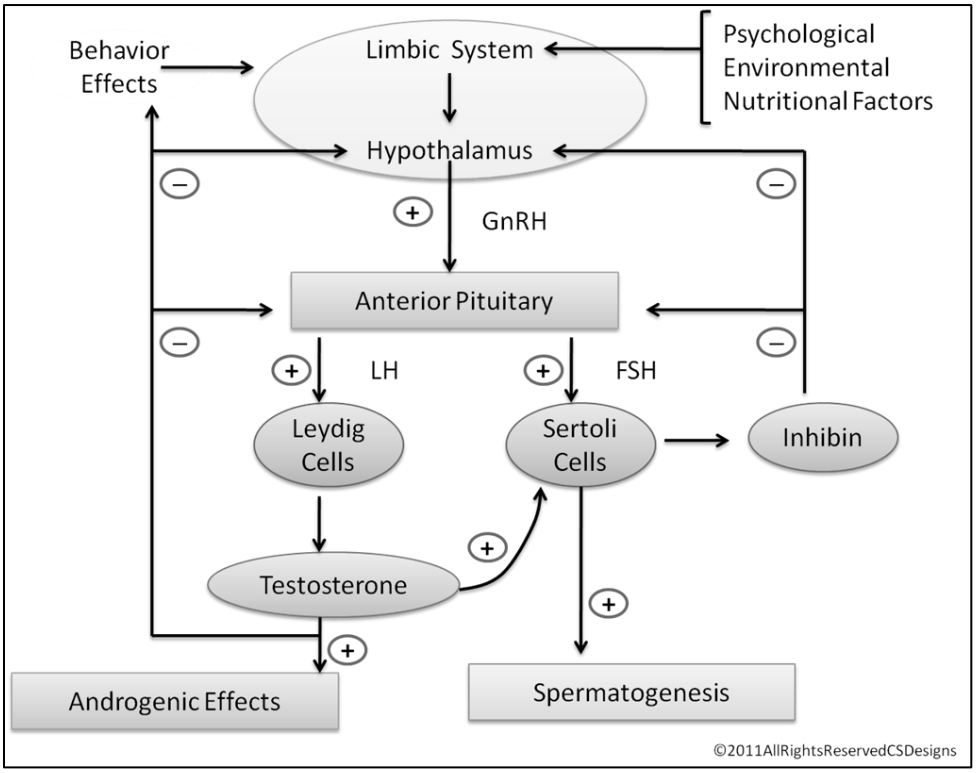
Inhibin B is a better marker of spermatogenesis than other hormones in the evaluation of male factor infertility,Philip Kumanov, M.D, PhD, Kalyana Nandipati, MD, Analia Tomova, MD, PhD, Ashok Agarwal, PhD, Clinical Centre of Endocrinology and Gerontology, Fertility and Sterility, Vol. 86, No. 2, August 2006

Hormonal Control of Male Sexual Function

A majority of the control of sexual functions in the male (and the female) begins with secretions of gonadotropin-releasing hormone (GnRH) by the hypothalamus.[1] You should remember from past lessons that the hypothalamus is driven by the limbic system, and therefore many psychological factors can influence the release of GnRH. As functional medicine practitioners, this concept should not be of surprise. GnRH stimulates the release of two other hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary.

Both LH and FSH are glycoproteins that exert their effect on the testes, which in turn activate specific enzyme systems in the testes. LH stimulates the interstitial cells of Leydig to synthesize and secrete testosterone. The majority of the circulating testosterone is made by the Leydig cells. FSH binds to the receptors on the Sertoli cells in the seminiferous tubules where it causes the Sertoli cells to grow and secrete spermatogenic substances. Testosterone and dihydroxytestosterone (DHT) enter into the interstitial spaces of the seminiferous tubules where they have a strong effect on spermatogenesis. Therefore, FSH and testosterone are the regulators of spermatogenesis.

The Sertoli cells also secrete a glycoprotein hormone called inhibin in respond to spermatogenesis occurring to rapidly. This hormone decreases the secretion of FSH and GnRH. (inhibins are also secreted by the ovary.)



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Inhibins in female and male reproductive physiology: role in gametogenesis, conception, implantation and early pregnancy

Inhibin B is a better marker of spermatogenesis than other hormones in the evaluation of male factor infertility

There is a symbiotic relationship between the brain and testosterone. Many of the central nervous system functions are regulated by testosterone, among them is behavior and cognition. The inputs to the central nervous system, such as psychological stress, can lower the release of GnRH, and therefore decrease serum testosterone levels. Low serum testosterone is also a component of insulin resistance. A research study in 2009 concluded that low serum testosterone was independently associated with insulin resistance in non-diabetic older men.[2]

From a functional medicine perspective, it's important to assess for environmental factors that can influence testosterone level. Since over 90% of the testosterone is produced in the testis by the Leydig cells, it important to assess for factors that might inhibit Leydig cell production of testosterone. Disruption of androgen biosynthesis and actions by environmental endocrine disrupting compounds can inhibit critical cellular processes controlling steroidogenesis in the Leydig cells. Disruption can occur with the transport and delivery of cholesterol to the mitochondria, interference with the enzymatic activity along the steroidogenesis pathway, or by interfering with the androgen receptor.

Natural and Synthetic Chemicals Affecting Leydig Cell Function

Chemical	Proposed target	Application or source
Procymidone	Androgen receptor antagonist	Fungicide, control of plant diseases
Linuron	Androgen receptor antagonist	Herbicide, postemergence control of weeds in crops
Vinclozolin	Androgen receptor antagonist	Fungicide
p,p′DDT	Androgen receptor antagonist	Pesticide
Dioxins	Aryl hydrocarbon receptor agonist	By-product of chlorinated hydrocarbons
Phthalates	Peroxisome proliferator-activated receptors (PPARs)?	Plasticizers
Genistein	ERs stimulator	Soy-derived food
Resveratrol	ERs stimulator	Red wine, red grape
Bisphenol A	ERs stimulator	Synthesis of polycarbonate plastics

Ref: Journal of Biomedicine and Biotechnology: Endocrine Disruptors and Leydig Cell Function Volume 2010 (2010), Article ID 684504

On the table above you will notice that compounds that stimulate estrogen receptors affect Leydig cell function. The inhibitory effect of estrogens on male reproductive function appears to be mediated by suppression of LH. A direct effect of estrogen on Leydig cell steroidogenesis has also been demonstrated.[3]

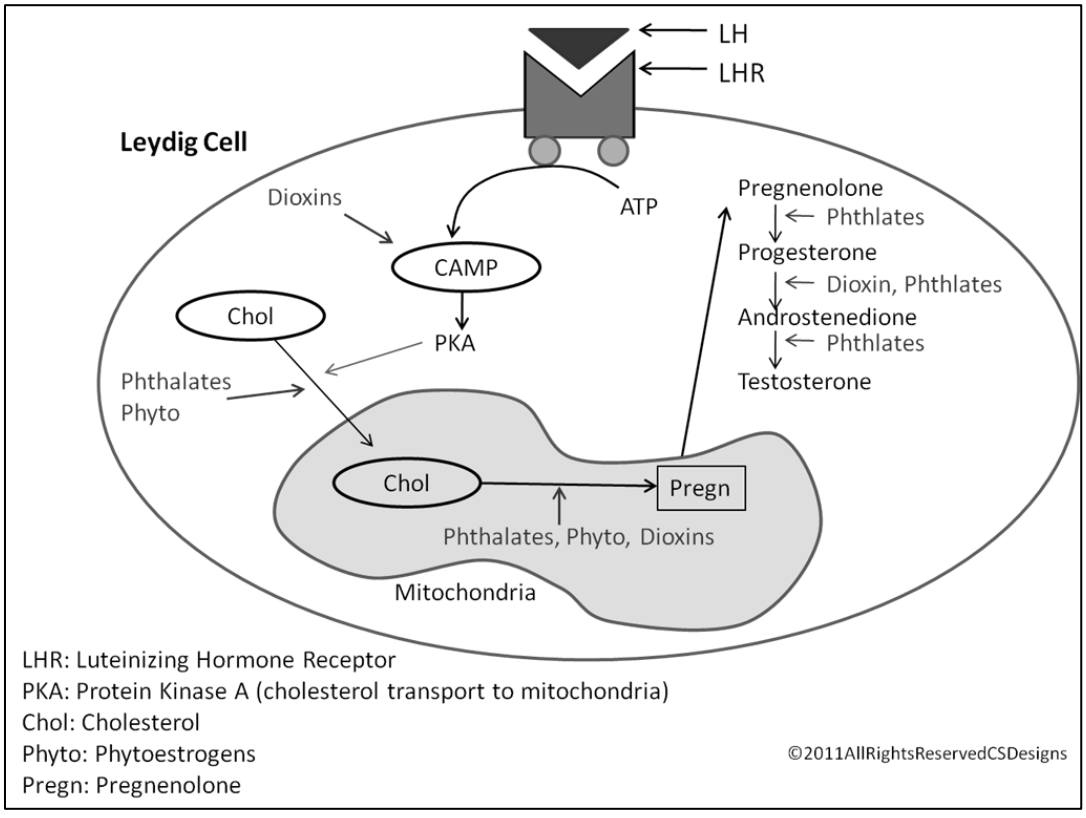
Phytoestrogens

Phytoestrogens are compounds that occur naturally in nature. There structure is similar to 17β-estradiol and therefore can have estrogenic and/or antiestrogenic effects. The main sources of phytoestrogens are fruits, vegetables, and legumes. The highest amount is found in soybeans and soy food. There are four main classes of phytoestrogens:

- Flavonoids – such as genistein, daidzein, naringenin, and kaempferol
- Coumestans – coumestrol
- Lignans – matairesinol and secoisolariciresinol
- Stilbene – resveratrol

I personally question the use of soy-based infant formula due to the high estrogenic effect on the developing infant.

The Potential Sites of Action of Endocrine Disrupting Compounds



'The action of endocrine disrupting compounds on Leydig cell function and the reproductive potential is a complex process that depends on the exposure route, dose, the developmental stage of the target organism and many other factors. Together, these factors determine the potential risk for adverse consequences with long-lasting effects on the male reproductive function'.[3]

'Together with Leydig cells, adult rat germ cells are able to express P450arom mRNA, which is translated as a biologically active enzyme involved in estrogen production (Fig. 1). Consequently, germ cells not only produce estrogens but contain estrogen receptors as well, which would explain part of the role (autocrine and/or paracrine) of estrogens in male germ cell development. The mechanism of action of estrogens in the reproductive organs of the male remains to be clarified, as well as the regulation of aromatase gene expression, especially in germ cells during testicular development. Nevertheless, we have begun to understand the physiological roles (as well as the pathological effects) of these female hormones in males, and, obviously, their involvement in several steps of sperm production and maturation. Thus it is anticipated that parts of male gonadal function are not only androgen regulated but also estrogen controlled in mammals.' [4]

Male Infertility

Research studies between the late 1930's and the mid-1990's have found a substantial decline in sperm concentration and sperm quality among men living in industrialized countries. Observational studies and animal research suggest that exposure to various environmental pollutants may be contributing to this decline in male fertility, possibly by exerting estrogenic or other endocrine-disrupting effects. [5]

Suspected Contributing Factors to Male Infertility[6]

- Toxins from cigarette smoke
- Alcohol and drugs that lower sperm count (cocaine, marijuana, [certain antifungals, antihypertensives, and antibiotics] cimetidine, methotrexate, sulfasalazine and others)
- Heavy metal – lead mercury and cadmium
- Obesity – excess body fat converting testosterone to estrogen
- Environmental toxins – bisphenol a, phthalates, vincolozolin (fungicide), pesticides, dry-cleaning agents, and others.
- High soy intake
- Oxidative stress – spermatozoa are highly sensitive to oxidative stress because of their high concentration of polyunsaturated fatty acids and inability to repair damages membranes.
- Hypothyroidism
- Celiac disease and food allergy
- Poor diet

Treatment and Advanced Lab Testing Considerations for Male Infertility

Aside from primary lab testing, advanced functional medicine test should be considered as indicated by the patient history, physical examination and primary lab testing. The functional/advanced tests of consideration include:

- Organic acid test
- Toxicity Profile test
- RBC Nutrient and Toxic Elements
- Urinary Porphyrin test
- Celiac test/Food allergy
- ASI test
- RBC fatty acid test

Treatment and Nutritional Considerations

The main treatment include: optimizing liver function, far-infrared sauna treatment, optimal fatty acid balance and the use of antioxidants.

- Zinc
- L-Arginine
- L-carnitine and acetyl-L-carnitine
- Vitamin E
- Selenium
- Vitamin C
- Lycopene
- B vitamins
- Essential fatty acids

The Role of Estrogen in Males

ERs and the aromatase enzyme are widely expressed in the male reproductive tract. The concept of a key estrogen action in the male reproductive tract is supported by the fact that male reproductive structures are able to produce and respond to estrogens. Estrogen receptors are also found in the brain. This finding suggests a role for estrogen in modulating brain function.

Estrogen in adult male reproductive tract; A review, *(Reproductive Biology and Endocrinology: 2003, 1:52)*

Abstract

Testosterone and estrogen are no longer considered male only and female only hormones. Both hormones are important in both sexes. It was known as early as the 1930's that developmental exposure to a high dose of estrogen causes malformation of the male reproductive tract, but the early formative years of reproductive biology as a discipline did not recognize the importance of estrogen in regulating the normal function of the adult male reproductive tract. In the adult testis, estrogen is synthesized by Leydig cells and the germ cells, producing a relatively high concentration in rete testis fluid. Estrogen receptors are present in the testis, efferent ductules and epididymis of most species. However, estrogen receptor-α is reported absent in the testis of a few species, including man. Estrogen receptors are abundant in the efferent ductule epithelium, where their primary function is to regulate the expression of proteins involved in fluid reabsorption. Disruption of the α-receptor, either in the knockout (αERKO) or by treatment with a pure antiestrogen, results in dilution of cauda epididymal sperm, disruption of sperm morphology, inhibition of sodium transport and subsequent water reabsorption, increased secretion of Cl^-, and eventual decreased fertility. In addition to this primary regulation of luminal fluid and ion transport, estrogen is also responsible for maintaining a differentiated epithelial morphology. Thus, we conclude that estrogen or its α-receptor is an absolute necessity for fertility in the male.

<u>Clinical Assessment of Testosterone</u>

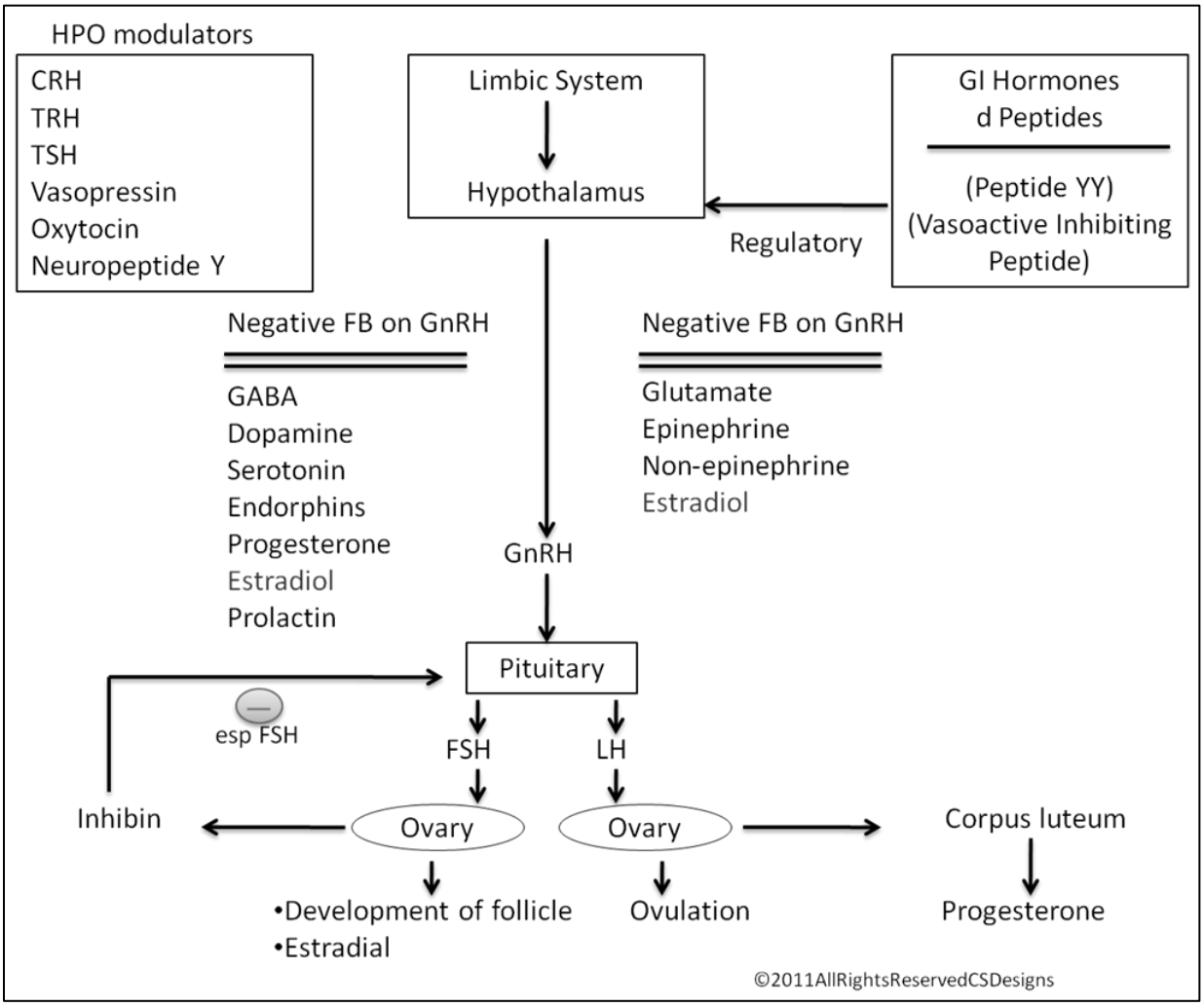
- Produced in the testes of males
- Produced in the adrenal glands (25%), ovaries (25%), and peripheral conversion of circulating androstenedione (50%) of females
- Total testosterone is the amount of free and protein bound testosterone
- 60 to 70% of plasma testosterone is bound to SHBG (biologically inactive)
- 30 to 40% is weakly bound to albumin (biologically active)
- about 2% is free or unbound (biologically active)

Free testosterone and albumin bound are frequently referred to as the biologically active or biological fraction. In most cases the bioavailable fraction increases as total testosterone increases or SHBG decreases. Testosterone testing may be done in saliva, which reflects the free testosterone in serum. Total serum testosterone is also useful to determine whether there is normal response of the Leydig cells to FSH and LH. Simultaneous determination of total testosterone and SHBG allows the calculation of free testosterone concentration, sometimes called the free androgen index (FAI).[7]

[FAI = total T/ SHBG] The FAI is often increased in severe acne, male balding, hirsutism and other conditions in which a normal serum testosterone is found with a low SHBG level. In non-obese, non oligomenorrheic women, an elevated FAI during the early follicular phase is reported to be a sensitive and specific indicator for PCOS. Measurement of FAI in infertile women reveals an association of ovarian dysfunction with hyperandrogenism.[7] Low SHBG and high FAI are strongly associated with cardiovascular (CV) risk factors in racially diverse women, and thus, androgens likely play a role in the CV risk profile of perimenopausal women.[10]

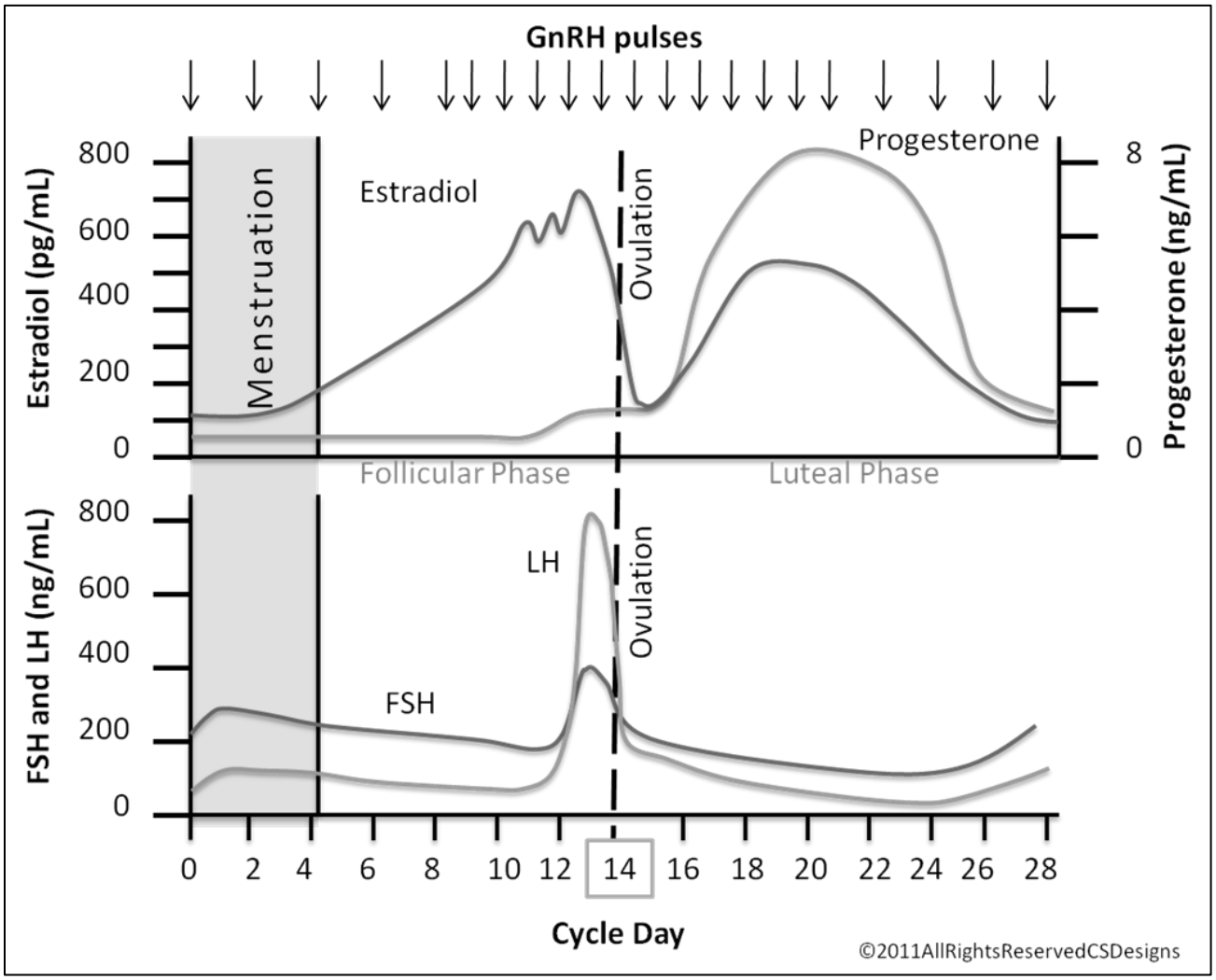
Testosterone is important in balancing the effects of estrogen. Testosterone decreases the liver production of SHBG making estrogen and testosterone more bioavailable. In women the proposed serum level of optimal testosterone is: (. 4ng/mL). Testosterone levels may be low in women due to ovarian dysfunction, adrenal insufficiency, thyroid dysfunction, and/or taking certain medications.

The Female Hormonal System



The hypothalamus plays a major role in hormonal regulation of the female reproductive system, of which the main regulator is gonadotropin-releasing hormone (GnRH). The influences on the production and secretion of GnRH are via brain stimuli and mediators of various origins. The preceding illustration displays the multitude of influences on the production and secretion of GnRH. These include; amino acids (glutamate and GABA), biogenic amines (dopamine, serotonin, epinephrine, and nor-epinephrine), hormones (prolactin, inhibin), opioids (endorphins), peptides (CRH, TRH, TSH, neuropeptide Y, vasopressin, oxytocin and GnRH itself. There is also a gut-brain connect that influences the hypothalamus. Several gut hormones and peptides influence neuropeptide Y receptors in the brain establishing a connection between the gut and reproductive function.[8]

GnRH, LH/FSH and Monthly Ovarian Cycle



The female sexual cycle is characterized by two main objectives.

1. The release of a single ovum (normally)
2. Preparing the uterine endometrium for implantation

GnRH causes the synthesis and secretion of two gonadotropin hormones; luteinizing hormone (LH) and follicle-stimulating hormone (FSH). GnRH has an intrinsic pusatile secretory pattern that can be influence or modified by many neurotransmitters. FSH and LH are completely responsible for the changes that occur in the ovary during the cycle. The target of LH and FSH is the receptors on the ovarian membrane.

Follicular Phase

The first half of the cycle is called the "follicular phase" because growth of the follicle occurs during this time. At the beginning of the cycle, the concentrations of LH and FSH increase slightly, with the FSH being the dominant hormone. FSH causes the accelerated growth of 6-12 primary follicles. (Only one follicle fully matures each month, the remaining undergo atresia- involution). After a few days, the cells of the mature primary follicle secrete estradiol. As more estradiol is secreted, it causes and increase in the number of FSH receptors (positive feedback). FSH and estrogens combine to promote LH receptors. The estrogens from the follicle and the LH from the anterior pituitary cause proliferation of the outer layer of the follicle (theca).

Ovulation

About mid-way through the cycle ovulation occurs. Ovulation occurs when a mature egg is released from the ovary, travels via the fallopian tubes and is available for fertilization. A surge in LH is necessary for ovulation. Without the surge of LH, ovulation will not take place. The premise is that high levels of estrogen during this time cause positive feedback on the anterior pituitary leading to the LH surge. The LH surge also causes the follicle to mainly produce progesterone. About one day before ovulation the rate of estrogen secretion decrease with a concomitant rise in progesterone.

The physical signs of ovulation include:

- A slight rise in basal body temperature (.5 to 1 degree)
- High levels of LH on urine, blood or saliva test
- Cervical mucus or vaginal discharge "egg white consistency"
- Abdominal bloating
- Breast tenderness
- Light spotting
- Slight pain or ache on one side of the abdomen

Luteal Phase (Corpus Luteum)

After the ovum (egg) is released from the follicle, the remaining cell form the corpus luteum. The cells in the corpus luteum produce large amounts of progesterone and estrogen, with progesterone being the dominant hormone. You should recall that the most important function of progesterone is to prepare the uterine lining for implantation. Progesterone promotes secretory changes in the uterine lining, as well as affecting the fallopian tubes and the breast tissue. The corpus luteum also secretes a hormone called inhibin. Inhibin causes a decrease in secretion of the anterior pituitary, especially FSH. A decrease in FHS and LH cause the corpus luteum to degenerate. Once the corpus luteum has degenerated, there is a drop in hormone concentration of estrogen, progesterone, and inhibin which removes the negative feedback on the anterior pituitary allowing FSH and LH to increase in secretion. The decrease in estrogen and progesterone during this time leads to menstruation.

Clinical Assessment of the Estrogens

Estrogens stimulate growth and development of tissues related to female reproduction. They also promote vascular smooth muscle tone, collagen production, brain activity and inhibit bone resorption. Estradiol, estrone and estriol are collectively known as estrogen.

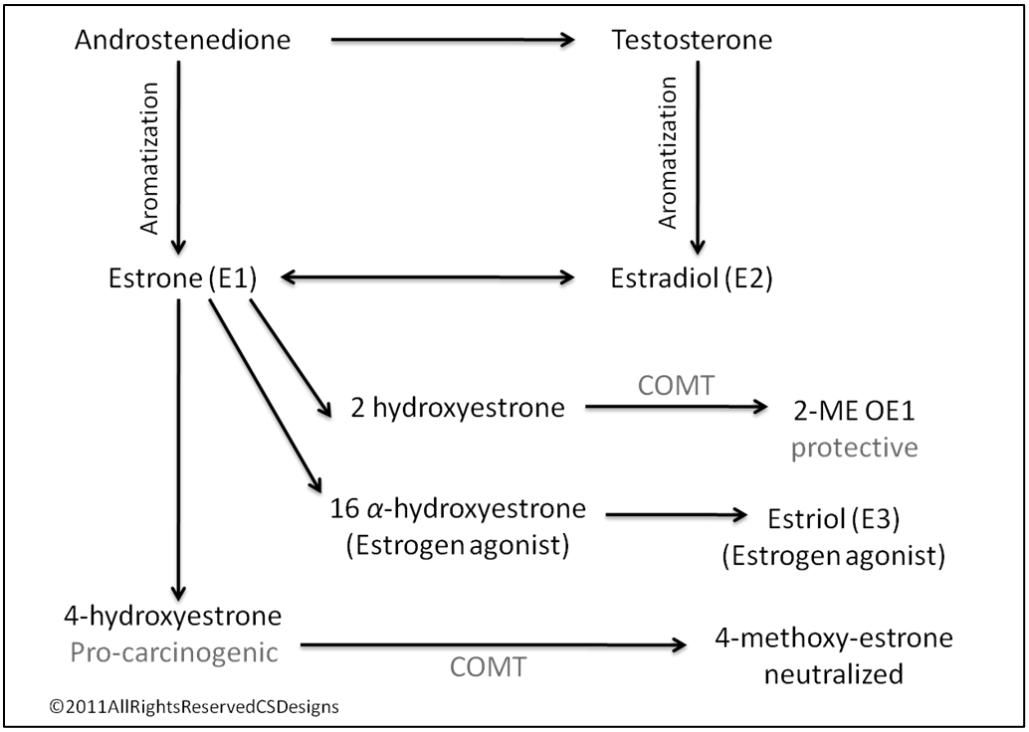
Estradiol (E2) is the most potent estrogen and is the major estrogen secreted by the ovaries in premenopausal women. Estradiol may also arise from the conversion of estrone or from testosterone via aromatization in peripheral tissues.

Estrone (E1) is the second most potent estrogen and is derived from estradiol or from adrenal androstenedione via aromatization in the peripheral tissues. Estrone is bound primarily to albumin rather than SHBG, and may be processed via either the 2- or 16 alpha –hydroxylation pathways to form 2-hydroxyestrone or 16 alpha-hydroxyestrone.

Estriol (E3) is the least potent estrogen. It originates from the conversion of estrone via 16 alpha – hydroxyestrone. Normal levels imply relative balance in enzyme conversion among its sources.

High levels of estrogens are characterized by symptoms, such as increased anxiety, difficulty sleeping, irritability, increased risk of cancer, and highly proliferative breast tissue, resulting in fibroids or cysts.[7]

Estrogen Metabolism



'The 2-OH and 4-OH metabolites (catochol estrogens) are readily oxidized to quinines, which are highly reactive and can damage DNA and promote carcinogenesis directly or indirectly through the generation of reactive oxygen species. This harmful pathway can be minimized through detoxification and excretion of the catechol estrogens via Phase II methylation by the catecol-O-methyltransferase (COMT) enzyme. This methylation pathway requires S-adenosylmethionine (SAMe) and magnesium as cofactors.' [9]

The estrogens, particularly estradiol and estrone, need to be in balance with the body in order to maintain optimal health. Deficiency in estrogen can cause osteoporosis, amenorrhea and menopausal symptoms. Excess of estrogen has been associated with uterine fibroids, breast cancer, autoimmune disease, menorrahgia and anxiety. You must also consider the effects of the estrogen metabolites. An imbalance of estrogen metabolites can increase the risk of breast cancer, osteoporosis and prostate cancer. However if estrogen metabolites are in balance, they can convey protection.

Estrogen metabolites provide valuable clinical information regarding cancer. Two significant metabolites are 16 alpha-hydroxyestrone (16α-OHE1) and 2-hydroxyestrone (2-OHE1). 16α-OHE1 is a powerful metabolite that stimulates the target tissue. High levels of 16α-OHE1 can increase the risk of breast cancer and autoimmune disease. 2-OHE1 is a metabolite that binds weakly to cell receptors and may slow cell proliferation. Excessive levels of 2-OHE1 may increase the risk of osteoporosis in post-menopausal women with low estrogen. Again, it's all about balance.

Expected Values for First Morning Urine Estrogen Metabolites (NG/MG Creatinine)			
Analyte	Premenopause	Postmenopause	Postmenopause with HRT
160HE[1]	3-30	208	5-25
20HE[1]	3-40	2-10	10-75
Urinary Estrogen Metabolites (UEM) Index	4-110	5-18	6-158
Estrogen Metabolite Ratio (20HE/160HE)	>2.0 (Health pre-and postmenopausal women)		

Reprinted with permission: Laboratory Evaluations for Integrative and Functional Medicine, 2nd ed., Richard S. Lord, J. Alexander Bralley

A low 2:16-hydroxyestrone ratio is associated with increased estrogen activity in the body and an increased risk of breast cancer and autoimmune disease. Low ratios have been associated with environmental toxicity, obesity, oral contraceptives, and high fat/low fiber diet and alcohol consumption.

Nutritional Considerations to Effect Estrogen Metabolism

'An abundance of evidence makes it clear that excessive estrogen exposure from both endogenous and exogenous sources is a causal factor in the development of cancer in hormone-dependent tissues, such as breast, endometrium, ovary, uterus, and prostate. Furthermore, hormonal imbalances between progesterone, testosterone and estrogen can lead to symptoms and conditions of estrogen dominance. These include PMS, endometriosis, uterine fibroids, fibrocystic or painful breasts, cervical dysplasia and systemic lupus erythematosis.' [9]

If the person has a high level of body toxins, you may need to recommend far infrared sauna treatment. Remember to go slow, and make sure the person is adequately hydrated and essential minerals are replaced. (It may take up 2 to 3 months of sauna treatments to see a significant positive change).

- Insoluble fiber – binds to unconjugated estrogens in the GI tract, reduce intestinal β-glucuronidase
- Fiber, Probiotics and calcium D-glucarate can inhibit the activity of β-glucuronidase
- Diet – complex carbohydrates, adequate protein, balance fatty acids
- To modify estrogen receptors activity- phytoestrogens (isofalvones)
- Increase SHBG – lignans (flaxseed, whole grains, legumes)
- Magnesium – is a cofactor for COMT. It is also needed for phase I and phase II detoxification
- Indole-3-carbinol – (cruciferous vegetables) promotes metabolism of beneficial estrogen metabolites
- B6, B12, and L-5-methyltetrahydofolate – cofactors for enzymes involved with phase I and phase II detoxification
- Antioxidants

Clinical Assessment of Progesterone

The effects of progesterone on target tissues include the following: endometrial transformation (prepares the endometrium for reproduction), stimulates the vaginal and cervical epithelium, decreases uterine contraction, neuroprotective, and immunoregulatory.

As stated in an earlier lesson, progesterone and estrogen must be in balance with one another for optimal function. Progesterone and estrogen receptors are both found in the same area of the brain and include the limbic system and the hypothalamus.[7] Thus, making balancing progesterone and estrogen essential.

Adrenal gland function must be evaluated when assessing for progesterone status. You should recall the condition called "pregnenolone steal" which is seen in individuals undergoing chronic stress and fatigue. Pregnenolone steal lowers the progesterone level in the body. Restoring optimal adrenal function is paramount when addressing hormonal imbalance. Vitamin C supplement has been show to increase progesterone levels possible due to improving adrenal function.[7]

Warning:

- High levels of progesterone will affect activity of other hormones
- High levels will increase free estrogen
- Excessive progesterone can decrease coordination, slow reflexes, and impair memory
- High levels may increase the risk of diabetes

It appears that progesterone administration is most effective short term, or in a pulsed fashion. Continuous dosing can result in paradoxical effects.[7]

Summary

The art and science of treating hormonal imbalances requires of comprehensive knowledge of the organ systems (esp. the liver and adrenal glands) and the biochemical pathways. Always remember to balance the primary hormones first and support the other hormonal imbalances. You must retest at more frequent intervals when prescribing any type of hormonal replacement. You must also consider the biochemical uniqueness of the individual you are treating. There have been significant advancements made in the field of genomic testing as it relates to gene SNPs of the enzymes critical for synthesis and detoxification of hormones. Genomic testing will allow you to identify the individual that has a malfunctioning enzyme or enzymes that are critical to maintain hormonal balance. An example of this is the enzyme COMT. This enzyme is responsible for transferring a methyl group during many metabolic reactions. COMT is need for the Phase II methylation of estrogen metabolism in order to make the metabolites of estrogen less active or beneficial. If an individual has a SNP for this gene, they may require specific supplementation to improve it enzymatic activity. In the case of a SNP for COMT, SAMe and magnesium may need to be taken in higher dosage to increase enzyme activity along with increased supplementation of antioxidants. This is patient-centered care. And finally, always consider environmental toxins as a potential cause of hormonal imbalance, especially since we know that 100% of people have environmental toxins in their bodies.

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