Functional Medicine University’s
Functional Diagnostic Medicine
Training Program

Module 7 * FMDT 565A

Functional Physiology of the Reproductive Hormones
(Part 1 of 2)

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One of the most complex body system to assess and treat is the reproductive hormone system due to interconnectedness with the other hormones, namely the adrenal hormones and the thyroid hormones. There is also the issue of environmental toxicity, nutritional influences on hormone metabolism and detoxification of the hormones, and their metabolites, that must be taken in consideration when addressing suspected hormone imbalances. Once you have an understanding of how these hormones interact, you will be able to design treatment strategies that are patient centered. This will avoid the “you’re low on this substance, so I’ll give you some to fix you” folly.

The paradigm of functional medicine approach is designed to assess the abnormal physiology and treat the underlying cause or causes. In order to assess hormonal imbalances, a working knowledge of the steriodal hormone pathway is paramount.

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Ref: Reprinted with permission: Laboratory Evaluations for Integrative and Functional Medicine, 2nd ed., Lord & Bralley, Metametrix Institute, Duluth, GA
The lesson on adrenal glands physiology illustrated the flow of the steroid hormone pathways. You should recall the condition known as “pregnenolone steal” that can occur with chronic stress. Pregnenolone is produced directly from cholesterol and is the precursor for the majority of the steroid hormones, namely the hormones from the adrenal cortex and the sex hormones. Under chronic stress, the body’s preferential pathway of pregnenolone is shifted toward to production of cortisol at the expense of all other steroidal hormones. This scenario sets up major hormonal imbalances in the body if left unchecked.

**Steroidal Hormone Principle Pathways**

Ref: reprinted with permission, http://www.biodia.com/
Balance the Major Hormones First

The main concept to understand when addressing hormone imbalance issues is to balance the major hormonal imbalances first. The major hormones of the body consist of epinephrine (adrenaline), cortisol, and insulin. You should recall that stress causes the secretion of both epinephrine (adrenaline) and cortisol, which cause an increase in blood glucose. (cortisol also suppresses the immune system) The increase in blood glucose causes a rise in blood insulin in order to facilitate glucose transport into the cells. Insulin also promotes fat synthesis and storage. Almost all of fat synthesis occurs in the liver cells, and fatty acids are then transported from the liver by way of the lipoproteins to the adipose tissue for storage.¹

Insulin resistance and hyperinsulinemia are associated with an increased risk of cardiovascular disease, obesity, non-alcoholic fatty liver, hyperuricemia, breast cancer, pre-hypertension, and polycystic ovary syndrome (PCOS).² It is interesting to note that insulin-lowering agents, such as metformin, are used in the management of PCOS. Functional medicine practitioners have long understood the connection to insulin resistance and hormonal imbalances. Think of how powerful this connection is: treating the insulin resistance may be the only treatment needed to be prescribed to effectively treat a patient with PCOS.
Insulin-Lowering Agents in the Management of Polycystic Ovary Syndrome

Endocrine Reviews 24 (5); 633-677 2003

Polycystic ovary syndrome (PCOS) is a medical condition that has brought multiple specialists together. Gynecologists, endocrinologists, cardiologists, pediatricians, and dermatologists are all concerned with PCOS patients and share research data and design clinical trials to learn more about the syndrome. Insulin resistance is a common feature of PCOS and is more marked in obese women, suggesting that PCOS and obesity have a synergistic effect on the magnitude of the insulin disorder. Hyperinsulinemia associated with insulin resistance has been causally linked to all features of the syndrome, such as hyperandrogenism, reproductive disorders, acne, hirsutism, and metabolic disturbances. Women with PCOS should be evaluated for cardiovascular risk factors, such as lipid profile and blood pressure. Modification of diet and lifestyle should be suggested to those who are obese. Several insulin-lowering agents have been tested in the management of PCOS. In particular, metformin is the only drug currently in widespread clinical use for treatment of PCOS. In a high percentage of patients, treatment with metformin is followed by regularization of menstrual cycle, reduction in hyperandrogenism and in cardiovascular risk factors, and improvement in response to therapies for induction of ovulation.
Summary of the Major Pathways of Steroid Hormone Synthesis

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Additional hormones are also produced in the ovaries and testes:

- Ovaries – progesterone, androstenedione, testosterone to estradiol
- Testes – DHEA and androstenedione
Cellular Location of Enzymes for Steroid Hormone Synthesis

Cellular Location of Enzymes for Steroid Hormone Synthesis

- Cholesterol
- Pregnenolone
- 17 x-hydroxy pregnenolone
- DHEA
- Androstenediol
- Dehydrotestosterone

- Progesterone
- 17 x-hydroxy progesterone
- Androstenedione
- Testosterone
- Deoxy-corticosterone
- Corticosterone
- Cortisol
- 11-deoxy-cortisol
- Estrone
- Estradiol
- Estriol

Liver
Mitochondria
Smooth endoplasmic reticulum
5 x-reductase

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Biosynthesis of Sex Hormones

After stimulation by FSH and LH, several reactions cause the conversion of cholesterol to the sex hormones in the ovaries and testes. Several of these same reactions use the same enzymes needed for steroid hormone synthesis in the adrenal glands. The diagram below offers another look at the pathway of sex hormone synthesis.

Ref: Reprinted with permission: Laboratory Evaluations for Integrative and Functional Medicine, 2nd ed., Lord & Bralley, Metametrix Institute, Duluth, GA
Aromatase is the enzyme responsible for the conversion of androgens to estrogens. It is a member of the cytochrome P450 family. The aromatase enzyme can be found on the testes, ovaries, adipose tissue, uterine fibroids, breast cancer cells, endometriosis and as other areas of the body. There appears to be a connection to increased aromatase activity and chronic inflammation.

The follow abstract will highlight the connection of rheumatoid arthritis and increased synovial fluid estrogens. The increase in estrogens in the synovial fluid may be due to upregulation of the aromatase enzyme induced by pro-inflammatory cytokines.
Synovial Fluid Estrogens in Rheumatoid Arthritis
Autoimmunity Reviews: Volume 3, issue 3, March 2004 pages 193 - 198

Abstract

Experimental and clinical evidence suggest that immune reactivity is modulated by gender. Immune reactivity is greater in females than in males and lymphocytes and monocytes from female subjects show higher antigen presenting activity and mitogenic responses. Steroid hormones can be converted along defined pathways to downstream hormones in the periphery. The conversion of dehydroepiandrosterone (DHEA) in target macrophages leads to an increase of downstream effector hormones (including estrogens), which may be an important factor for local immunomodulation at least in RA synovitis. The presence in the RA synovial fluids (SF) of an altered sex hormone balance resulting in lower immunosuppressive androgens and higher immunoenhancing estrogens, might determine a favorable condition for the development of the immunemediated RA synovitis and synovial hyperplasia. The increased estrogen concentration observed in RA SF of both sexes are characterized by the hydroxylated forms, in particular 16α-hydroxyestrone, that is a mitogenic and proliferative endogenous hormone. In contrast to 16α-hydroxylated estrogens, the 2-hydroxylated forms inhibit growth promoting effects of E2 and were found low in RA SF. Therefore, dose-related conversion to pro- or anti-inflammatory downstream metabolites of estrogens might support the dual role of estrogens (pro or anti-inflammatory) for example during estrogen replacement therapy, depending on local concentration (i.e. SF in RA) of 16α-hydroxyestrone or 2-hydroxyestrogens.

Aromatase Inhibitors

Aromatase inhibitors cannot stop the ovaries form synthesizing estrogens, so aromatase inhibitors only work in post-menopausal women with breast cancer. Currently three aromatase inhibitors are approved for use in the US; anastrazole, exemestane, and letrozole. Tamoxifen is also used to prevent growth of estrogen-sensitive breast tumors; however is works by blocking the tumors ability to use estrogen.
Grape seed extract is an aromatase inhibitor and a suppressor of aromatase expression

Cancer Res. 2006 Jun 1;66(11):5960-7

Abstract
Aromatase is the enzyme that converts androgen to estrogen. It is expressed at higher levels in breast cancer tissues than normal breast tissues. Grape seed extract (GSE) contains high levels of procyanidin dimers that have been shown in our laboratory to be potent inhibitors of aromatase. In this study, GSE was found to inhibit aromatase activity in a dose-dependent manner and reduce androgen-dependent tumor growth in an aromatase-transfected MCF-7 (MCF-7aro) breast cancer xenograft model, agreeing with our previous findings. We have also examined the effect of GSE on aromatase expression. Reverse transcription-PCR experiments showed that treatment with 60 μg/mL of GSE suppressed the levels of exon I.3-, exon PII-, and exon I.6-containing aromatase mRNAs in MCF-7 and SK-BR-3 cells. The levels of exon I.1-containing mRNA, however, did not change with GSE treatment. Transient transfection experiments with luciferase-aromatase promoter I.3/II or I.4 reporter vectors showed the suppression of the promoter activity in a dose-dependent manner. The GSE treatment also led to the down-regulation of two transcription factors, cyclic AMP-responsive element binding protein-1 (CREB-1) and glucocorticoid receptor (GR). CREB-1 and GR are known to up-regulate aromatase gene expression through promoters I.3/II and I.4, respectively. We believe that these results are exciting in that they show GSE to be potentially useful in the prevention/treatment of hormone-dependent breast cancer through the inhibition of aromatase activity as well as its expression.

(Note: A high level of procyanidin dimers as also found in red wine. Procyanidins are a subgroup of the phenolic compounds called proanthocyanidins. Black tea and green tea polyphenols have aromatase inhibitory activity. Citrus fruits contain naringenin chalcone, a flavonoid with aromatase inhibitory activity.5)
To further illustrate the major hormonal connection to reproductive hormone imbalances, let's look at the condition known as polycystic ovary syndrome. PCOS is associated with marked increases in androgen production and insulin resistance, and is one of the most common endocrine disorders in women, affecting about 6% of all women during their reproductive life. Through the functional medicine lens, the possible cause of PCOS can be elucidated by examining the hormonal interactions.

The ovary continues to respond to the effects of insulin in insulin resistance. The ovaries have insulin receptor that can stimulate androgen production in the ovary. (Normal insulin levels in a patient who does not have insulin resistance will not cause an increase in androgen production) Hyperinsulinemia also reduces circulating sex-hormone binding globulin (SHBG), which increases the amount of free testosterone. However, not all insulin resistant or hyperinsulinemic individuals develop polycystic ovary syndrome (PCOS).
Sex Hormone Binding Globulin

Sex hormone binding globulin is a glycoprotein mainly produced in the liver that binds mainly to estradiol and testosterone. Levels of circulating SHBG are under the positive influence of estrogens and thyroid hormone, and therefore its production is increased. Circulating levels of SHBG are suppressed by androgens causing a decrease in production of SHBG. This means that thyroid hormone, androgens and estrogens influence dynamic control of liver synthesis of SHBG. You need to remember that a hormone bound to its protein carrier is inactive and that the free form of the hormone will affect the target tissue. With this in mind, SHBG can be a major player in the availability of steroid hormones.

SHBG binds up to ninety-eight percent of the steroid hormones in the blood including testosterone, dihydrotestosterone (DHT), and estradiol and estrone. SHBG binds sex-steroids with high affinity, dihydrotestosterone (DHT) >testosterone (T) >estrone/estradiol (E). Because of the higher affinity of SHBG for DHT and testosterone, compared to esteron/estradiol, SHBG also has profound effects on the balance between bioavailable androgens and estrogens. Both high levels of estrogens and low levels of testosterone circulating through the liver cause an increase in production of SHBG.

- Decreased level of SHBG (causing an increase in free androgens) – Decreased levels of SHBG are often seen in hirsutism, PCOS, virilization, adult acne, obese postmenopausal women and women with diffuse hair loss. Hypothyroidism, hyperinsulinemia, and elevated cortisol levels can cause a reduction in SHBG. From a functional medicine perspective, the preceding conditions must be evaluated before recommending hormonal replacement. Other conditions that reduce SHBG level include acromegaly, Cushing’s disease and hyperprolactinemia.

- Increased level of SHBG – Increased levels of SHBG may be present in hyperthyroidism (autoimmune), cirrhosis of the liver, pregnancy, women using oral contraception, estrogen dominance and low progesterone.
Abstract
In conclusion, our data show that the consumption of a low protein, low-calorie diet; exercise training; and decreased adiposity are associated with low plasma insulin, C-peptide, FAI, leptin, and C-reactive protein and high SHBG concentrations, which are circulating factors linked with some types of cancer. Furthermore, our data suggest that a lower protein and calorie intake may have additional protective effects against some types of cancer, because it is associated with a decrease in circulating IGF-I independent of body fat mass. American Journal of Clinical Nutrition, Vol. 84, No. 6, 1456-1462, December 2006

Caution: Please remember that therapies that affect SHBG level will also affect the level of free (active) hormone. This needs to be considered and perhaps monitored during treatment.

Overview of Steroid Hormones

The steroid hormones are all derived from cholesterol. Moreover, with the exception of vitamin D, they all contain the same (cyclopentanophenanthrene) ring and atomic numbering system as cholesterol. The conversion of C27 cholesterol to the 18-, 19-, and 21-carbon steroid hormones involves the rate-limiting, irreversible cleavage of a 6-carbon residue from cholesterol; producing pregnenolone (C21). Retinoic acid and vitamin D are not derived from pregnenolone, but from vitamin A and cholesterol respectively.

Steroid Hormone Biosynthesis Reactions

The particular steroid hormone class synthesized by a given cell type depends upon its complement of peptide hormone receptors, its response to peptide hormone stimulation and its genetically expressed complement of enzymes. The following indicates which peptide hormone is responsible for stimulating the synthesis of which steroid hormone:

- Luteinizing Hormone (LH):
  - progesterone and testosterone
- Adrenocorticotropic hormone (ACTH):
  - cortisol
- Follicle Stimulating Hormone (FSH):
  - estradiol
- Angiotensin II/III:
  - Aldosterone
The major steroid hormones include vitamin A, vitamin D, retinoic acid, and the steroid hormones (androgens, estrogens, glucocorticoids and mineralocorticoids). Steroid hormones are ligands for steroid hormone receptors. A ligand is a substance that forms a complex with another substance to serve a biological function. Ligand binding to a receptor alters the chemical conformation of the receptor and thus, determines the functional state of the receptor.

All the steroid hormones exert their action by passing through the plasma membrane and binding to intracellular receptors. The mechanism of action of the thyroid hormones is similar; they interact with intracellular receptors. Both the steroid and thyroid hormone-receptor complexes exert their action by binding to specific nucleotide sequences in the DNA of responsive genes. These DNA sequences are identified as hormone response elements, HREs. The interaction of steroid-receptor complexes with DNA leads to altered rates of transcription of the associated genes.
The following is a detailed biochemistry description of the steroid hormone receptors. Take note that peroxisome proliferator-activated receptor (PPAR) is included as nuclear receptor protein. Endogenous ligands for PPARs include free fatty acids and the eicosanoids. As fatty acid receptors that influence genetic expression via suppression of NF-kappaB activation as well as via independent pathways, PPARs when activated in moderation induce numerous beneficial physiological responses, including direct and indirect anti-inflammatory, anti-cancer and cardioprotective effects. In other words, this is how the anti-inflammatory effects of some of the fatty acids work. The following fatty acids can activated the beneficial effects of PPARs: EPA, GLA, and DGLA.

The receptors to which steroid hormones bind are ligand-activated proteins that regulate transcription of selected genes. Unlike peptide hormone receptors, that span the plasma membrane and bind ligand outside the cell, steroid hormone receptors are found in the cytosol and the nucleus. The steroid hormone receptors belong to the steroid and thyroid hormone receptor super-family of proteins that includes receptors for steroid hormones, thyroid hormones, vitamin D and vitamin A (retinoic acid).

When these receptors bind ligand they undergo a conformational change that renders them activated to recognize and bind to specific nucleotide sequences. These specific nucleotide sequences in the DNA are referred to as hormone-response elements (HREs). When ligand-receptor complexes interact with DNA they alter the transcriptional level (responses can be either activating or repressing) of the associated gene. Thus, the steroid-thyroid family of receptors all have three distinct domains: a ligand-binding domain, a DNA-binding domain and a transcriptional regulatory domain. Although there is the commonly observed effect of altered transcriptional activity in response to hormone-receptor interaction, there are family member-specific effects with ligand-receptor interaction. Binding of thyroid hormone to its receptor results in release of the receptor from DNA. Several receptors are induced to interact with other transcriptional mediators in response to ligand binding. Binding of glucocorticoid leads to translocation of the ligand-receptor complex from the cytosol to the nucleus.

The receptors for the retinoids (vitamin A and its derivatives) are identified as RARs (for retinoic acid, RA receptors) and exist in at least three subtypes, RARα, RARβ and RARγ. In addition, there is another family of nuclear receptors termed the retinoid X receptors (RXRs) that represents a second class of retinoid-responsive transcription factors. The RXRs have been shown to enhance the DNA-binding activity of RARs and the thyroid hormone receptors (TRs). There are also three distinct RXRs (α, β, and γ). The major difference between the RARs and RXRs is that the former exhibit highest affinity for all-trans-retinoic acid (all-trans-RA) and the latter for 9-cis-RA.
Additional super-family members are the peroxisome proliferator-activated receptors (PPARs). These receptors were originally discovered as proteins activated by agents that stimulate proliferation of peroxisomes in rat liver. An intracellular lipid-binding protein identified as aP2 is expressed exclusively in differentiated adipocytes. An adipocyte-specific enhancer of the aP2 gene is a target for peroxisome proliferators, fatty acids and 9-cis-RA. Subsequent to these observations it was found that there is an adipocyte-specific PPAR family identified as PPARγ. The PPARγ proteins form heterodimers with RXRs to activate adipocyte-specific enhancers such as the one in the aP2 gene.

Recent evidence has demonstrated a role for PPARγ proteins in the etiology of type 2 diabetes. A relatively new class of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of PPARγ. Mutations in the gene for PPARγ have been correlated with insulin resistance. It is still not completely clear how impaired PPARγ signaling can affect the sensitivity of the body to insulin or indeed if the observed mutations are a direct or indirect cause of the symptoms of insulin resistance.

The Estrogens

Ref: Reprinted with permission: Laboratory Evaluations for Integrative and Functional Medicine, 2nd ed., Lord & Bralley
Metametrix Institute, Duluth, GA
Only three estrogens are present in significant quantities in the plasma of the female: $\beta$-estradiol ($E_2$), estrone ($E_1$), and estriol ($E_3$). A primary function of the estrogens is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction. The estrogenic potency of estradiol is 12 times that of estrone and 80 times that of estriol making estradiol the major estrogen. Estriol has intermediate activity and estrone is the least active. Estrone increases with menopause and is mostly derived from androstenedione. There are three types of estrogen receptors: estrogen receptor-α, estrogen receptor-β, and estrogen receptor-γ.

**The Effects of the Estrogens**

- Proliferation of the endometrium and fallopian glandular tissue
- Initial growth of breasts and of the milk-producing apparatus
- Inhibit osteoclastic activity in bones
- Slightly increase whole-body metabolism
- Cause deposition of subcutaneous fat
- Cause the skin to develop a smooth soft texture
- Can cause some sodium and water retention (similar to aldosterone only much less significant except during pregnancy)

**The Estrogen Pool**

- Free estrogens
- Bound estrogen (SHBG)
- Sulfated estrogens
- Estrogen metabolites
- Exogenous estrogens
- Reabsorbed estrogens

**Estrogen Actions**

- Estrogens can have a stimulant or agonist effect depending on the receptor and/or tissue. After estrogen engages the receptor it may be inactivated and excreted

**Estrogen Clearance**

- Phase I detoxification – compounds must be rapidly detoxified via phase II pathways due to the high toxicity of the metabolites
- Phase II detoxification – Phase II makes the estrogen metabolites water soluble, non-reactive and ready for excretion in the urine or bile. These conjugated forms do not have any hormonal effects.
Cytochrome P450 isoforms catalyze formation of catechol estrogen quinones that react with DNA.
Metabolism 2007 Jul;56(7):887-94

Abstract

Accumulating evidence suggests that specific metabolites of estrogens, namely, catechol estrogen quinones, react with DNA to form adducts and generate apurinic sites, which can lead to the mutations that induce breast cancer. Oxidation of estradiol (E(2)) produces 2 catechol estrogens, 4-hydroxyestradiol (4-OHE(2)) and 2-OHE(2) among the major metabolites. These, in turn, are oxidized to the quinones, E(2)-3,4-quinone (E(2)-3,4-Q) and E(2)-2,3-Q, which can react with DNA. Oxidation of E(2) to 2-OHE(2) is mainly catalyzed by cytochrome P450 (CYP) 1A1, and CYP3A4, whereas oxidation of E(2) to 4-OHE(2) in extrahepatic tissues is mainly catalyzed by CYP1B1 as well as some CYP3As. The potential involvement of CYP isoforms in the further oxidation of catechols to semiquinones and quinones has, however, not been investigated in detail. In this project, to identify the potential function of various CYPs in oxidizing catechol estrogens to quinones, we used different recombinant human CYP isoforms, namely, CYP1A1, CYP1B1, and CYP3A4, with the scope of oxidizing the catechol estrogens 2-OHE(2) and 4-OHE(2) to their respective estrogen quinones, which then reacted with DNA. The depurinating adducts 2-OHE(2)-6-N3Ade, 4-OHE(2)-1-N3Ade, and 4-OHE(2)-1-N7Gua were observed in the respective reaction systems by ultraperformance liquid chromatography/tandem mass spectrometry. Furthermore, more than 100-fold higher levels of estrogen-glutathione (GSH) conjugates were detected in the reactions. Glutathione conjugates were observed, in much smaller amounts, when control microsomes were used. Depurinating adducts, as well as GSH conjugates, were obtained when E(2)-3,4-Q was incubated with CYP1B1 or control microsomes in a 30-minute reaction, further demonstrating that GSH is present in these recombinant enzyme preparations. These experiments demonstrated that CYP1A1, CYP1B1, and CYP3A4 are able to oxidize catechol estrogens to their respective quinones, which can further react with GSH, protein, and DNA, the last resulting in depurinating adducts that can lead to mutagenesis.

Beta- Glucuronidase

Bacterial β-glucuronidase is an enzyme that can effectively reverse detoxification that has taken place in the liver during phase II conjugation reactions. Bacterial flora may express large amounts of glycosidase enzyme activity, the principle glycosidase being β-glucuronidase. A report showing high levels of β-glucuronidase calls attention to the need to restore beneficial bacterial populations and to the potential for greater enterohepatic circulation that can affect metabolites such as estrogen. Increasing fiber, beneficial bacteria and D-glucarate can increase the excretion of estrogens and decrease enterhepatic recirculation.
The Catabolism of Estradiol

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Metametrix Institute, Duluth, GA
Progesterone

Progesterone is mainly involved with preparing the reproductive tract to support and maintain pregnancy by keeping the endometrial tissue intact. Progesterone is known to affect sleep quality, respiration, mood, appetite, learning, memory and sexual activity. Progesterone and 17-α hydroxyprogesterone are the natural forms of the hormone, of which, progesterone is the most abundant and most potent. Progesterone is made in the ovaries, testes, adrenal cortex and placenta.

Abstract

BACKGROUND: The preovulatory rise of progesterone is important for ovulation, but both its regulation and its origin are controversial. Three experiments were performed to determine whether follicular phase progesterone arises from the ovary, the adrenal cortex or both. METHODS: The first study was performed in patients scheduled for assisted reproduction, who received a long-acting GnRH agonist either during intake of an oral contraceptive or during the luteal phase of an otherwise untreated menstrual cycle. The second study was also performed during down-regulation with a GnRH agonist: some patients with elevated progesterone levels received dexamethasone (DXM). Others with similarly elevated basal progesterone levels and those with low progesterone levels were not treated with DXM and served as controls. Finally, adrenocorticotropic hormone (ACTH) tests were performed in normocyclic volunteers both during early and late follicular phase and during intake of a contraceptive pill. RESULTS: During the suppression of endogenous gonadotrophin secretion progesterone levels rose after the administration of ACTH, but not of GnRH. DXM did not prevent the preovulatory rise of the serum progesterone concentration. The ACTH-stimulated concentration of progesterone and of 17α-hydroxyprogesterone were significantly reduced during intake of ethinyl estradiol. CONCLUSIONS: Progesterone arises in the adrenal cortex during most of the follicular phase, whereby its function is modulated by an unknown ovarian factor, which is suppressed by ethinyl estradiol. The source of progesterone shifts towards the ovaries prior to ovulation. (Human Reproduction; Volume 17, issue 4, pp 933-939 2001)
Progesterone is bound in the serum by albumin and corticosteroid-binding globulin. Progesterone is metabolized and inactivated in the liver by hydroxylation, sulfation and glucuronidation. The mechanism of action of progesterone is the same as the estrogens, which is genomic. Progesterone receptors function the same as estrogen receptor via the nuclear receptor.

One of the most important concepts to remember is that progesterone and estrogen work in concert with one another. Estrogens cause the inductions of expression of progesterone receptors in many tissues and thereby priming the tissue to respond to progesterone. Progesterone also down-regulates estrogen receptors. High levels of progesterone can increase free estrogen by increasing the enzymatic activity of sulfatase. Sulfatase releases the sulfur from the conjugated estrogen (Sulfated estrogen) restoring it to its active form. In regard to estrogen and progesterone, it’s a matter of balance between the two in order to maintain optimal hormonal expression of each. Progesterone and estrogen receptors are both found in the same area of the brain and include the hypothalamus and the limbic system.

Progesterone has anti-inflammatory properties. Progesterone modules immune functions by inhibiting the enzyme in the prostaglandin cascade responsible for production of cyclooxygenase, matrix metalloproteinase, and different cytokines. Progesterone can also modulate neuronal activity. Progesterone has been found to reduce anxiety and modulate fear and pain. It appears the progesterone may modulate the gamma aminobutyric acid receptors.

**Testosterone**

![Testosterone](image)
Testosterone is formed by hydroxylation of androstenedione in the testes, the ovaries, and the adrenal glands. Testosterone secretion has a diurnal variation with peak secretion in the morning. Testosterone is an anabolic steroid that has the following effects on the target tissue:

- Promotes protein synthesis, increasing muscle and bone mass
- Promotes male secondary sex characteristics
- Increases sebaceous gland activity
- Cardioprotective via androgen receptor and estrogen receptor effects on may tissues

Dihydrotestosterone is synthesized from testosterone in the prostate gland, testes, hair follicles and adrenal glands by 5-alpha reductase. Dihydrotestosterone exerts its action similar to testosterone, which binds to and activates specific nuclear androgen receptors. After translocation into the nucleus, the activated hormone-receptor complex binds to the androgen response elements on the DNA and activates gene expressions that are required for sex development. Dihydrotestosterone is responsible for the formation of male primary sex characteristics and most male secondary sex characteristics during puberty, such as muscular growth, facial and body hair growth, and deepening of the voice. DHT appears to have an obligatory role in the development of BPH.

Low testosterone has also been associated with an increased risk for autoimmune disease; therefore assessing testosterone levels is paramount if you suspect an immunological disorder. The ovaries provide approximately half the circulating testosterone in premenopausal women. After bilateral oophorectomy, many women report impaired sexual functioning despite estrogen replacement. Testosterone also increases the estrogen effects by lowering sex-hormone binding globulin which then increases the level of free estrogen.
High frequency of association of rheumatic/autoimmune diseases and untreated male hypogonadism with severe testicular dysfunction


**Abstract**
Our goal in the present work was to determine whether male patients with untreated hypogonadism have an increased risk of developing rheumatic/autoimmune disease (RAD), and, if so, whether there is a relation to the type of hypogonadism. We carried out neuroendocrine, genetic, and rheumatologic investigations in 13 such patients and 10 healthy male 46,XY normogonadic control subjects. Age and body mass index were similar in the two groups. Nine of the 13 patients had hypergonadotropic hypogonadism (five of whom had Klinefelter’s syndrome [karyotype 47,XXY]) and 4 of the 13 had hypogonadotropic hypogonadism (46,XY). Of these last four, two had Kallmann’s syndrome and two had idiopathic cryptorchidism. Eight (61%) of the 13 patients studied had RADs unrelated to the etiology of their hypogonadism. Of these, four had ankylosing spondylitis and histocompatibility B27 antigen, two had systemic lupus erythematosus (in one case associated with antiphospholipids), one had juvenile rheumatoid arthritis, and one had juvenile dermatomyositis. In comparison with the low frequencies of RADs in the general population (about 0.83%, including systemic lupus erythematosus, 0.03%; dermatomyositis, 0.04%; juvenile rheumatoid arthritis, 0.03%; ankylosing spondylitis, 0.01%; rheumatoid arthritis, 0.62%; and other RAD, 0.1%), there were surprisingly high frequencies of such disorders in this small group of patients with untreated hypogonadism ($P < 0.001$) and very low serum testosterone levels ($P = 0.0005$). The presence of RADs in these patients was independent of the etiology of their hypogonadism and was associated with marked gonadal failure with very low testosterone levels.
Summary

The goal of this lesson is to provide you with a basic and advanced understanding of the interconnectedness of the steroid hormonal pathways. Hopefully you should have concluded by now, that you will need to evaluate all systems when addressing hormonal imbalances. These include diet, environmental, emotional, gastrointestinal, immune, detoxification, and energy production. As always, your comprehensive patient history, physical exam and primary lab testing will be your directional guide to optimize clinical outcomes.

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