Overview

Research shows that fluctuating levels of estradiol, progesterone, and testosterone play a key role in shaping the course of a woman's menstrual cycle, affecting changes in mood, sleep patterns, appetite, sexual drive and PMS symptoms.1-4 As clinicians and their patients become increasingly aware of the role that these hormones play in health, they are choosing more reliable, clinically relevant assessments of hormone function.

The Female Hormone Profile analyzes levels of progesterone, testosterone and β-estradiol over 28 days using 11 saliva samples. This profile provides clinical direction for successful treatment of individuals with menstrual irregularities, difficulties with ovulation, functional infertility, premenstrual syndrome, perimenopausal symptoms, osteoporosis, and other hormone-related disorders.

The test report includes numeric values of β-estradiol and progesterone for all 11 samples, as well as a graphic representation of β-estradiol and progesterone activity. Reference ranges are based on non-supplementing women. Transdermal and other forms of hormone replacement may cause significant elevations in salivary hormone levels. This assessment is thus recommended only as a baseline analysis in non-supplementing women.

A progesterone-to-estradiol ratio analysis is also included, along with a report of the salivary testosterone level. All data is beautifully presented and clearly interpreted, to help you readily identify any abnormal patterns and devise an effective, customized treatment plan to support your patient's natural hormonal rhythms.

Collection of samples: saliva vs. serum

The collection of female sex hormones in saliva is a convenient, non-invasive, and stress-free procedure. Collection of saliva is cost-effective, because the samples can be collected by the patient at home or in the workplace, without the assistance or supervision of medical personnel. Patient instructions are simple and easy to follow. In addition, saliva samples reveal critical information about hormones. Unlike plasma samples, salivary samples represent the free (unbound), bioavailable fraction of the hormone.5-7 These concentrations are independent of saliva flow rate.8

What are estrogens and progestins?

Three steroid hormones—estrone (E1), β-estradiol (E2), and estriol (E3)—are known collectively by their function as estrogens. Estradiol is the most physiologically active estrogen in non-pregnant women. Its potency is 12 times that of estrone and 80 times that of estriol.

In non-pregnant women, estrogens are mainly produced in the ovaries and adrenal cortex. In pregnant women, estrogens are also produced in the placenta. β-estradiol is produced in the ovaries; estrone is synthesized in the ovaries and adrenal cortices from β-estradiol and androstenedione; and estriol is formed in the liver by conversion of either β-estradiol or estrone.

Progestins are comprised of progesterone and 17-alpha-hydroxyprogesterone. They exhibit similar potency. Because 17-alpha-hydroxyprogesterone is produced in minute quantities compared to progesterone, the latter is considered the most significant progestin. As is the case with estrogen, progesterone is produced in the ovaries and adrenal cortex in non-pregnant women, while in pregnant women it is also secreted in the placenta.
Both progesterone and estradiol are formed from cholesterol via progressive modification by enzymes of the steriodogenic pathways. In the luteal phase progesterone levels increase dramatically, in spite of a portion of available steroids still being converted to estrogens. Conversion of β-estradiol to the less potent estrone or estriol diminishes circulating β-estradiol, and further functional degradation occurs as formation of glucuronides and sulfates in the liver takes place. Similarly, progesterone is functionally degraded to less potent steroids in the liver.

**Effects of estrogens on female physiology**

During puberty, estrogens play a significant role in the maturation of such female reproductive organs as the vagina, uterus, fallopian tubes, and ovaries. Estrogens also trigger secondary sexual characteristics, namely the development of breasts and increased osteoblastic activity resulting in characteristically feminine skeletal development.

Estrogens stimulate an increase in total body protein, promoting body development during puberty. These hormones also stimulate deposition of fat in subcutaneous tissues, particularly breasts, buttocks, and thighs. Estrogens influence development of vascular function and soft textured skin and have a minor effect on pubic and underarm hair growth. Furthermore, estrogens cause a slight retention of sodium and water by the kidneys and more pronounced retention during pregnancy.

**Effects of progesterone on female physiology**

Like estrogen, progesterone plays a role in increasing the size of breasts by stimulating the development of lobules and alveoli. During the menstrual cycle, progesterone promotes secretory changes in the endometrium preparatory to the implantation of a fertilized ovum. Progesterone also has a minor effect on the retention of sodium, chloride, and water by the kidneys.

**Effects of testosterone on female physiology**

In the adult female, testosterone plays an important role in maintaining lean body mass, bone density, skin elasticity, and libido. In addition, testosterone is involved in blood cell production. Low testosterone levels have been linked to increased risk for osteoporosis, decreased lean body mass, and decreased libido, and may suggest ovarian insufficiency and/or adrenal insufficiency. Elevated testosterone levels have been linked to masculinization, hirsutism, and increased risk of insulin resistance. Elevated testosterone levels have been noted in polycystic ovary disease and adrenal hyperplasia and suggest the presence of ovarian dysfunction or adrenal dysfunction.
The menstrual cycle

The average menstrual cycle takes about 28 days (25-35 days) to complete and falls into three phases.

The **follicular phase** (figure 1) is a period of ovarian follicular growth in which the uterine endometrium develops in preparation for the implantation of fertilized ovum. The growing follicles themselves produce high amounts of estrogen, which stimulates the uterine endometrium to proliferate and to synthesize cytosolic receptors for progesterone. Progesterone levels during this phase remain low.

The follicular phase can be divided into two stages. In the **preantral stage** of follicular growth, luteinizing hormone (LH) stimulates theca interna cells to produce androgens (mainly androstenedione), which diffuse through the basal lamina into the granulosa cell compartment to stimulate proliferation. The follicle grows, accumulates fluid, and forms an antrum. Estradiol levels are not high enough to diffuse into general circulation, so follicle-stimulating hormone (FSH) and LH are not inhibited.

In the **antral stage** of follicular growth, the combined effects of FSH and estradiol induce LH receptors on the granulosa cells. This enables them to begin producing estradiol from pregnenolone (de novo estradiol synthesis). Spillage of estradiol into the general circulation results from this increased estradiol pool and accelerated follicle growth. Subsequently, a relatively rapid increase in circulating estradiol level is seen during the last 5 or 6 days of the follicular phase.

Initially this rise in estradiol exerts a negative feedback on FSH release. Continued high levels (about a three-fold increase) presented over a 2- to 3-day period exert a positive feedback effect, resulting in a large surge of LH and FSH. The large bolus of LH (preovulatory LH surge) released induces ovulation in about 1 day.

The follicular phase lasts for about 9-15 days, and its duration determines the period of the menstrual cycle itself, since the length of the two subsequent phases remains fairly constant.

The **ovulatory phase** involves the release of the ovum or egg (ovulation) from the follicles and lasts about 36 hours. Ovulation is probably induced when LH stimulates the production of granulosa plasminogen activator, triggering the formation of plasmin, an enzyme responsible for digesting the basal lamina, and thus the rupture of the follicle.

Women generally experience an increase in the basal body temperature of 0.5 to 1.0 degree F following ovulation. This increase is due to the thermogenic effect of pregnanediol, a metabolite of progesterone.

After ovulation, granulosa cells proliferate in response to the preovulatory LH surge, while theca interna cells and perifollicular blood vessels invade the cavity of the collapsed follicle. Under the influence of LH, the granulosa and eovasive theca cells differentiate into luteal cells.

During the **luteal phase** (figure 2), the ruptured follicles in the ovary form a corpus luteum. Luteal cells are steroidogenic and produce large amounts of progesterone and moderate amounts of estradiol.

The increase of estrogen and progesterone during the first 4-5 days of the luteal phase promotes endometrium and fallopian tube secretions that allow for proper nourishment and implantation of the fertilized ovum. During this time, circulating levels of estradiol are reduced, a decrease necessary for the proper transport of the ovum through the fallopian tube into the uterus. Exposure to high levels of estrogen during this interval would lead to expulsion of the ovum or to blockage of ovum transport.

The corpus luteum has a life span of about 12 days. If fertilization and implantation do not occur, the corpus luteum degenerates (luteolysis), and its production of progesterone and estradiol rapidly declines, resulting in deterioration of the endometrium and its shedding (menstruation). The first day of menstruation is the first day of the menstrual cycle.

The endometrium is most conducive to implantation during the progesterone peak secretion period, about the 5th day into the luteal phase. If fertilization of the ovum occurs, secretion of chorionic gonadotropin (hCG) by the implanted blastocyst stimulates the corpus luteum to continue producing progesterone, and luteolysis is prevented.9
The use of the Female Hormone Profile (FHP) to enhance female health

FHP and anovulation

If the preovulatory surge of LH is not sufficient, anovulation can occur. The pre-ovulatory surge of LH is linked to the positive feedback of the pre-ovulatory estrogen peak. Lack of ovulation leads to the failure of corpus luteum development and reduced production of progesterone.

One study found a lack of appropriate progesterone levels in healthy women with anovulatory cycles. Several researchers confirmed that a study of estrogen/progesterone cycles would help diagnose anovulatory cycles and corpus luteum dysfunction. Anovulation during puberty is not an uncommon problem, even among otherwise normal young women. A case study involving 65 healthy adolescent girls (14-19 years of age) suggested that about one-third of them had anovulatory cycles. Another study showed a 22% anovulation rate among healthy women aged between 20 and 31.

FHP and infertility

Infertility is defined as a year of unprotected intercourse without achieving pregnancy. Infertility occurs in about 10% of the population. The probability of anovulation or luteal phase defect causing infertility is 20-40% and 3-10%, respectively. Functional infertility occurs as a result of several conditions. Excessive estrogen and progesterone levels inhibit FSH and LH, impairing ovulation and the formation of the corpus luteum. Corpus lutea may degenerate and become refractory to LH. Finally, if the corpus luteum falters in its production of progesterone ("luteal defect"), the endometrium deteriorates and is incapable of supporting the implanted embryo.

FHP and premenstrual syndrome (PMS)

PMS is described as a group of symptoms that include abdominal bloating, headaches, mood swings, irritability, and other complaints occurring during the luteal phase of the menstrual cycle. With the onset of menses, the symptoms usually disappear. Progesterone deficiency, increased estrogen, or estrogen/progesterone imbalances can all trigger PMS.

FHP and osteoporosis

Because estrogen participates in the functioning of osteoclasts and osteoblasts in bone tissue, the hormone influences the rate of absorption and deposition of calcium. Estrogen deprivation following menopause results in increased activity of osteoclasts which may exceed the capacity of osteoblasts to build new bone. Under these conditions osteopenia and ultimately osteoporosis occur.

FHP and amenorrhea

Functional secondary amenorrhea or oligomenorrhea is defined as the failure of a woman with periodic menses to experience menstruation for six consecutive months. The association between high intensity athletic training and menstrual disturbances may be attributable in part to altered nutritional intake and body mass and in part to exercise- and competition-induced stress. One study observed that salivary progesterone levels change with age, that lower progesterone peaks were recorded in women aged 18-19 and 40-44 years, and that women experienced a gradual increase in peak progesterone levels from age 20-39.

FHP and luteal phase defects

Patients with prolonged, unexplained infertility experienced a high frequency of luteal phase defects, including pre-ovulatory progesterone peaks, interruption of progesterone secretion during the luteal phase, and high progesterone levels at the beginning of menstruation. Researchers recorded a correlation of 0.71 (10 of 14) between low progesterone levels and luteinized unruptured follicle cycles. Another study of 50 infertile women with regular menstrual cycles of normal length revealed low progesterone levels in subgroups with three menstrual patterns: cycles with luteinized unruptured follicles, cycles with an early luteinizing surge, and normal controls.
FHP and endometriosis
A significant number of infertile women show ovarian dysfunction with endometriosis. Higher progesterone levels in late follicular and luteal phases have been associated with endometriosis. A recent study of women with infertility and endometriosis found that 50% had normal progesterone cycles, while 45% showed higher progesterone levels. Among the latter, 18% of the subjects exhibited elevated levels in the follicular phase, 20% in the luteal phase, and 7.5% in both phases.

FHP and stress
Stress has been shown to decrease the production of sex steroids, which could lead to reduced libido and menstrual irregularities. Maladaptation of the adrenocortex in producing high cortisol levels is, at least in part, responsible for the reduction of sex steroid levels.

FHP and diet
There is strong evidence that the foods consumed by women have an effect on hormone levels. Investigation into dietary habits and, in particular, vegetarian diets has established that certain foods can modify gonadal estrogen metabolism. Researchers have also speculated that early menarche recorded in girls of developed countries could be due to consumption of steroid hormones in meats.

FHP and breast cancer
Elevated estrogen levels are generally considered an increased risk factor for breast cancer, especially in women after menopause. A study of 276 British and Thai women with different levels of progesterone indicated that higher levels of progesterone may also be a risk factor for breast cancer. This hypothesis was further strengthened by another study of 362 young women.

FHP and menopause
In the United States, the cessation of menstruation normally occurs between 40 and 60 years of age. The initial symptoms of the perimenopause include irregular menstrual cycles, anovulation, and hot flashes. A decline in the levels of progesterone and estrogen also occurs at this time. Estradiol values decline to subfunctional levels after menopause. In some women, maintaining adequate estrogen levels after menopause may alleviate the typical symptoms of menopause, but hormone replacement therapy may increase a woman’s risk of developing endometrial cancer. A decrease in progesterone levels also results in a reduced anti-estradiol effect. The inability of a woman’s body to maintain the secretory activity of the endometrium may lead to endometrial hyperplasia, irregular bleeding, and related conditions. The information provided by FHP concerning hormone levels can provide a baseline to help determine the need for hormone replacement therapy.

FHP and exercise
Menstrual irregularities (oligomenorrhea, amenorrhea, anovulation) in athletic women have been attributed to strenuous physical exercise. These patients showed increased estrogen and decreased progesterone levels in the luteal phase. This pattern could be due to an impaired metabolic clearance rate (MCR) of estradiol during physical exercise and decreased sex steroid production under stress.

FHP and cigarette smoking
Although there is evidence of reduced fertility caused by cigarette smoking, the relationship between cigarette smoking and the anti-estrogenic effect related to infertility remains unclear. Several studies show a positive correlation. However, a recent publication suggests no significant correlation between hormone levels and smoking.

Related Tests to Consider
Because hormones work together and influence each other in complex ways, an analysis of the hormones melatonin, DHEA and cortisol can give a more complete picture of how endocrine function may be influencing female reproductive health. Assays of these additional hormones are included in the Comprehensive version of the Female Hormone Profile or as components of two separate profiles (see below).
Adrenocortex Stress Profile
DHEA serves as the metabolic source for estrogen production, and levels decline dramatically with age, affecting weight gain, energy level, and the aging process itself. Additionally, imbalances of cortisol, the stress hormone, are linked to obesity, depression, chronic fatigue, and other health problems. The Adrenocortex Stress Profile plots the circadian activity of cortisol, along with measuring the level of DHEA.

Comprehensive Melatonin Profile
Researchers theorize that sex hormones regulate melatonin production by modifying beta-adrenergic mechanisms. This may partially explain why significantly increased levels of melatonin are found in women during the luteal phase of ovulation. Melatonin generally exerts a strong antioxidant effect and a tendency to inhibit growth of estrogen-dependent tumors. Oversecretion, however, is associated with Seasonal Affective Disorder (SAD), while deficiencies are strongly linked to a variety of sleep disorders. This profile evaluates the circadian pattern of melatonin secretion over a complete light-dark cycle.

Bone Resorption Assessment
It would be hard to overemphasize the importance of early identification of bone loss. The Bone Resorption Assessment should be part of an overall reproductive health evaluation for any woman over thirty, the age when bone loss begins to accelerate. If bone loss is detected early enough, interventions can arrest loss and protect against osteoporosis and bone fractures in the years following menopause. By measuring current bone turnover, this profile can help patients avoid future bone loss and fractures while monitoring the effectiveness of preventative treatments such as calcium supplementation.

Detoxification Profile
Steroid hormones are detoxified through phase II processes in the liver, and imbalances in detoxification pathways can partially influence the levels of circulating steroids. Conversion of β-estradiol to the less potent estrone or estriol, for example, diminishes circulating β-estradiol. On the other hand, impaired sulfation or glucuronidation may result in increased levels of estradiol and progesterone. The Detoxification Profile uses breakthrough testing procedures to assess the body’s capacity to carry out detoxification through functional challenges. This profile reveals the detoxification capacity of specific metabolic pathways, along with the body’s potential susceptibility to oxidative stress.

Comprehensive Digestive Stool Analysis
Because the endocrine system relies on good nutrition for proper function, maldigestion and malabsorption of nutrients can interfere with normal hormonal function and greatly affect a woman’s reproductive health. If a patient exhibits any indication of digestion problems, the Comprehensive Digestive Stool Analysis and related tests of gastrointestinal function are useful for identifying other factors that may be contributing to hormonal imbalances.

How do I order this test?
For Female Hormone Profile kits or information, please call a GSDL Accounts Receivable representative at 888-201-8333 or use our secure web contact center at www.gsdl.com/billing.
References


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