



The Salivary Hormone Profile

in the Clinical Evaluation of Women

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Women presenting to primary care physicians may have symptoms consistent with hormonal dysfunction or diagnoses exacerbated by hormonal factors. In my experience, salivary hormone analysis allows accurate and readily accessible evaluation of a woman's hormonal status. Salivary measurement of hormones has been performed in clinical research for over 30 years, including studies conducted at the National Institutes of Health (NIH), and it has remained a mainstay in clinical research studies. The hormones most extensively investigated¹⁻⁴ include: estradiol, estrone, estriol, progesterone, dehydroepiandrosterone (DHEA), testosterone and cortisol. Saliva tests of sex and steroid hormones have moved into the clinical practice arena in the United States within the last decade;⁵⁻⁷ however, although the validity and application of the tests are well supported and Medicare and private insurers offer reimbursement for such testing, they are not in wide use in the primary care of women. In this article, I present some general background regarding the diagnosis and treatment of hormonally related symptoms and disadvantages and advantages of both saliva and serum testing and discuss other factors for consideration, guidelines for testing and interpretation and clinical application.

Background

Estrogens, progesterone, testosterone, DHEA and cortisol play a vital role in many aspects of a woman's physiology and quality of life, including body composition, libido, sexual satisfaction, mood, cognition, vasomotor symptoms, sense of

well-being, bone density, sleep quality and musculoskeletal pain. However, primary care physicians are often challenged in their clinical evaluation of women's hormonal changes. Patients may report constitutional symptoms self-attributed to hormonal changes that significantly impact their quality of life; yet conventional diagnostic testing of metabolic and endocrine status may show them to be in the normal range. Though physicians may suspect sex steroid and steroid influences as contributing to the patient's symptoms, they may be unable to quantify such associations objectively and accurately through traditional testing methods.

Conditions secondary to hormone elevations or decreases in bioavailability of hormones include:

- Female sexual dysfunction
- Luteal phase insufficiency
- Perimenopause
- Polycystic ovarian syndrome
- Postmenopause
- Premenstrual dysphoric disorder
- Premenstrual syndrome⁶

Other diagnoses that may be impacted by sex steroid hormone changes in women include:

- Asthma
- Chronic pain syndrome
- Connective tissue diseases
- Fatigue
- Fibromyalgia
- Hypothyroidism
- Irritable bowel syndrome
- Metabolic syndrome
- Migraine headache
- Mood disorders
- Obesity
- Seizure disorders⁸⁻²⁵

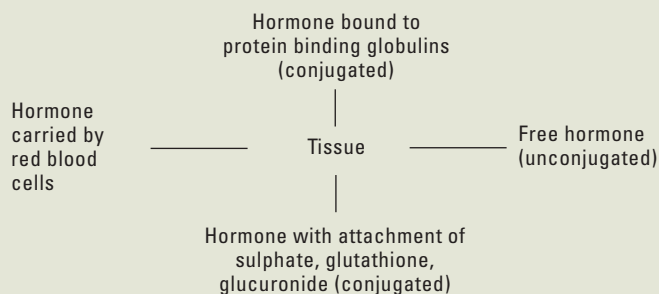
Advantages and Disadvantages of Serum and Saliva Testing

Serum Testing

Perhaps the most obvious advantage of serum testing is that, during medical training, physicians are educated regarding serum hormone evaluation. Tables of normal serum values for sex and steroid hormones are published in reference texts and most physicians have reference laboratories readily available. Thus, this testing vehicle is readily accessible and has established standards for evaluating results.

However, serum testing may not accurately predict hormone bioavailability.²⁶ Conventional thinking is consistent with the concept that only free (unbound) hormones are able to exit the capillary and traverse the cell membrane, thereby triggering intracellular changes. Research has revealed that hormones traveling in the blood in free forms, as well as conjugated by the attachment of a sulphate, glutathione or glucuronide (to enhance water solubility); hormones bound to albumin; sex-hormone binding globulins (SHBGs); and hormones carried by red blood cells (RBCs), *all* form reservoirs that are available to the tissue (Figure 1). A process known as *facilitated dissociation* allows protein-bound hormone to be available to tissues,

Figure 1. Reservoirs That Are Formed and Available to Tissue as a Result of Hormones Traveling in the Blood.



Note: The target tissue receives hormones from various circulatory reservoirs. Under endogenous conditions, a state of equilibrium exists, with different tissues exhibiting variability in hormone bioavailability.

including some that are bound to SHBG.¹⁵ Studies²⁷⁻³¹ reveal that RBCs with bound hormone serve as a significant circulation reservoir of sex hormone, making up as much as 5% to 35% of total exchange hormones in the bloodstream.

Most serum tests define the normal range of hormones very broadly, which is a distinct disadvantage to their use, especially

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for women with levels in the low analyte ranges. After the patient's blood is drawn, only a portion of the blood sample, called the *serum*, is used for measuring hormone levels. Most methods only measure a "free" or "total" hormone level or a calculated combination of both, and values have been shown to be inconsistent, especially at the lower ranges of normal. This type of testing is not an accurate reflection of the bioavailable hormone (ie, the amount of hormone that is active in organs and tissues).³¹⁻³⁷

Saliva Testing

Salivary hormone analysis is a useful clinical tool in the assessment of women, and scientific evidence supports its use because it offers an accurate and comprehensive reflection of hormone bioavailability at the tissue level.⁵ Reference values for salivary hormone levels have been established for women. Salivary hormone levels reflect the delivery of hormone to tissue from all mechanisms—free, protein-bound, red blood cell-bound and conjugated.

One advantage to salivary hormone testing is that it is easy, as well as more convenient for the patient. In evaluations of bi-urnal and diurnal cortisol levels secondary to patient circadian rhythms or luteal-phase hormonal changes, physicians and patients are often frustrated in their attempts to have phlebotomy performed at precise times of the day or the menstrual cycle. In contrast, saliva can be easily obtained at desired times without disrupting laboratory schedules for phlebotomy stations. Furthermore, since saliva collection is typically performed at home or in the workplace, there is high patient compliance. For women who work in an occupational setting, followed by 24 to 40 hours per week of tasks related to child-care, eldercare, household duties, community and/or volunteer work, being required to go to a laboratory 1 to 4 times during a day or at specific phases of her menstrual cycle may well be impractical and inconvenient.

Studies^{15,34,35} also reveal that some patients are significantly stressed when undergoing phlebotomy, and changes induced by venipuncture stress can significantly affect serum values. Thus, the serum value may not be an accurate measure of the patient's usual endogenous hormone level. In contrast, saliva testing has not been shown to cause a stress response in patients.

Some physicians have criticized salivary testing for inaccuracy in measuring hormone levels after transdermal hormone replacement therapy (HRT), since there is a discrepancy in serum and salivary hormone levels immediately after dosing. Salivary levels are much higher than serum levels following topical administration of hormones. This phenomenon is explained by the important role of erythrocytes in steroid hormone transport. Some studies^{33,36,38} demonstrate that, when progesterone is delivered topically, serum testing of steroid hormones may not accurately reflect tissue bioavailability. Saliva-testing laboratories with technical expertise have established expected ranges for oral and transdermal dosing. When sex hormones are delivered topically, saliva provides a more

accurate hormone activity at the tissue levels.

Another advantage of salivary testing is cost. The cost of salivary hormone analysis is markedly less than that of serum testing. For example, a single hormone test for salivary estradiol averages less than one-fourth the cost of a single serum level. Considering that patients usually undergo evaluation of more than one hormone, such cost differences can be pronounced.³⁹

However, salivary testing does have some disadvantages. First, College of American Pathologists (CAP) and American Association of Bioanalysts (AAB) proficiency standards have not been established specifically for salivary testing. Laboratories that offer such testing may be Clinical Laboratory Improvement Amendments (CLIA)-certified; however, this is based on serum testing procedures. In addition, salivary hormone assays are technically challenging, which limits the number of laboratories capable of offering this assay. Furthermore, contamination of saliva samples may occur during sample collection, resulting in falsely elevated hormone levels. This may occur through the patient's use of topical substances (eg, facial serums, lipsticks) on the face, lips or hands, and care must be taken to ensure that the patient follows test collection instructions to avoid such contamination. The patient must



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Table 1. Physical Symptoms and Associated Health Risks of Hormone Imbalance in Women.

<p>Dysregulation of Cortisol Circadian Pattern⁵⁷⁻⁶⁹</p> <ul style="list-style-type: none"> Acne Arthralgias and myalgias Decrease in muscle mass and stamina Decreased libido Elevated levels of triglycerides Fatigue Food cravings (eg, for sugar) Headaches Heart palpitations Increased morbidity of breast cancer Increased risk of breast cancer Increased risk of dementia Increased risk of heart disease Increased risk of immune system dysfunction Irritability, depression or anxiety Loss of scalp hair Lowered basal body temperature Mid-body weight gain Osteoporosis or osteopenia Short-term memory impairment Sleep disorders 	<p>Insufficient Estrogen and/or Progesterone^{15,16,41,53,54,75}</p> <ul style="list-style-type: none"> Aches and pains Decreased clarity of thinking Depression Dry hair and skin Fatigue Headaches Heart palpitations Hot flashes Impairment of short-term memory Incontinence Night sweats Osteoporosis or osteopenia Sleep disorders Tearfulness Vaginal dryness 	
<p>Excess Estrogen and Insufficient Progesterone (Estrogen Dominance)^{8,41,47,70-76}</p> <ul style="list-style-type: none"> Accelerated aging Anxiety Bloating Breast tenderness Decreased libido Fibrocystic breast disease Fibroids of the uterus Food cravings (eg, for sugar) Headaches Heavy menstrual periods Hypersensitivity Increased levels of triglycerides Increased risk of blood clots Increased risk of breast cancer Increased risk of fibroids Increased risk of gallstones Increased risk of postpartum depression Irregular menstrual cycles Irritability Mood swings Ovarian cysts Symptoms of premenstrual syndrome Weight gain (hips, waist, thighs) 	<p>Insufficient Testosterone or Dehydroepiandrosterone^{48-50,59,78-80}</p> <ul style="list-style-type: none"> Blunted motivation Body aches and pains Decreased attention span Decreased clarity of thought Decreased libido, sexual receptivity and pleasure Decrease in muscle mass and stamina Diminished sense of psychological well-being Disturbed sleep Depressed mood Hot flashes Impairment of short-term memory Incontinence Increased risk of fibromyalgia Increased risk of heart disease Increased risk of rheumatoid arthritis Low energy and persistent unexplained fatigue Osteoporosis or osteopenia Thinning of the skin Vaginal dryness 	<p>Excess Testosterone and/or Dehydroepiandrosterone^{51,55,77}</p> <ul style="list-style-type: none"> Acne Depression Disturbed sleep High levels of triglycerides Increased risk of breast cancer Increased risk of bulimia and anorexia nervosa Increased risk of heart disease Increased risk of metabolic syndrome Increased risk of polycystic ovary syndrome Increase in abdominal fat Increase in facial and body hair Irritable mood Loss of scalp hair Ovarian cysts

also avoid eating, drinking, chewing gum, flossing and brushing teeth 2 hours prior to saliva collection, as these activities may affect hormone levels. Finally, the route of administration (oral, sublingual, topical, vaginal) of hormone supplementation must be considered prior to saliva sample collection for laboratory application of appropriate reference ranges.

Other Factors for Consideration

Follicle-Stimulating Hormone Testing

The follicle-stimulating hormone (FSH) test is often used as the primary indicator of a woman's hormonal status. A properly conducted FSH test requires that blood be drawn three times at sixty-minute intervals beginning precisely at 8:00 AM.⁴⁰ Follicle-stimulating hormone reference ranges are

based on the average of the three levels in a properly performed test. Follicle-stimulating hormone directs the maturation of ovarian follicles and the release of estrogen. It also prepares the uterus for the changes that occur during the first half of the menstrual cycle. The FSH test is frequently used to determine the hormonal status of premenopausal patients who may complain of hot flashes, mood ranges, or other symptoms identified in Table 1. It may be concluded that a patient's symptoms are not related to hormones because her FSH test is normal. The FSH test should not be used as an accurate measure of sex hormone production or an indication of reproductive status for most women because the level of FSH fluctuates widely during the decade preceding menopause.⁴¹ Follicle-stimulating hormone is a clinical marker for inhibin, which is secreted by ovarian follicles; and a decrease in inhibin levels begins around age 35 and accelerates after age 40 due to follicle damage, atresia and senescence. Follicle-stimulating hormone should not be used as a measure of endogenous sex hormone production or reproductive status because women may experience ovulation with normal follicle release between the age of 40 and menopause.

Patient History

The patient's history is critical in determining both the selection of hormones for testing and the time of testing. The physician may ask the patient to complete a questionnaire or may elicit information by questioning the patient. Numerous studies and books^{37,42-44} have documented the psychoneuroendocrine sequelae along with physical symptoms related to hormonal factors (Table 1). An example of the importance of history taking would be the case of a patient who reports moderate-to-severe palpitations and abdominal bloating that interfere with her quality of life, with onset 7 to 10 days prior to menses and the absence of such symptoms in other phases of her menstrual cycle. This patient should be tested for estradiol, progesterone and testosterone in the luteal phase when her symptoms occur.⁴⁵ Another patient might report daily fatigue with consistent onset at midday, followed by some lifting of fatigue in the evenings, coupled with nocturnal-associated anxiety contributing to sleep disturbance. Appropriate testing in this patient would include cortisol salivary collection on awakening, at noon, in the afternoon and in the evening, along with sex steroid levels. Another typical example is a woman in her 40s who has had a hysterectomy and bilateral salpingo oophorectomy and reports chronic constitutional symptoms of fatigue, low libido, cognitive changes, centripetal weight gain, body aches and decreased stamina. Salivary hormone analysis in this patient should include measurement of estradiol, estrone, estrone, DHEA, testosterone, progesterone and diurnal cortisol.⁴⁶⁻⁴⁹ Assessment of the hypothalamic pituitary adrenal axis via salivary testing is helpful in the evaluation and treatment of patients with mood disorders.⁵⁰⁻⁵⁵

Physical Exam

Women with symptoms possibly related to hormonal changes should also undergo a physical exam, including a

breast exam and genital exam. Examples of physical findings related to hormonal changes are listed in Table 2.

Guidelines for Testing

For primary care physicians who desire to integrate saliva testing into their clinical setting, collaboration with a laboratory that has proficiency and expertise in this area is necessary. Although CAP and AAB have not established proficiency standards for salivary testing, CLIA certification may be helpful as a starting point. The laboratory can furnish the physician with saliva test kits, which include patient instructions and mailing supplies that meet current postal standards for shipping. Laboratories with medical directors and knowledgeable staff in this discipline should be available to consult with the ordering physician.

Interpretation and Clinical Application

A CLIA-certified laboratory with technical expertise in salivary hormonal assays will provide a hormone evaluation report that will serve as a guide for understanding how hormones can affect a patient's health and well-being. An example of such a report can be accessed on the *International Journal of Pharmaceutical Compounding's* website. Physicians may wish to consult

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Table 2. Physical Findings in Women with Hormonal Imbalance.

<i>Physical Exam</i>	<i>Clinical Feature or Abnormality</i>
Abdomen	Striae, increased visceral fat distribution
Back and musculoskeletal	Degenerative changes, loss of muscle tone, muscle spasm, trigger points
Blood pressure	Equal to or greater than 130 systolic and 85 diastolic
Breast	Fibrocystic changes, edema, atrophic changes
Extremities	Peripheral edema, brittleness of nails, cool temperature of hands and feet
Head, eyes, ears, nose, throat	Dry eyes, dental changes of gum decay, scalp hair thinning, hair loss, premature graying of hair, dryness or coarseness of hair
Neck	Goiter, nodules
Neurologic	Cognitive changes (ie, difficulty with word and name retrieval, diminished capacity for short-term memory)
Pelvic	Atrophic vulvitis or vaginitis, clitoramegaly, uterine enlargement or fibroids, ovarian cysts, vulvar dystrophy
Psychiatric	Flat or blunted affect, depression, anxiety, irritability
Skin	Acanthosis nigricans, acne, folliculitis, furunculosis, hirsute changes, hyperpigmentation, ichthyosis, premature wrinkling, striae, thinning or splitting of fingernails
Weight	Body Mass Index less than 18.5 or equal to or greater than 25

with testing laboratory consultants in the initial phases of interpretation. During a follow-up appointment, the patient should be educated by the physician

regarding laboratory findings. The visit should include a discussion of nutrition, exercise, lifestyle issues and pharmacotherapy. Patients are usually highly

satisfied with this individualized approach, and such satisfaction contributes to patient motivation and spousal and family support for lifestyle changes, exercise and nutritional modifications.

Findings⁵⁶ of the Women's Health Initiative have caused patients and physicians to proceed with caution in the use of HRT in postmenopausal women. However, despite findings that HRT may increase the risk of heart disease, stroke, venous thrombosis and breast cancer, many women with severe menopausal symptoms have chosen to continue HRT due to quality-of-life issues. Physicians may use the salivary assay as a quantitative measurement of hormone changes in prescribing effective treatment strategies, rather than guessing about hormone doses or relying on serum testing results, which may conflict with patient-reported symptoms. Such patients and their physicians may appreciate salivary hormone assays for evaluating the effects of exogenous hormones to achieve a goal of normal physiological levels and to more closely mimic an endogenous state, rather than creating or exacerbating hormonal imbalances.

Occasionally, spurious results occur, as the salivary hormone test is a highly sensitive assay. In such a case, the physician should question the patient regarding compliance with instructions and

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might also wish to discuss the results with the medical director of the testing lab. Clinical correlation is mandatory, as there is variability in each patient's hormone receptor affinity, sensitivity and pharmacokinetics that cannot be measured in the clinical practice setting; however, the majority of patient symptoms closely correlate with the salivary profile. In my experience in working with thousands of hormonal assays on women, salivary hormone testing has enhanced diagnostic and therapeutic decision making.

Summary

The adaptability of the salivary hormone assay to the clinical evaluation of women can be beneficial to primary care physicians in diagnosing and treating conditions secondary to hormonal excess or deficiency or conditions exacerbated by such hormonal changes. In comparison with serum testing, the saliva test offers significant advantages and can be easily integrated into the primary care setting. Furthermore, patient acceptance, compliance and satisfaction are high and may result in increased compliance with physician-recommended regimens for nutrition, exercise, lifestyle changes and pharmacotherapy.

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