

**RESULTS: 24 hr Comprehensive Urine Hormone Profile Plus**

Accession #: 100035688 • Patient: JANE SMITH

**Patient:** JANE SMITH

**Tel:** (123) 456-789      **Email:** test@tets.com

**Sex:** Female      **Age:** 35 yr

**Height:** Not Entered      **Weight:** Not Entered      **Date of Birth:** 1989-09-29

**1st day of last menses:** Day 12, Month 09

**Menstrual status:** Regular

**Hormones (Medication):** Not Specified

**Health Care Professional:** Jane Smith

**Accession #:** 100035688

**Sample received:** 2024-11-05

**Report issued:** 2024-11-25

**Sample collection:**
**Date:** 2024-11-05

**Volume in 24hrs.:** 569 ml

**Time of First Void:** 08:30 AM

**End of Collection Time:** 23:15 AM

**Company:** Gabriel Roman

**24 HR COMPREHENSIVE URINE HORMONE PROFILE PLUS**

Estrogens	Result (µg/24hrs.)
Estrone (E1)	Low 0.8
Estrone (E1) - Women on HRT	Low 0.8
2-Hydroxyestrone (2-OH-E1)	Low 0.5
16α-Hydroxyestrone (16α-OH-E1)	Low 0.2
4-Hydroxyestrone (4-OH-E1)	3.7
2-OH/16α-OH Estrone Ratio	2.3
Estradiol (E2)	Low 0.5
Estradiol (E2) - Women on HRT	Low 0.5
Potent Estrogen Ratio (E1 / E2)	1.6
Estriol (E3)	Low 2.4
Estriol (E3) - Women on HRT	Low 2.4
Total Estrogens (E1+E2+E3)	Low 3.8
Total Estrogens (E1+E2+E3) - Women on HRT	Low 3.8

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Progesterone		Result (µg/24hrs.)
Pregnanediol (PD)	1463 2095 2727 3550 4400	<b>High</b> 6160
Pregnanediol (PD) - Women on HRT	800 1500 2500 4300 6500	<b>High</b> 6160
Androgens		
Testosterone (T)	5 7.4 13 18 24	<b>Low</b> 3.4
Dihydrotestosterone (DHT)	3 15	<b>&lt;= 3.0</b>
Androstenediol	9 16 40 56 69	30.7
DHEA	20 108 492 1000 1260	38.1
7-keto DHEA	4 6 34 45 56	5.9
5-Pregnenetriol (5-PT)	44 77 260 342 390	208
Androsterone (AN)	312 1057 2175 2920 3650	983
Etiocolanolone (ET)	742 1097 2160 2869 3600	1359
Corticosteroids		
Cortisol (F)	37 63 102 115 150	86.4
Tetrahydrocortisol (THF)	465 839 1801 2763 3500	1597
5α-Tetrahydrocortisol (5α-THF)	142 436 1039 1441 1800	579
Cortisone (E)	55 94 189 215 270	209.8
Tetrahydrocortisone (THE)	777 1805 3861 4889 5917	3506
Cortisone / Cortisol (E/F)	1 1.5 2.5 3.5 4	2.4
THE + THF + 5α-THF	1000 3000 5000 6000 12000	5682
Corticosterone		
Tetrahydro-11-dehydrocorticosterone (THA)	39 105 202 265 330	224

**ND = NONE DETECTED**

Analysis performed by Rhein Consulting Laboratories, F.J. Nordt, Ph.D., Director, 4475 SW Scholls Ferry Road, Suite101, Portland, OR 97225, USA

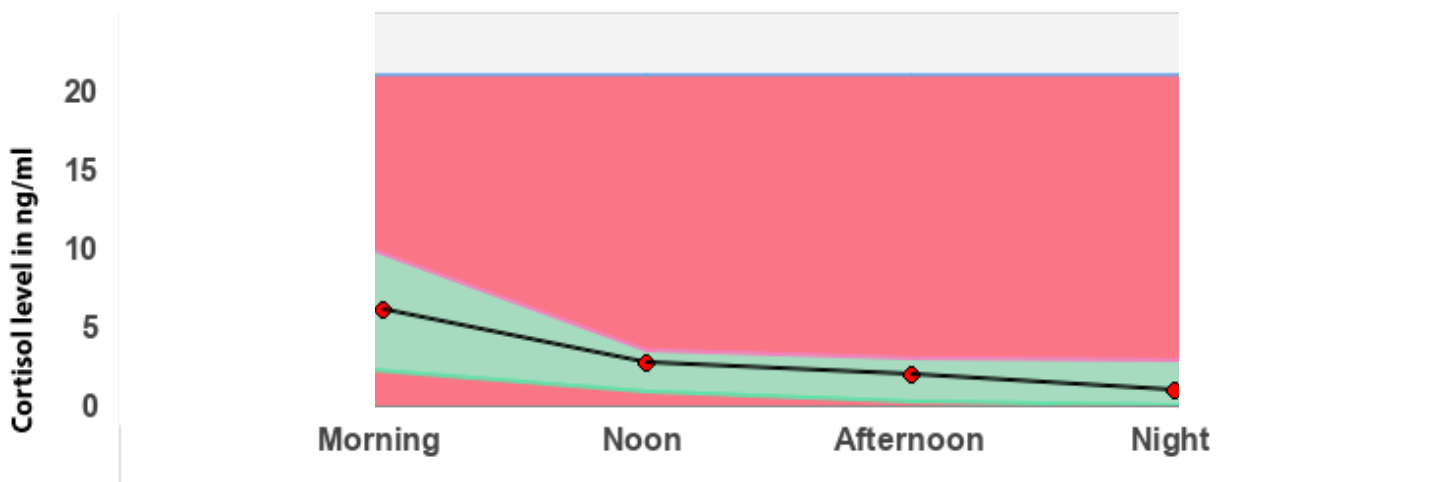
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**24 HR COMPREHENSIVE URINE HORMONE PROFILE PLUS - DIURNAL CORTISOL**

HORMONE ng/ml	RESULT	REFERENCE RANGE	MEDIAN
Cortisol - morning	<b>6.5</b>	2.2 - 9.8	3.9
Cortisol - noon	<b>2.8</b>	0.9 - 3.5	0.9
Cortisol - afternoon	<b>2</b>	0.3 - 3.0	0.6
Cortisol - night	<b>1.5</b>	0.1 - 2.8	0.3
CORTISOL - TOTAL	<b>12.8</b>	3.5 - 19.1	5.6

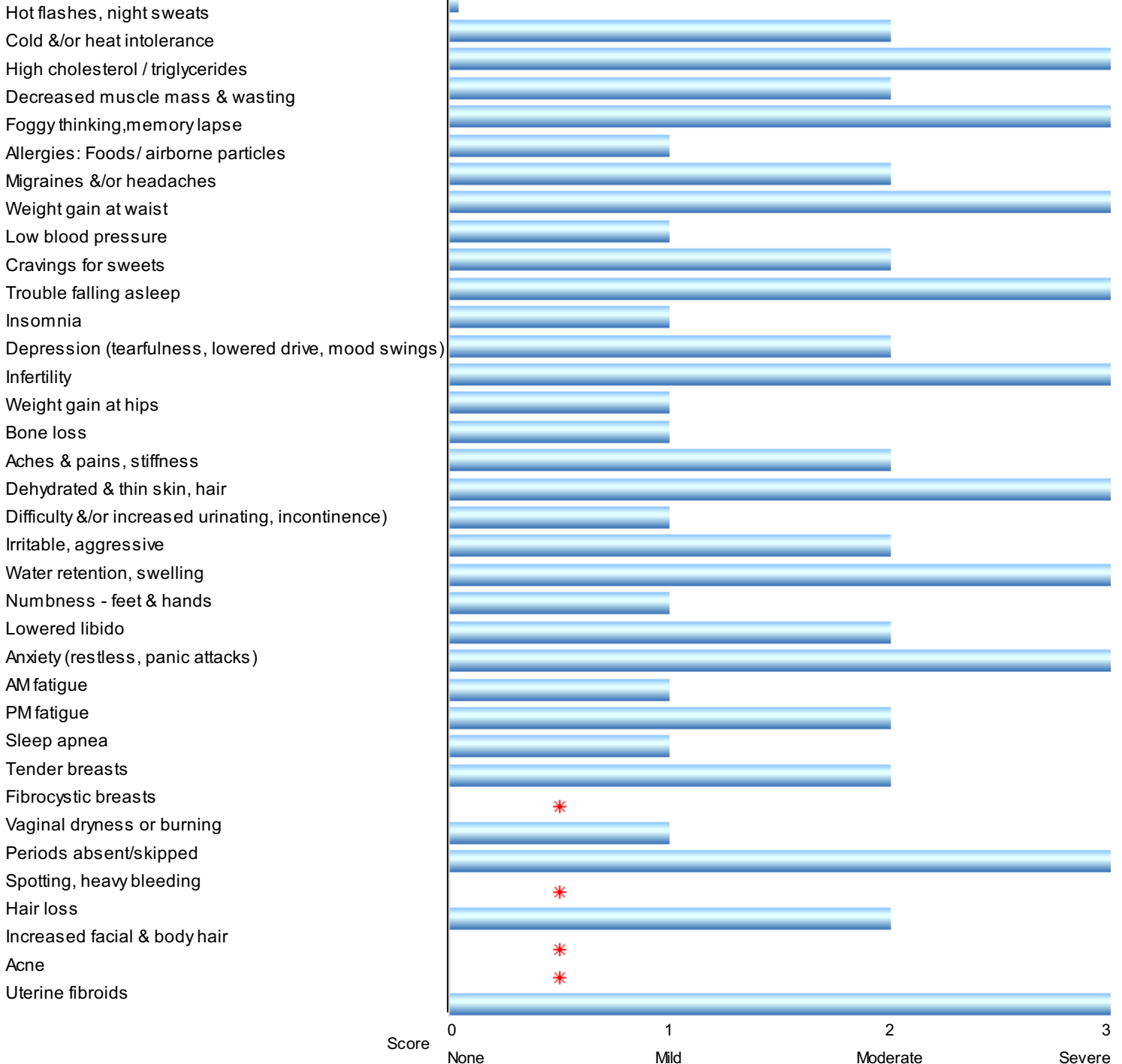


Green shade represents the normal range

 represents the patient results

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**Symptoms**


\* Indicates that symptom left blank

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The comments provided here are for educational purposes only. They should not be interpreted as being diagnostic or treatment recommendations. Those decisions are the responsibility of the health care professional.

**General Considerations:**

Hormones, measured in urine, comprise a major end-pool of steroids. As a result, the steroids that are present in a 24-hour urine sample are a good approximation of the daily turnover of steroids in the organism as a whole. In general, the levels of steroids in urine mirror those found in plasma/serum.

Some situations exist in which steroids are compartmentalized, especially when individuals undergo hormone replacement therapy via injectable steroids, via transdermal / transmucosal routes, or as orally administered steroids. It is interesting to note that urinary steroid levels represent, in most cases, the best laboratory correlate to the clinical and pathological status of the patient.

The steroids measured in urine are the sum total of unconjugated steroids that remain after solid phase extraction and chemical and/or enzymatic hydrolysis of glucuronidated and sulfated steroid hormones. Steroids, as a rule, are not water soluble. In order to be metabolized, turned over and excreted in the urine, they must be made water soluble. This is accomplished in the liver via glucuronidation and sulfation of "free" non-protein bound steroids, which can then pass through the glomerular membrane. Thus, steroids measured in urine are by definition "free", i.e., non-protein-bound, either specifically or non-specifically.

One major advantage of measuring steroid hormones in 24-hour urine samples is that their pulsatile fluctuations are integrated out, whether they be ultradian (repeating cycles throughout a 24-hour period) and/or circadian (one complete cycle/ 24-hour day). The peaks and valleys in hormone levels that, confound interpretation of results obtained in serum, which represent one moment in time, are not an issue when 24-hour urine analysis is used as the analytical method.

The FLUIDS iQ, 24 hour CUHP is presented with a graphic report format. The results are presented under the headings that are divided into the following subcategories: Estrogens, Androgens, Progesterone and Corticosteroids. Under each of these subcategories is a listing of the primary hormones and their metabolites. The names of the individual analytes are listed in a column on the left. The levels are shown graphically, with the green zone as the preferred or ideal zone. On either side of the green (ideal) range are yellow ranges, which denote values still within the classic reference range, but in need of attention and monitoring. Beyond the yellow are the red ranges, which represent values outside the normal range. These are marked 'high' or 'low', as appropriate. The numerical values are shown both on the graph (via a diamond), and on the right side of the report in numerical form. Note that values above this high range are shown with // and the diamond to the right, as well as the numeric value in a red box.

The green, yellow, and red zones have been derived from thousands of normal, healthy individuals, and are age-adjusted by decade. In females, when showing the estrogens and pregnanediol (the marker for progesterone), no assumption has been made as to whether the patient is pre-, post-, or surgically menopausal. Women in the age range encompassed by the beginning of the second decade up to the fifth decade of life, may be considered to be premenopausal.

When evaluating and interpreting results, it is essential that the patient's clinical presentation be taken into account. Reference ranges for the sex hormones are not reflective of individuals on hormone replacement therapy (HRT).

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**ESTROGENS: Primary Hormones and Metabolites**

Estrogens are mainly involved in female reproduction, but also have a significant role in the differentiation, growth and function of tissues throughout the female body. They are important in the protection of the cardiovascular system, in bone health, and in their important role in behavior and mood. Increased estrogen exposure increases the risk of a number of cancers, including ovarian, breast and thyroid. In addition, higher-than-normal estrogen exposure can lead to other health problems, including premenstrual syndrome (PMS), endometriosis, polycystic ovarian syndrome (PCOS) and fibrocystic breast tenderness.

Various environmental and lifestyle factors, as well as genetics, can influence estrogen production, metabolism, and balance. These include but are not limited to diet, obesity, high levels of insulin, excessive alcohol consumption, medications such as birth control pills and hormone replacement therapy, and excess exposure to pesticides and industrial chemicals, as well as to agricultural hormones in animal products for human consumption.

**Primary Hormones****Estrone (E1):**

Estrone (E1), and its conjugate Estrone Sulfate (E1S), represent perhaps the most significant estrogen, certainly from a quantitative point of view. Although it is less estrogenic than Estradiol (E2), when E1 is measured in urine, it represents the estrogen reservoir of the body. E1 and E2 can interconvert, and administration of E2 often shows no increase, neither in E1 nor E2 in serum, although elevations of E1 in urine are marked. This is a result of excretion of estrone glucuronide (E1G) and E1S, which are hydrolyzed for quantitation via GC MS, with concomitant small increases in E2. Generally, levels of E1 in urine are 2 to 6 times higher than that of E2. As well, 1-7% of Androstenedione (precursor) is converted to E1, mostly in peripheral adipose tissue, which is one of the reasons higher E1 levels are often seen in obese post-menopausal women.

**Estradiol (E2):**

In women, E2 is secreted primarily by the ovaries, and represents the most physiologically active pre-menopausal estrogen, with 100-300 µg produced per day. Besides its reproductive function E2 plays an important role in a variety of other physiological processes, most importantly in the skeletal system, where it regulates growth as well as bone density. Also, the cardiovascular system, particularly in the coronary arteries, where it can improve blood flow, and in the central nervous systems, where it exerts neuroprotective functions and plays a role in the mental health of women, including mood and feelings of well-being. Many women in their late 40s or early 50s, having entered perimenopause, or who, in their later years become post-menopausal, or those who are surgically menopausal, may be at greater risk of developing many conditions often associated with aging. In 2002 a report was published, based on the Women's Health Initiative (WHI)<sup>1</sup>, the results of which implicated Hormone Replacement Therapy (HRT) in the increased risk for breast cancer, heart attack and stroke. This led to the recommendation to stop HRT in most post-menopausal women. However, in recent years there has been a dramatic reversal in this point of view, as evidence has accumulated showing the safety<sup>2</sup> and benefits<sup>3,4</sup> of HRT, especially Bioidentical HRT (BHRT), with various galenic formulations of E2; eg., topical creams, gels, patches and sprays, and albeit less popular pills, in combination with progesterone in women with an intact uterus.

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These benefits include improved cardiovascular health, which has been shown not to increase the risk of ischemic stroke associated with myocardial infarction, but to actually lead to a reduction in cardiovascular mortality. This, of course, is in addition to the alleviation of climacteric symptoms associated with the onset of menopause; vaginal dryness, lack of libido and depression amongst others. All that said, ultimately the decision to institute HRT is personal, and should be based on family/personal medical history, the severity of symptoms and be made with the assistance and advice of a qualified and certified healthcare provider.

**Estriol (E3):**

Estriol (E3) is considerably less estrogenic than either E1 or E2, and as a result has been considered by some to be the "safe" or "protective" estrogen. It is the most prevalent estrogen in pregnancy (from the placenta) and binds to the estrogen receptor B (ErB), increasing cell differentiation & decreasing cell proliferation. Large amounts of E3 receptors are found in vaginal tissue. E3 represents the metabolic end product of estrogen metabolism, and most of it is converted from E1 in the liver.

**Estrogen Ratios****1. Potent Estrogen Ratio (E1/E2):**

Normally there is a relative equilibrium between E1 & E2.

- A high ratio indicates an E1 buildup, as well as an inadequate amount of E1 detoxification.
- A ratio less than 1 will usually indicate some form of urine contamination, most often due to exogenously applied E2 to the vagina or labia, rather than to the inner thigh.

**2. Total Potent Estrogens (E1 + E2) – Women on HRT:**

The normal range is associated with an alleviation of climacteric symptoms, without causing symptoms of estrogen dominance, eg, breast tenderness. Climacteric symptoms are defined as gradual changes of ovarian function that start before menopause and continue thereafter. These include symptoms associated with sleep disturbances, mood changes, and sexual problems, such as loss of libido, dyspareunia (persistent or recurrent genital pain that occurs just before, during, or after sex), as well as urinary tract & other bodily symptom changes.

**3. Total Estrogens Ratio (E1 + E2 + E3):**

In any estrogen analysis, it is important to assess the effect that Total Estrogens (E1 + E2 + E3), & their metabolites, are having on the target tissues. This is crucial because, with aging, the different estrogens may assume dominance.

In younger adults, E2 is the primary estrogen. With advancing age, E1 becomes the primary estrogen. In that regard, measuring only E2 is not advisable when trying to determine whether pre or post-menopausal women need estrogen therapy. This is because many aging women with estrogen dominance or elevated estrogens may still have low E2 levels.

High, or out-of-range, ratio levels may be seen when an individual is taking oral, or sub-lingual, estrogen supplements. High ratio levels are also seen in pregnancy & with urine contamination from vaginally or labially-applied supplemental estrogens. Non-bioidentical hormones (eg; birth control pills) may result in lower estrogen levels.

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Urinary hormone testing provides a more in-depth clinical picture, because it measures hormone metabolites along the steroidogenic pathway. These metabolites indicate how the primary hormones are affected by enzymes & cofactors from hormone synthesis to elimination. That reveals how the body is breaking down key hormones, including estrogens, progestogens, androgens and cortisol.

**Why Test?** One of the main reasons for testing metabolites comes from a recent focus on estrogen metabolism & hormone-driven cancer risk. There is increasing evidence that the amount of estrogen produced, & how it is metabolized, has significant implications for cancer risk, especially breast cancer in women and prostate cancer in men.

**When to Test?** Metabolite testing is indicated when one encounters some of the following symptoms:

- Adrenal dysfunction with normal saliva cortisol levels
- Hormonal imbalance, such as insomnia &/or weight gain
- Polycystic Ovary Syndrome (PCOS): acne & excess facial hair
- Menopause & set to begin HRT: Estrogen dominance while on physiological dosages of HRT

**Phase I Estrogen Metabolites: E1 Catechols****2-Hydroxyestrone (2-OH- E1) and 16 $\alpha$ -Hydroxyestrone (16 $\alpha$ -OH-E1):**

Much effort has been expended in determining the metabolic fate of estrogens. Specific focus has been given to 2-OH-E1 and 16 $\alpha$ -OH-E1.

- 2-OH-E1 represents the largest amounts of the E1 metabolites.
- 16 $\alpha$ -OH-E1, although not produced in the same quantity as 2-OH-E1, plays an important role in the maintenance of bone density. When the level is too low, there is an increased risk for osteopenia & osteoporosis.

**2-OH-E1/16 $\alpha$ -OH-E1 Ratio:**

This ratio highlights the balance between protective & carcinogenic Phase I metabolites. It is clinically significant during pre- or peri-menopause, but also in post-menopause, for those using HRT.

2-OH-E1, in contrast to 16 $\alpha$ -OH-E1, is considered to be the "good" metabolite, since it manifests weak binding to estrogen receptors and has almost no uterotrophic effects (relating to uterine development).

Generally, it is considered that a ratio in excess of two (2) is preferred, with 2-7 considered optimal. If the ratio is < 2, there is an increased risk of developing estrogen-related breast cancer, rheumatoid arthritis and Systemic Lupus Erythematosus (SLE). If the ratio is > 7, there is an increased osteopenia risk, especially when the actual 16 $\alpha$ -OH-E1 value is very low. Osteopenia is a loss of bone mass resulting in bone weakness.

In the absence of significant levels of E1, the ratio of the hydroxy metabolites is probably insignificant, even though it is mathematically possible to calculate a ratio. Division of small numbers into themselves will also lead to misleading ratios. Therefore, the significance of these ratios should be viewed with some caution in post-menopausal women, who are not on HRT.



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**4-Hydroxyestrone (4-OH-E1):**

4-OH-E1 is a free radical generator and highly estrogenic. As with other hydroxylated E1 metabolites, levels of 4-OH-E1 are likely to be significant only in pre-menopausal women, or post-menopausal women on HRT, who also have significant levels of E1 greater than approximately 5 µg/24-hours.

High levels of the enzyme that produces 4-OH-E1 are found in both benign & malignant breast tumors, as well as prostate, ovarian & endometrial cancers.

One can rank estrogen metabolites, as to their likelihood of inducing DNA carcinogenic adducts, ie, the covalent bonding of DNA to a chemical that could be the start of a cancerous cell. The ranking is 4-OH-E1 > 2-OH-E1 > 4-OH-E2 > 2-OH-E2

**Phase II Estrogen Metabolites: E1 Catechols****2-Methoxyestrone (2-Meth-E1) and 4-Methoxyestrone (4-Meth-E1):**

2-Methoxyestrone (2-Meth-E1) and 4-Methoxyestrone (4-Meth-E1): 2 & 4-Meth-E1 are phase II catechol estrogens metabolized in the liver. Their levels show the balance between Phase I & Phase II detoxification in the liver. The optimal ratio of 2-Meth-E1 to 2-OH-E1 should be > 0.50 (> 50%). 2-Meth-E2 is the most protective estrogen metabolite & is also produced in the smallest amounts. Under poor Phase II liver inactivation, the catechol estrogens are oxidized to reactive quinones.

The methoxy metabolites contribute to estrogen-induced cancer. They are detectable in significant quantities only in pre-menopause and when there are appreciable levels of E1 (eg; >15µg/24 hrs).

In this report only 2-Meth-E1 is shown. The 4-Meth-E1 is normally in such low levels that its results are unreliable.

**Estrogens in Males**

Estrogens are an important part of normal male hormone function & balance. They contribute to bone density, libido, cognition and cardiovascular health. In the adult male the estrogen amounts are quite small, with Estradiol levels between 10-40 pg/ml & Estrone levels of 10-50 pg/ml.

The male body needs estrogen to function properly, but high estrogen levels may cause health problems, such as gynecomastia (breast tissue development), erectile dysfunction, or infertility.

**Estrogens in Males relative to Testosterone levels**

The 24 hr urine ratio of Testosterone / total E1+E2+E3 should be > 4. If there is a lower ratio, it means that there has probably been an over-aromatization of Testosterone to Estrogen, which can lead to insulin resistance.

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**ANDROGENS: Primary Hormones and Metabolites****Primary ANDROGEN: Testosterone (T):**

Testosterone is the major androgen, in both males and females. It declines with age in both males and females, although the ovaries continue to produce some T, even after menopause. In general, T in urine correlates with free T, as measured in plasma. Total T in plasma often does not decline, even as production of T is declining with age. Thus, total T in plasma may be within the normal range, while levels of T in urine are markedly low. **For example, clinical correlation between symptoms of hypogonadism in males and levels of T in urine is generally better than between free T levels in plasma.** This is likely due to marked fluctuation in free T levels during the day. Also, the quality of antibody- based free T assays in serum/plasma leaves much to be desired.

**Diurnal Pattern of Testosterone (T) Secretion**

T levels fluctuate, peaking at around 8 AM & diminishing throughout the day. Levels are lowest at about 8 PM, and then climb during the night. Peaks & valleys are larger for men 40 & younger, when compared to men in their 70s. For a 40-year-old, morning T readings may be 200 points higher than in evening, versus a 50-point difference for a 70-year-old. Therefore, reliable interpretation of results of **pulsatile** hormone measurements requires a recognition of the biological daytime and day-to-day changes of hormones.

**ANDROGEN Metabolites****Dihydrotestosterone (DHT):**

DHT is produced from T, primarily in the peripheral tissue. Obese males, especially those with truncal (central) obesity, tend to produce more DHT than correspondingly normal males. DHT is of particular significance in males receiving testosterone replacement therapy (TRT). DHT promotes cell growth and plays a role in both prostate hyperplasia (increased cell proliferation potentially leading to malignant transformation) and prostate cancer. DHT is formed from T via the 5-alpha reductase (5aR) enzyme system. An indirect indicator of 5aR activity can also be inferred from the ratio of THF/5a-THF (see below).

DHT is a much more potent androgen than T, and excess levels of DHT should be avoided. In fact, many would advocate suspension of TRT in the face of elevated levels of DHT. DHT levels may also be reduced via utilization of 5aR inhibitors, such as finasteride (marketed as Proscar or Propecia -- the latter being a low-dose form of Proscar, used in the treatment of male pattern baldness), or even supplements, such saw palmetto. The indiscriminate use of 5aR inhibitors has been thrown open to question because of a lack of knowledge regarding the effects of inhibiting 5aR on a system-wide basis, notably in the brain, where its function remains nebulous and poorly understood. Inhibition of 5aR is extremely marked in the case of finasteride and not easily reversible, often for 6 months or more after cessation of the drug. The 5aR inhibitors are also known to have sexual side effects, including impotence.

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**(3 $\alpha$ ) Androstenediol**

(3 $\alpha$ ) Androstenediol is a metabolite of DHT, and acts as an endogenous steroid hormone & neurosteroid. It is a positive modulator of GABA, and acts as an anxiolytic, with libido-enhancing & anti-convulsive effects.

Similar to testosterone, in blood it has high binding affinity for the sex hormone binding globulin (SHBG), a protein made mostly in the liver. When the SHBG protein binds to sex hormones, tissues can't use those hormones.

**Dehydroepiandrosterone (DHEA)**

DHEA is primarily an adrenal hormone and serves as a precursor to both androgens and estrogens. It plays a significant role in the control of bone density, stress response, mood & cognition, as well as autoimmunity. Levels begin to decline somewhere between the middle and end of the second decade of life. DHEA levels may be depleted by the use of corticosteroids and insulin, as well as a variety of drugs. DHEA levels are often quite low in individuals with chronic disease. Because of the potential of DHEA conversion to testosterone, men often use DHEA indiscriminately, only to find their levels of estrogens surging.

DHEA should be used with caution and may play a role in hormone-sensitive cancers. Cases of gynecomastia (overdevelopment or enlargement of breast tissue in men or boys) have been reported, due to ingestion of larger doses of DHEA. Oral administration of DHEA is best accomplished in smaller divided doses.

DHEA has a very marked first pass effect. This is a phenomenon of drug metabolism in the body that leads to a reduction in the concentration of the active drug. An example is taking a hormonal supplement, like DHEA, by the oral route. After being swallowed, the DHEA is absorbed into the digestive system and enters the hepatic portal system. It is carried by the portal vein to the liver before it reaches the blood stream, where its concentration is significantly diminished.

Low DHEA levels: DHEA is depleted by corticosteroids & insulin use. Low levels are a sign of adrenal stress and/or reduced androgen production.

High DHEA levels: Often occurring with PCOS, high DHEA levels are a sign of over-supplementation. One of the main effects is hirsutism.

**7-Keto DHEA**

7-keto DHEA is one of 3 oxygenated metabolites of DHEA. They interconvert with one another but do not convert back into the parent, DHEA.

7-keto DHEA has anti-cortisol mechanisms. The enzymes that activate cortisol (from the relatively inactive precursors of cortisone and corticosterone) are the same ones that interconvert these oxygenated metabolites.

Whether DHEA will be primarily converted to estrogen or androgen can only be accurately determined by measurement of the potentially affected hormones. The effectiveness of 7-keto derivatives of DHEA in preventing conversion to estrogen has not been clearly confirmed in humans.

**5-Pregnenetriol (5-PT):**

5-PT is a relatively minor metabolite of DHEA & Testosterone. Marked elevations of 5-PT are associated with hirsutism in women and can be a marker for PCOS.

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**Androsterone (AN) and Etiocholanolone (ET):**

Androsterone and Etiocholanolone are both major androgen metabolites of testosterone. AN is a 5 $\alpha$ R product, whereas ET is the corresponding 5- $\beta$ R product. In some instances, the ratio of AN to ET can be used to evaluate the presence or absence of 5 $\alpha$ R, its up or down-regulation, or 5 $\alpha$ R inhibition. A ratio of ET:AN  $\ll$  1 would connote 5 $\alpha$ R up-regulation, whereas a ratio  $\gg$  1 would connote down-regulation of 5 $\alpha$ R, or exogenous 5 $\alpha$ R inhibition. DHEA supplementation often results in excess levels of ET. Because of the diversity of hormones feeding into this pathway, the ratio of ET:AN is less useful as a marker for 5 $\alpha$ R activity than the ratio of THF:5 $\alpha$ -THF (see below). Androsterone is also a neuro steroid, which acts as a positive allosteric modulator of GABA. Both AN and ET have been reported to have anticonvulsant activities.

**PROGESTERONE: Primary Hormone and Metabolites****Daytime Variation in Serum Progesterone (P)**

Progesterone is released into the bloodstream in pulsations. This leads to large fluctuations in serum P - up to 8-fold within 90 minutes & 2 - 40 ng/ml over 24 hrs. This means that in taking a single, or even multiple, moment-in-time blood or urine sample, there is a great risk of the resulting data being unreliable. Ideally, one should test blood or urine over a 24 hr period, or even 2-3 days in sequence, to get reliable averages.

**Progesterone (P):**

P is a progestogen sex hormone that is involved in pregnancy, the menstrual cycle and embryogenesis. It is part of a group of steroid hormones called the progestogens, and is the major progestogen in the body. P has a number of important body functions. It is a key metabolic intermediate in the production of other endogenous steroids, including the corticosteroids and sex hormones. It also plays an important role as a neurosteroid in the brain. In addition to its function as a natural hormone, P is also used as a medication. This includes its use as a contraceptive in combination with the estrogens to reduce the risk of cervical and uterine cancer, in hormone replacement therapy, and in feminizing hormone therapy.

P is not normally excreted in human urine. It is derived to a minor degree from Pregnenolone, which also is not excreted in urine in appreciable amounts, unless orally supplemented. In pre-menopausal women, relatively large amounts of P are produced during the luteal phase of the menstrual cycle by the corpus luteum. In post-menopausal women and in men, P production takes place in the adrenal glands. Although endogenous P metabolism in the adrenals leads to production of glucocorticoids and mineralocorticoids, with some P also produced by the testes in males, there appears to be no evidence in the literature that exogenous administration of P leads to increased levels of corticosteroids; e.g., cortisol or its metabolites.

**Pregnanediol (PD):**

Quantitatively, PD is the most important P metabolite, and it is easily measured in urine. Therefore, it is the most practical marker for P determinations in urine and has been successfully used for this purpose for decades. Because it is excreted in relatively large amounts, it is both a very sensitive and very specific marker for P. Normally, PD is quantitatively affected to only a minor degree by the metabolism of pregnenolone and 17(OH) pregnenolone. Only if pregnenolone is supplemented orally is it necessary to allow for the conversion of pregnenolone to PD via P.

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PD urinary levels generally correlate very well with serum levels of P, even though the latter are problematic to measure, because of the rapid clearance of P from the blood.

P levels are much more stable than those of estrogen. Estrogens have relatively short half-lives. Exogenous estrogen vanishes from the body in a 24hr period of use. P has a much longer half-life. It remains stable in serum after 5 days of daily use, with no return to baseline for 2-3 weeks after stoppage. P levels decline earlier in reproductive life than estrogens. PD levels for a woman in her mid-to-late forties are often well below the normal luteal range.

### Pregnenetriol (5-PT):

5-PT is metabolized indirectly from Pregnenolone & P. Elevations occur with congenital hyperplasia. In adults, elevations will prevent sufficient production of cortisol & cortisone. These individuals will need to have replacement hydrocortisone.

5-PT has been found to be a marker for hirsutism in women, independent of DHEA. Thus, marked elevations of 5-PT are associated with hirsutism.

### GLUCOCORTICOIDS: Primary Hormones and Metabolites

Interpretation of glucocorticoid results most often focus on the following analyses:

- The level of free (active) cortisol / 24 hrs
- The ratio of cortisol (active) vs cortisone (inactive)
- Metabolized cortisol, as part of total cortisol production, specifically looking at metabolites of cortisol (THF, 5a-THF) & cortisone (THE)

### GLUCOCORTICOIDS: Primary Hormones

#### 1. Free Cortisol (F) and Cortisone (E)

Cortisol and cortisone are the major glucocorticoids measured in urine. They are primarily derived from the adrenal cortex and are responsible for glucose mobilization in response to stress, physical exertion and inflammatory stimuli.

**Free cortisol** is the active fraction of adrenal glucocorticoid cortisol production, and represents ~ 2-3 % of total cortisol production. Cortisol is responsible for gluconeogenesis, due to stress & inflammatory stimuli. It is a potent anti-inflammatory; it helps maintain blood pressure & modulates immune function, as well as being a mineralocorticoid stimulator. The Measurement of free cortisol is important, because it shows if there is **adequate active circulating cortisol**

**Cortisone represents the inactive, or 'storage form' of cortisol.**

In the liver cortisone is converted to cortisol. In the kidneys cortisol is inactivated to cortisone. That is a protective measure, given that elevated cortisol activates mineralocorticoid receptors, leading to an increase in sodium (Na<sup>+</sup>) reabsorption and a decrease in potassium (K<sup>+</sup>) secretion, thereby raising blood pressure if not inactivated.

**RESULTS: 24 hr Comprehensive Urine Hormone Profile Plus**Accession #: 100035688 • Patient: JANE SMITH

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**2. Cortisol / Cortisone Ratio:**

In urine, cortisone levels are ideally ~30% higher than cortisol, when both are at optimal levels. Values at the low or high ends of the reference range are generally not optimal. The determination of the urinary cortisol/cortisone ratio is of clinical importance in cases of Cushing's syndrome, a disorder that occurs when too much cortisol is produced over an extended period of time. The ratio also provides information on the activity of 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD), the enzyme that converts cortisol to cortisone. To prevent over-stimulation of the mineralocorticoid receptors of a cell by cortisol, HSD-11 $\beta$ s converts the biologically active cortisol to the inactive cortisone, which can no longer bind the mineralocorticoid receptor.

**GLUCOCORTICOIDS: Cortisol & Cortisone Metabolites****3. 17-hydroxy steroids: THF, 5 $\alpha$ -THF and THE**

Tetrahydrocortisol (THF) and Allo-Tetrahydrocortisol (5 $\alpha$ -THF) are cortisol metabolites, while Tetrahydrocortisone (THE) is the cortisone metabolite. Moderately elevated metabolite levels, with no elevation of cortisone or cortisol, is observed in cases of mild adrenal stress. For this reason, THE has been used as an early marker for physiological/psychological stress.

The sum of these 3 metabolites represents ~50% of total endogenous cortisol production, with a reference range of 3000-6000  $\mu$ g/day. If the sum is > 6 or 7,000  $\mu$ g/day, then one should consider the following possibilities: **insulin resistance, metabolic syndrome, pre-diabetes diabetes**

All forms of hyper-cortisolism will lead to an up-regulation of the "deactivating" enzymes of cortisol & cortisone (5 $\alpha$ / $\beta$ R), resulting in increased production of THF, 5 $\alpha$ -THF & THE

If the sum of the 3 metabolites is >15,000  $\mu$ g/day, while Cortisol & Cortisone levels may remain normal, one needs to consider the possibility of adrenal adenoma.

**Corticosterone (mineralocorticoids) Metabolites****Tetrahydro-11-Dehydrocorticosterone (THA)**

There are a number of metabolites of corticosterone, an intermediate hormone that forms Aldosterone. THA is the only one shown in this report. THA is formed by the same enzyme that creates the cortisol metabolite THF, 5 $\beta$  Reductase (5 $\beta$ R)

Low levels of THA are an indicator of chronic adrenal fatigue, while high levels are associated with acute stress.

**Together with DHEA & glucocorticoids, THA plays a role in providing a comprehensive assessment of overall adrenal-cortical health.**

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**SALIVARY DIURNAL CORTISOL**

The comments provided here are for educational purposes only. They should not be interpreted as being diagnostic or treatment recommendations. Those decisions are the responsibility of the health care professional. Moreover, the reference range shown in this report is derived from a normal distribution of results that encompass 95% of randomly selected individuals in a population.

**IN THE PRESENT TEST****CORTISOL**

The Morning cortisol level lies inside the reference range. Cortisol levels are normally highest shortly after waking and indicate normal adrenal function at its circadian peak.

The Noon cortisol level lies inside the reference range and indicate that the adrenal glands are responding well to the needs of the day, especially in glycemic control. This highlights the importance of the adrenal glands in the regulation of blood glucose levels.

The Afternoon cortisol level lies inside the reference range and indicate that the adrenal glands are responding well to the needs of the day, especially in glycemic control.

The Nighttime cortisol level lies inside the reference range, and indicates that adrenal glands are functioning normally within the circadian cycle. It is a good indicator of a normal baseline level of adrenal activity.

## General Discussion

### CORTISOL

**About Cortisol:** Cortisol is produced by the adrenal glands, which are controlled by parts of the brain called the hypothalamus and pituitary. Cortisol plays an important role in breaking down glycogen to glucose in liver and muscle tissue. It mobilizes glucose, so as to maintain normal blood sugar levels, the primary energy source for the brain. Cortisol levels are highest in the early morning (approximately 8 am) and reach the lowest level about midnight to 4 am, or three to five hours after the onset of sleep. Diurnal cycles of cortisol levels are found in human saliva. Cortisol production comes in response to daily stress, as well as emotional upset, infections and surgery. It prevents the release of substances in the body that cause inflammation. It is used to treat conditions resulting from over activity of the B-cell-mediated antibody response. Examples include inflammatory and rheumatoid diseases, as well as allergies. Low-potency hydrocortisone, available as a non-prescription medicine in some countries, is used to treat skin problems such as rashes, and eczema<sup>5,6,7</sup>.

**Low Cortisol**, especially if it remains so throughout the day, may indicate **Adrenal Exhaustion**, which is caused by stress, such as sleep deprivation, emotional stress, poor diet, nutrient deficiencies, and/or synthetic glucocorticoid medications that suppress cortisol production. Chronic stress depletes cortisol and is associated with symptoms of morning and evening fatigue, aches and pains, fibromyalgia, cold body temperature, decreased stamina, slow pulse rate, low blood sugar (sugar craving) and low blood pressure. In addition one often encounters increased allergies (immune dysfunction), and sensitivity to chemicals. Symptoms of thyroid deficiency can also be due to low cortisol levels. Exercise, more adequate sleep, a diet with adequate protein, 'bio-identical' progesterone, adrenal extracts and nutritional supplements are often helpful in correcting low cortisol.

**High Cortisol.** Although normal cortisol levels are essential for life, chronically elevated levels can be very detrimental. Increased cortisol production by the adrenals is a normal response to routine stress, but when stress is chronic and cortisol output remains high over a prolonged period (months/years), break-down of normal tissues (muscle wasting, thinning of skin, bone loss) and immune suppression can result. Common symptoms of chronic high cortisol include sleep disturbances, fatigue, depression and weight gain in the waist and anxiety. Stress and persistently elevated cortisol levels can contribute to premature aging and chronic illness.



## RESULTS: 24 hr Comprehensive Urine Hormone Profile Plus

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