Test Results

ZRT LABORATORY
8605 SW Creekside Place
Beaverton, OR 97008
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2015 00 00 000 U

Samples Arrived: 09/23/2015
Date Closed: 09/26/2015

Samples Collected:
Urine: 09/11/15 07:50
Urine: 09/11/15 09:30
Urine: 09/11/15 17:00
Urine: 09/11/15 22:00

Ordering Provider:

Jane Doe MD
1234 Fake St
Beaverton, OR 97008

Molly Metabolite
1111 Main St
Beaverton, OR 97008

BMI: 22.1
Height: 5 ft 6 in
Weight: 137 lb
Waist: 28 in

Menses Status: Pre-Menopausal
Gender: Female
Last Menses: 08/22/2015
DOB: 7/4/1966 (49 yrs)
Patient Ph#: 555 555 5555

Test Name	Result		Range
Urinary Estrogens (µg/g Cr)			
Estradiol (Urine)	1.75		0.78-1.79 Premeno-luteal or ERT
Estrone (Urine)	6.2	H	2.27-5.22 Premeno-luteal or ERT
Estriol (Urine)	3.21	H	0.78-1.98 Premeno-luteal or ERT
E3/(E1+E2) (Urine)	0.40		>0.3 (> median value)
2-OH Estradiol (Urine)	0.70		0.17-0.70 Premeno-luteal or ERT
2-OH Estrone (Urine)	4.43	H	0.70-2.54 Premeno-luteal or ERT
4-OH Estradiol (Urine)	0.28	H	0.10-0.18 Premeno-luteal or ERT
4-OH Estrone (Urine)	0.95	H	0.17-0.47 Premeno-luteal or ERT
16α-OH Estrone (Urine)	0.69		0.35-1.07 Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1 (Urine)	7.43	H	1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol (Urine)	0.09	H	0.03-0.08 Premeno-luteal or ERT
2-MeO Estrone (Urine)	1.01	H	0.26-0.68 Premeno-luteal or ERT
2-MeO E1/2-OH E1 (Urine)	0.23		0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol (Urine)	<0.04		< 0.04
4-MeO Estrone (Urine)	0.04		< 0.04
4-MeO E1/4-OH E1 (Urine)	0.04	L	0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2 (Urine)	0.04	L	0.10-0.29 Premeno-luteal or ERT
Bisphenol A (Urine)	2.70		1.11-3.74 Premeno-luteal
Urinary Progestogens (µg/g Cr)			
Pregnanediol (Urine)	525		465-1609 Premeno-luteal or PgRT
Pgdiol/E2 (Urine)	300	L	1000-1500 (Optimal Luteal Only)
Allopregnanolone (Urine)	0.50	L	2.23-14.87 Premeno-luteal or PgRT
Allopregnanediol (Urine)	7.34	L	14.65-76.71 Premeno-luteal or PgRT
3α-Dihydroprogesterone (Urine)	0.67		0.67-2.03 Premeno-luteal or PgRT
20α-Dihydroprogesterone (Urine)	4.45		3.93-11.62 Premeno-luteal or PgRT
Deoxycorticosterone (Urine)	1.38		0.69-2.23 Premeno-luteal or PgRT
Corticosterone (Urine)	15.94	H	3.19-9.59 Premeno-luteal or PgRT
Urinary Androgens (µg/g Cr)			
Testosterone (Urine)	5.51	H	1.22-3.97 Premeno-luteal or ART
Epi-Testosterone (Urine)	2.97		2.01-4.66 Premeno-luteal
T/Epi-T (Urine)	1.86		0.5-3.0
5α-DHT (Urine)	0.46		0.28-1.52 Premeno-luteal or ART

The above results and comments are for informational purposes only and are not to be construed as medical advice. Please consult your healthcare practitioner for diagnosis and treatment.

David T. Zava, Ph.D.
(Laboratory Director)

Alison McAllister, ND
(Ordering Provider unless otherwise specified on pg1)

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Test Name	Result		Range
Androstenedione (Urine)	17.6	H	3.93-13.53 Premeno-luteal or ART
DHEA (Urine)	15	L	15.82-129.17 Premeno-luteal or DHEAT
5α,3α-Androstanediol (Urine)	3.77		2.98-13.10 Premeno-luteal or ART
Urinary Glucocorticoids (µg/g Cr)			
Total Cortisol (Urine)	77.02	H	12.26-33.12 Premeno-luteal
Total Cortisone (Urine)	141.48	H	23.27-50.88 Premeno-luteal
Cortisol/Cortisone (Urine)	0.54		0.5-0.7
Tetrahydrocortisol (Urine)	1117	H	214-546 Premeno-luteal
Tetrahydrocortisone (Urine)	2326	H	437-1184 Premeno-luteal
Urinary Free Diurnal Cortisol (µg/g Cr)			
Free Cortisol (Urine)	24.02		7.8-29.5 (1st Morning)
Free Cortisol (Urine)	19.86	L	23.4-68.9 (2nd Morning)
Free Cortisol (Urine)	15.67		6.0-19.2 (Evening)
Free Cortisol (Urine)	10.22	H	2.6-8.4 (Night)
Urinary Free Diurnal Cortisone (µg/g Cr)			
Free Cortisone (Urine)	369.07	H	31.6-91.6 (1st Morning)
Free Cortisone (Urine)	294.98	H	63.3-175.8 (2nd Morning)
Free Cortisone (Urine)	160.58	H	30.6-88.5 (Evening)
Free Cortisone (Urine)	119.94	H	15.5-44.7 (Night)
Urinary Diurnal Melatonin MT6s (µg/g Cr)			
Melatonin (Urine)	51.27	H	18.0 - 40.9 (1st Morning)
Melatonin (Urine)	30.99		7.3 - 31.9 (2nd Morning)
Melatonin (Urine)	3.33	H	0.7 - 2.2 (Evening)
Melatonin (Urine)	5.14		1.7 - 11.1 (Night)
Urinary Creatinine (mg/mL)			
Creatinine (pooled) (Urine)	0.35		0.3-2.0
Creatinine (Urine)	0.30		0.3-2.0 (1st morning)
Creatinine (Urine)	0.56		0.3-2.0 (2nd morning)
Creatinine (Urine)	0.51		0.3-2.0 (Evening)
Creatinine (Urine)	0.52		0.3-2.0 (Night)

Therapies

12.5mg topical Progesterone (compounded) (1 Days Last used); oral Iodine/Iodide (OTC) (1 Days Last used); oral Vitamin D3 (OTC) (1 Days Last used); oral Vitamin D (unknown type) (OTC) (1 Days Last used)

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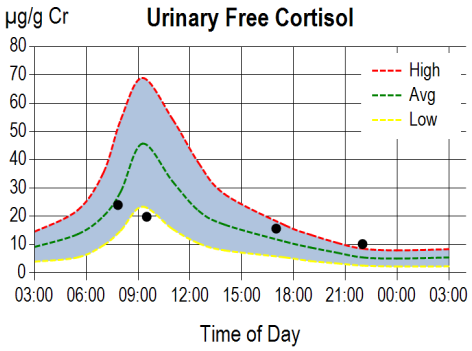

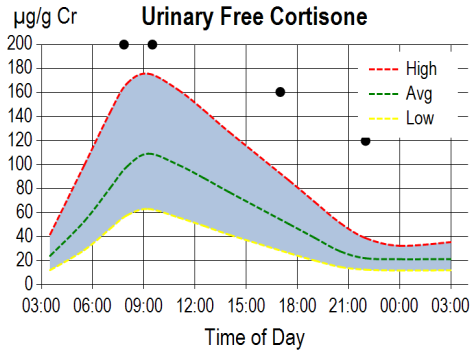

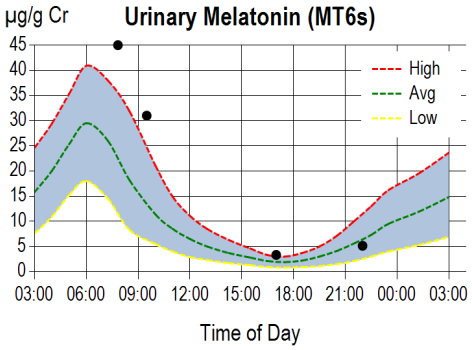

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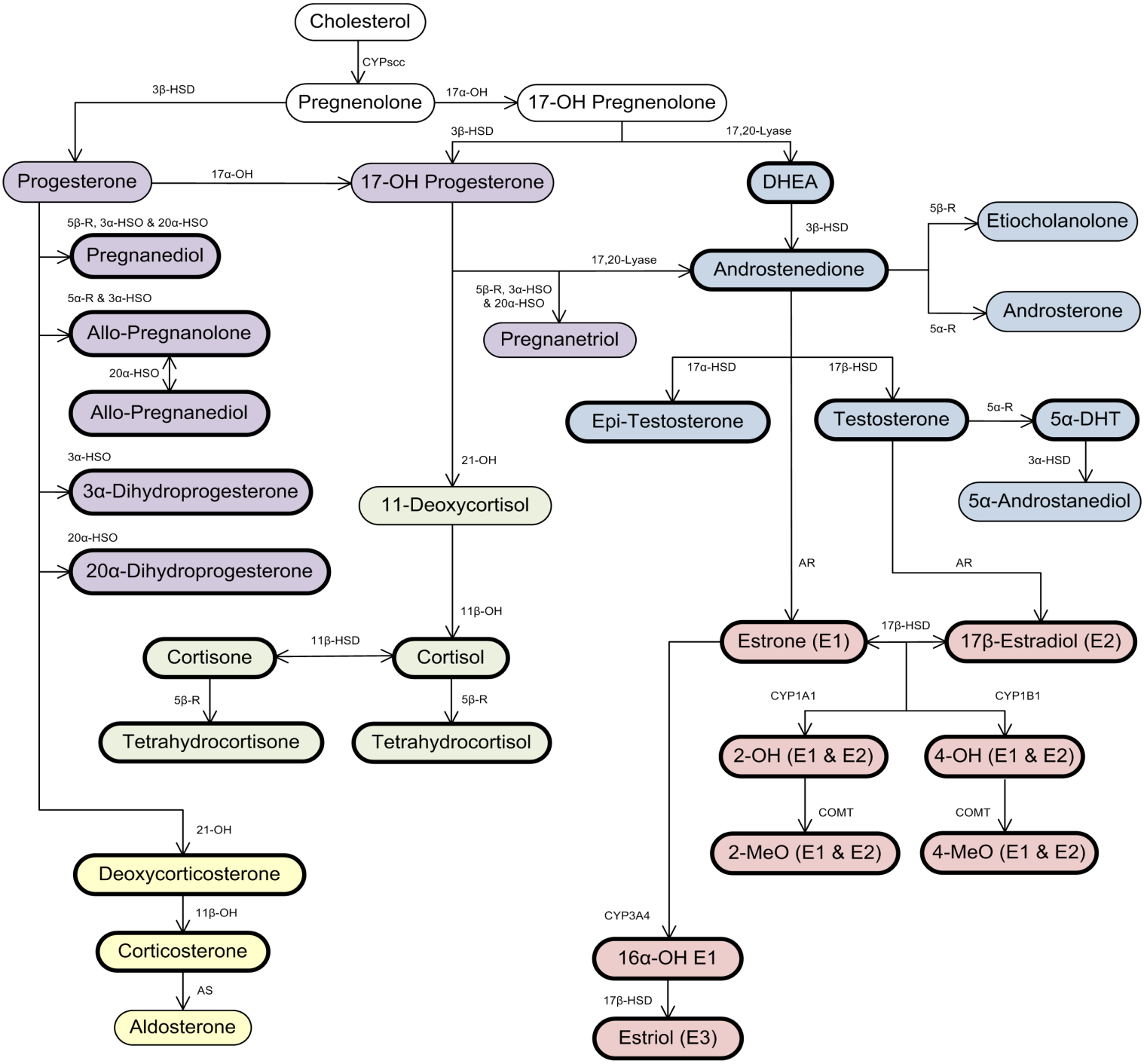
The Steroid Hormone Cascade

Metabolites in **Bold** are reported by ZRT



Androgens

Estrogens

Glucocorticoids

Mineralocorticoids

Progestogens

Enzyme Abbreviations

(3α-HSO) 3α-Hydroxysteroid oxidoreductase
(3β-HSD) 3β-Hydroxysteroid dehydrogenase
(20α-HSO) 20α-Hydroxysteroid oxidoreductase
(11β-HSD) 11β-Hydroxysteroid dehydrogenase
(5α-R) 5α-Reductase
(17α-HSD) 17α-Hydroxysteroid dehydrogenase
(5β-R) 5β-Reductase
(17β-HSD) 17β-Hydroxysteroid dehydrogenase
(11β-OH) 11β-Hydroxylase
(AR) Aromatase
(17α-OH) 17α-Hydroxylase
(AS) Aldosterone Synthase
(21-OH) 21-Hydroxylase
(CYP) Cytochrome p450 (scc, 1A1, 1B1 & 3A4)
(3α-HSD) 3α-Hydroxysteroid dehydrogenase
(COMT) Catechol-O-Methyl-Transferase

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**Category	Symptom	None	Mild	Moderate	Severe
	Hot Flashes				
	Night Sweats				
	Vaginal Dryness				
	Incontinence				
	Foggy Thinking				
	Memory Lapse				
	Tearful				
	Depressed				
	Heart Palpitations				
	Bone Loss				
	Sleep Disturbed				
	Headaches				
	Aches and Pains				
	Fibromyalgia				
	Morning Fatigue				
	Evening Fatigue				
	Allergies				
	Sensitivity To Chemicals				
	Stress				
	Cold Body Temperature				
	Sugar Craving				
	Elevated Triglycerides				
	Weight Gain - Waist				
	Decreased Libido				
	Loss Scalp Hair				
	Increased Facial or Body Hair				
	Acne				
	Mood Swings				
	Tender Breasts				
	Bleeding Changes				
	Nervous				
	Irritable				
	Anxious				
	Water Retention				
	Fibrocystic Breasts				
	Uterine Fibroids				
	Weight Gain - Hips				
	Decreased Stamina				
	Decreased Muscle Size				
	Rapid Aging				
	High Cholesterol				
	Swelling or Puffy Eyes/Face				
	Slow Pulse Rate				
	Decreased Sweating				
	Hair Dry or Brittle				
	Nails Breaking or Brittle				
	Thinning Skin				
	Infertility Problems				
	Constipation				
	Rapid Heartbeat				
	Hearing Loss				
	Goiter				
	Hoarseness				
	Increased Urinary Urge				
	Low Blood Sugar				
	High Blood Pressure				
	Low Blood Pressure				
	Numbness - Feet or Hands				
	Breast Cancer				

Metabolic Syndrome	40.0
Hypometabolism	31.6
High Cortisol	42.9
Low Cortisol	34.5
High Androgens (DHEA/Testosterone)	56.7
Low Androgens (DHEA/Testosterone)	26.7
Estrogen Dominance / Progesterone Deficiency	46.2
Estrogen / Progesterone Deficiency	27.2

***Category refers to the most common symptoms experienced when specific hormone types (eg estrogens, androgens, cortisol) are out of balance, i.e., either high or low.*

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Lab Comments

Please note: this 49 y/o peri-menopausal patient has self-reported breast cancer (3=severe) and is supplementing with low dose (12.5 mg) topical progesterone, iodine, and Vitamin D3.

PARENT ESTROGENS (ESTRADIOL-E2, ESTRONE-E1, ESTRIOL-E3)

The parent estrogens (E2, E1, E3) are within the high-normal to slightly elevated (E1) reference ranges seen in premenopausal women. While estradiol, the most potent of the three estrogens, is within normal range it is high relative to the urinary progesterone metabolite, pregnanediol (low PgDiol/E2 ratio) (see below for a more detailed explanation). This often precipitates symptoms of both estrogen dominance and deficiency as levels of estrogens fluctuate erratically during the menopause transition (most common age range 45-52).

HYDROXYLATED (CATECHOL) ESTROGENS (2-OH E2 & E1, 4-OH E2 & E1, 16-OH E1)

The hydroxylated estrogens (2-OH-E2, 2-OH-E1, 4-OH-E2, 4-OH-E1), referred to as catechol estrogens, are higher than reference ranges, especially the 4-hydroxylated estrogens (considered potentially harmful).

The 2- and 4-hydroxylation of estradiol and estrone represent the first phase of metabolism and elimination of these estrogens via urine. Research and clinical studies show that the 2-hydroxylated estrogens (2-OH E2 and 2-OH E1) are a safer pathway of metabolism than the 4-hydroxyestrogens (4-OH E2 and 4-OH E1), the latter of which are considered more toxic as they bind to DNA causing mutations that are associated with increased breast cancer risk. For reviews see: Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010; and Lee, JR, Zava DT What Your Doctor May Not Tell You About BREAST CANCER: How Hormone Balance Can Help Save Your Life: Chapter 7.

The safer 2-hydroxylated estrogen metabolism can be increased with consumption of cruciferous vegetables and extracts of them. The most commonly used cruciferous extracts are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM), both commercially available OTC. Eating a healthy diet of plants with beneficial phytochemicals (e.g. leafy vegetables with color, soy foods, flax, and turmeric) also helps increase 2-hydroxylation and prevents metabolism of estrogens down more toxic 4-hydroxy pathways. Iodine also increases the 2-hydroxylation of estrogens (Stoddard FR et.al. Int J Med Sci 5: 189-196, 2008).

Metabolism of E2 and E1 to the more toxic/mutagenic 4-hydroxylated estrogens is enhanced by exposure to environmental toxins, mostly petrochemical-based products. These man-made petrochemicals induce the cytochrome p450 enzyme 1B1 that increases hydroxylation of E2 and E1 in the 4-position. Reactive Oxygen Species (ROS) resulting from exposure to trans-hydrogenated fats and heavy metals further co-oxidize the catechol estrogens to much more reactive 4-quinone estrogens, which if not inactivated by glutathione, can potentially bind to and damage DNA leading to mutations that increase lifetime risk for cancers of estrogen-sensitive tissues (i.e. breasts, uterus, prostate).

16-hydroxyestrone is another pathway of estrone metabolism and is a precursor to estriol (see Steroid Hormone Cascade). Early clinical research in humans suggested that a high urinary level of 16-hydroxyestrone relative to low 2-hydroxylated estradiol + estrone (i.e. a low 2-OH E1 + 2-OH E2/16-OH E1 ratio), was associated with an increased risk of breast cancer in premenopausal women, but not in postmenopausal women. This has remained controversial and newer research suggests instead that while higher levels of 16-hydroxy estrone may indeed be slightly associated with increased breast cancer risk in premenopausal women, higher levels are associated with a decreased risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012). A meta-analysis of nine studies investigating the relationship of the urinary 2/16 ratio have NOT shown it to be useful for predicting breast cancer risk (Obi N et.al. Int J Women's Health 3: 37-51, 2011).

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2-hydroxyestrogens (2-MeO-E2 and 2-MeO-E1) are high, which is considered beneficial. On the other hand, the methylated forms of the 4-hydroxyestrogens (4-MeO-E2 and 4-MeO-E1) are low. In addition to the lower levels of the 4-MeO-E1 and 4-MeO-E2 metabolites, the ratios of 4-MeO-E1/4-OH-E1 and 4-MeO-E2/4-OH-E2 are low, indicating that the 4-hydroxyestrogens are in excess of the methylation capacity. Inadequate methylation of the 4-hydroxyestrogens is associated with a higher breast cancer risk (note, this individual self-reports breast cancer).

The 2- and 4-hydroxyl estrogens are methylated by the enzyme Catechol-o-Methyl Transferase (COMT), which renders them inert and harmless (Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010). In this form, the methylated catechol estrogens are rapidly excreted in urine. However, if methylation pathways are inadequate, due to low levels of COMT or lack of precursors of methylation (i.e. vitamins B6, B12, folate, betaine), the 2- and 4-hydroxyl estrogens can take a more insidious and dangerous pathway of metabolism, which is oxidation to 4-estrogen quinones. Estrogen quinones, especially the 4-quinone of estradiol and estrone are highly reactive and bind to DNA, forming adducts that lead to permanent mutations that increase cancer risk. Estrogen quinones are inactivated by glutathione. When glutathione is low, due to insufficient levels of minerals (selenium,

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iodine), vitamins (C and E) and the amino acid precursor N-acetyl-cysteine, the quinone estrogens are less likely to be detoxified (inactivated) and have greater potential to bind and damage the DNA of cells where they form (i.e. the breast cell/DNA), which increases cancer risk.

PROGESTERONE METABOLITE (Pregnanediol-Pgdiol)

The progesterone metabolite, pregnanediol (Pgdiol), is within the lower quadrant of the reference range for luteal phase of the menstrual cycle. This indicates very little endogenous progesterone is being manufactured by the ovaries, which is common during the menopausal transition. Topical progesterone is being used in this individual, which contributes very little to urinary PgDiol levels (or serum progesterone levels), but paradoxically results in a striking dose-dependent increase in salivary, capillary blood, and tissue (breast) levels of progesterone (Zava et.al. Maturitas 77, 91-92, 2014). For this reason, salivary or capillary blood (Dried Blood Spot-DBS) are more appropriate body fluids to test for progesterone when using topically delivered progesterone (Du..Zava et.al. Menopause Journal 20 (11) 1169-1175, 2013).

PROGESTERONE METABOLITES (PREGNANES AND PREGNENES)

The pregnane (allopregnanolone and allopregnanediol) categories of progesterone metabolites are low, or lower than the median, of the expected reference ranges for a premenopausal woman, whereas the pregnene category of metabolites (3-alpha-dihydroxyprogesterone and 20-alpha-dihydroprogesterone) are within normal range. This indicates that progesterone is not converting to the pregnane category of down-stream progesterone metabolites, which is likely due to low 5-alpha-reductase (same enzyme that converts testosterone to the more potent dihydrotestosterone).

One of the pregnane metabolites is allopregnanolone, which is well studied and a known anxiolytic neurosteroid that is synthesized directly within the CNS or peripherally in tissues and then freely enters the brain where it binds to GABA receptors that are mostly responsible for tuning down brain activity. At high levels, usually achieved with high luteal production, during pregnancy, or with progesterone supplementation (more with oral progesterone than topical) this leads to a calming and sleep-inducing effect as well as a lower incidence of PMS and PMDD in premenopausal women. In striking contrast to the anxiolytic effect seen with high levels of allopregnanolone, lower levels of allopregnanolone (ovulation with luteal insufficiency) paradoxically induce an anxiogenic effect associated with increased aggression and anxiety, symptoms characteristic of PMS/PMDD (Wang et.al. Neuroactive Steroids in Brain Function, 2008, Chapter 1, pp 3-42).

MINERALCORTICOID PRECURSORS (DEOXYCORTICOSTERONE-DOC; CORTICOSTERONE-CC

Deoxycorticosterone (DOC) is within reference range but corticosterone (CC) is higher than reference range. Both DOC and CC are down-stream metabolites of progesterone. DOC is a weak mineralocorticoid, and DOC and CC are precursors to the more potent mineralocorticoid aldosterone (see Steroid Hormone Cascade). High CC could indicate that aldosterone is elevated (expect high blood pressure, as reported by this individual). In women the conversion of progesterone to DOC varies by up to 20-fold (MacDonald Endocrine Reviews 12: 372-401, 1991) p. 390), with higher levels associated with adverse symptoms (e.g. water retention, headaches, increased blood pressure) characteristic of PMS/PMDD.

ANDROGEN PRECURSORS (ANDROSTENEDIOL, DHEA)

DHEA(S) is within the lower quadrant of the reference range seen in premenopausal women whereas androstenedione is within the upper quadrant of the reference range. Cancer patients often present with lower levels of DHEA(S), which likely reflects an increase in enzymes (see Steroid Hormone Cascade: follow DHEA to E2) that accelerate conversion of DHEA(S) to androgens (androstenedione and testosterone) and then to estrogens (estradiol and estrone) instead of DHT. Research studies have shown that the inflammation of cancer cells causes a preferential cascade of DHEA(S) to estradiol, which is growth-promoting, instead of DHT, which is growth-inhibitory in breast cancer cells. Low DHEA(S) has been associated with increased risk for developing breast cancer (Purohit A et.al. Breast Cancer Res 4 (2): 65-69, 2002), particularly when diurnal cortisol profiles are flat and night cortisol is high (Sephton SE et.al. JNCI 92: 994-1000, 2000). Studies also have shown that testosterone conversion to DHT via 5 alpha reductase, as opposed to testosterone conversion to E2 via aromatase, has a protective effect as regards breast cancer risk (Glaser RL, Maturitas 76: 342-349, 2013).

ANDROGENS AND METABOLITES (TESTOSTERONE, EPI-TESTOSTERONE, AND 5-ALPHA-DIHYDROTESTOSTERONE)

Testosterone (T) is higher than the expected reference range for a premenopausal woman, and is higher than its epimer, Epi-Testosterone (Epi-T). With endogenous production, the T/Epi-T ratio is usually about 1, and ranges from about 0.5-2.

In premenopausal women about half of the testosterone is derived from androstenedione produced by the ovaries, and the other

half from peripheral conversion of DHEA manufactured in the adrenals. DHEA(S) is low, while androstenedione is elevated in this individual, indicating that DHEA(S) production by the adrenals is low, and/or it is being rapidly converted down-stream to other androgens and estrogens. High androstenedione and estrogens (E2 and E1) suggests the latter.

Despite high T, the more potent down-stream metabolite of T, 5-alpha dihydrotestosterone (DHT), is within the lower quadrant of the reference range, suggesting low 5-alpha reductase activity. When progesterone is high, as a result of supplementation, it can competitively inhibit 5 alpha reductase mediated conversion of T to DHT. Thus, concomitant supplementation with progesterone, as reported by this individual, could decrease T conversion to DHT and account for the low DHT results seen in this test report.

Androgens, particularly the most potent of them, DHT, play an important role in maintaining the integrity of structural tissues such as skin, connective tissues, bone, and muscles. Androgens also play an important role in the brain to increase the level of neurotransmitters such as dopamine, which are important for mood elevation and sex drive. DHT is metabolized at the 3 position to 3alpha, 5alpha androstanediol, which is considered a neuroactive steroid that enhances dopamine activity at the dopaminergic neurons (Wang et.al. Neuroactive Steroids in Brain Function, 2008, Chapter 1, pp 3-42). Testosterone, while it is a precursor to DHT, is also a precursor to the estrogens, estradiol and estrone. Recent studies have shown that testosterone, through its conversion to DHT, protects against breast cancer caused by excessive conversion of T to estrogens via the enzyme aromatase (Glaser RL, Maturitas 76: 342-349, 2013). Means to decrease aromatase and optimize 5alpha reductase are likely to be beneficial in breast cancer patients, or those at high risk.

TOTAL GLUCOCORTICOIDS

Total cortisol (F) and cortisone (E) are higher than the expected reference ranges for a premenopausal woman, suggesting some type of adrenal stressor (please note this individual has self-reported breast cancer, which is associated with higher cortisol levels, and abnormal diurnal patterns). The down-stream metabolites of cortisol and cortisone, tetrahydrocortisol (THF) and tetrahydrocortisone (THE) are also elevated, indicating high cortisol output by the adrenal glands and rapid metabolism to inert metabolites. Total glucocorticoid production, while important, should be viewed in light of the diurnal cortisol pattern, which can be determined from testing cortisol at four time points throughout the day (referred to as UFC-Urinary Free Cortisol-see below).

While a high cortisol is a normal and healthy response to an acute stressor, a persistent stressor such as breast cancer can lead to additional symptoms and diseases associated with aging. Typical acute symptoms/signs of high cortisol can include anxiety, nervous-irritability, self-perceived stress, sleep disturbances. More chronic elevated cortisol is commonly associated with the same symptoms seen with acutely high cortisol but also include memory problems, depression, loss of muscle mass, and weight gain in the waist. Insulin resistance and metabolic syndrome are also a consequence and cause of elevated cortisol, as are the diseases of aging such as diabetes, cardiovascular disease, cancer, and bone loss. When cortisol remains high these symptoms/conditions/syndromes/diseases progressively become more problematic over time.

URINARY FREE CORTISOL (UFC)

The UFCs (cortisol) are elevated throughout most of the day. This individual has self-reported breast cancer, the inflammation of which raises inflammatory cytokines (e.g. IL6) than increase adrenal production of cortisol in response to the stressor (cancer). High cortisol, particularly high levels at night, as well as a flat circadian cortisol profile, as seen in this individual, have been observed in breast cancer patients (Sephton SE et.al. J Natl Cancer Instit 92(12): 994-1000, 2000) and indicates HPA axis hyperactivation, a hallmark of cancer.
Cortisone, the inactive metabolite of cortisol, is very high throughout the day. Cortisol is converted to cortisone by the enzyme 11-beta hydroxysteroid dehydrogenase type II (11-beta HSD-II) (for review see: Seckl JR and Chapman KE Eur J Biochem 249, 361-364, 1997). This enzyme plays an important role in preventing excess buildup of cortisol, which at high level activates the mineralocorticoid receptor (at normal levels cortisol only activates the glucocorticoid receptors) and can lead to mineralocorticoid excess syndrome, causing high blood pressure (note that this individual lists high blood pressure as problematic) and low potassium levels.

Chronic high cortisol, particularly at night, leads to conditions such as weight gain in the waist, muscle and bone loss, depression, immune suppression and insulin resistance/metabolic syndrome. A persistently high night cortisol can eventually lower melatonin production, which is important for maintaining normal biorhythms and immune function. Because chronic stressors and associated high night cortisol can have adverse effects on health and wellbeing, it is important to develop strategies to identify and eliminate or reduce the stressors or consider bioidentical hormone replacement therapies, foods, and/or nutritional supplements that help lower high cortisol. For additional information about HPA axis dysfunction and hypercortisolism the following books and journal articles are worth reading: "Adrenal Fatigue," by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection," by Shawn Talbott, Ph.D.; "The End of Stress As We Know It," by Bruce McEwen; "The Role of Stress and the HPA Axis in Chronic Disease Management", by Thomas Guilliams.

MELATONIN METABOLITE: 6-SULFATOXYMELATONIN (MT6s)

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The urinary metabolite of melatonin, 6-sulfatoxymelatonin (MT6s), is slightly above normal reference ranges throughout most of the day. This usually indicates use of a low-dose melatonin supplement the night before collection (none listed on the requisition form), or medications that increase melatonin synthesis, metabolism to MT6s, or excretion by the kidneys into urine.

Melatonin is known to have many different beneficial effects in the body. It helps slow the aging process, is a potent anti-oxidant, regulates the immune system, inhibits formation and growth of tumors such as breast and prostate cancers, and helps regulate the synthesis of the sex-hormones estradiol and progesterone (melatonin increases progesterone, decreases estrogens by inhibiting aromatase, and down-regulates cellular estrogen receptors, which diminishes response of estrogen-sensitive tissues to estrogens). Low melatonin, caused by excessive light exposure during the dark hours, or calcification of the pineal gland caused by aging, has been associated with many different dysfunctions and diseases such as immune dysfunction, neurodegenerative disorders (Alzheimer's disease, senile dementia), pain disorders, cardiovascular disease, cancers of the breast and prostate, and type 2 diabetes (Hardeland R. Aging and Disease 3 (2): 194-225, 2012). Low melatonin is also thought to contribute to obesity in people with insomnia or those who do night shift work.

Low night time melatonin levels (seen as low first and last void urinary MT6s) are seen commonly in breast and prostate cancer patients. This results in a low and flat MT6s diurnal profile. The WHO's International Agency for Research on Cancer has concluded that shift work that involves circadian disruption is probably carcinogenic to humans, because of the suppression of melatonin production by exposure to light during the night.

When melatonin is within normal range but sleep issues are problematic, this condition may, more likely, be related to excessive stress(ors) or to other hormonal imbalances (low or high) in estrogens (necessary for REM sleep, excessive levels can be over stimulating), progesterone (metabolite allopregnanolone binds GABA receptors and has a calming effect), cortisol (low or high levels can disrupt sleep) and/or thyroid. If any of the symptoms of estrogen, progesterone, cortisol, or thyroid hormones appear to be imbalanced, consider testing them and correcting imbalances to facilitate better sleep.

If melatonin is taken as a supplement (available OTC) to correct low levels or treat a condition, the timing and dosage are important to its effectiveness, especially as a sleep aid. Response to supplemental melatonin can be very individual. For optimal benefit it is best to work with a health care provider familiar with melatonin dosage and timing. Excessive dosing can result in spillover of melatonin into daylight hours, excessive sleepiness during the day, and disruption of the normal melatonin-cortisol circadian rhythms. This will be seen as very high levels of MT6s in the first and second urine voids, and often carry-over into the evening when levels should be low. Consider dosage reduction if MT6s levels are excessive throughout the daylight hours and this is associated with persistent sleepiness during the day.

For more general information about melatonin please see: http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html

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