NutriPATH
Integrative Pathology Services
P: 1300 688 522
E: info@nutripath.com.au
A: PO Box 442 Ashburton VIC 3142

**TEST PATIENT**
Sample Test Name
Sex : F
Date Collected : 00-00-0000
111 TEST ROAD TEST SUBURB
**LAB ID: 00000000** UR#:0000000

**TEST PHYSICIAN**
DR JOHN DOE
111 CLINIC STREET
CLINIC SUBURB VIC 3000

## MICRO SAMPLE ASSAYS

| DRIED URINE | Result | Range | Units |
|---|---|---|---|
| **Estrogen Elite, Dried Urine** | | | |
| **Dried Urine Hormone Comments** | Please refer to PDF attached. | | |

**Patient Name:** TEST TEST **Samples Collected** Urine - 00:00 Urine - 00:00 Urine - 00:00 Urine - 00:00

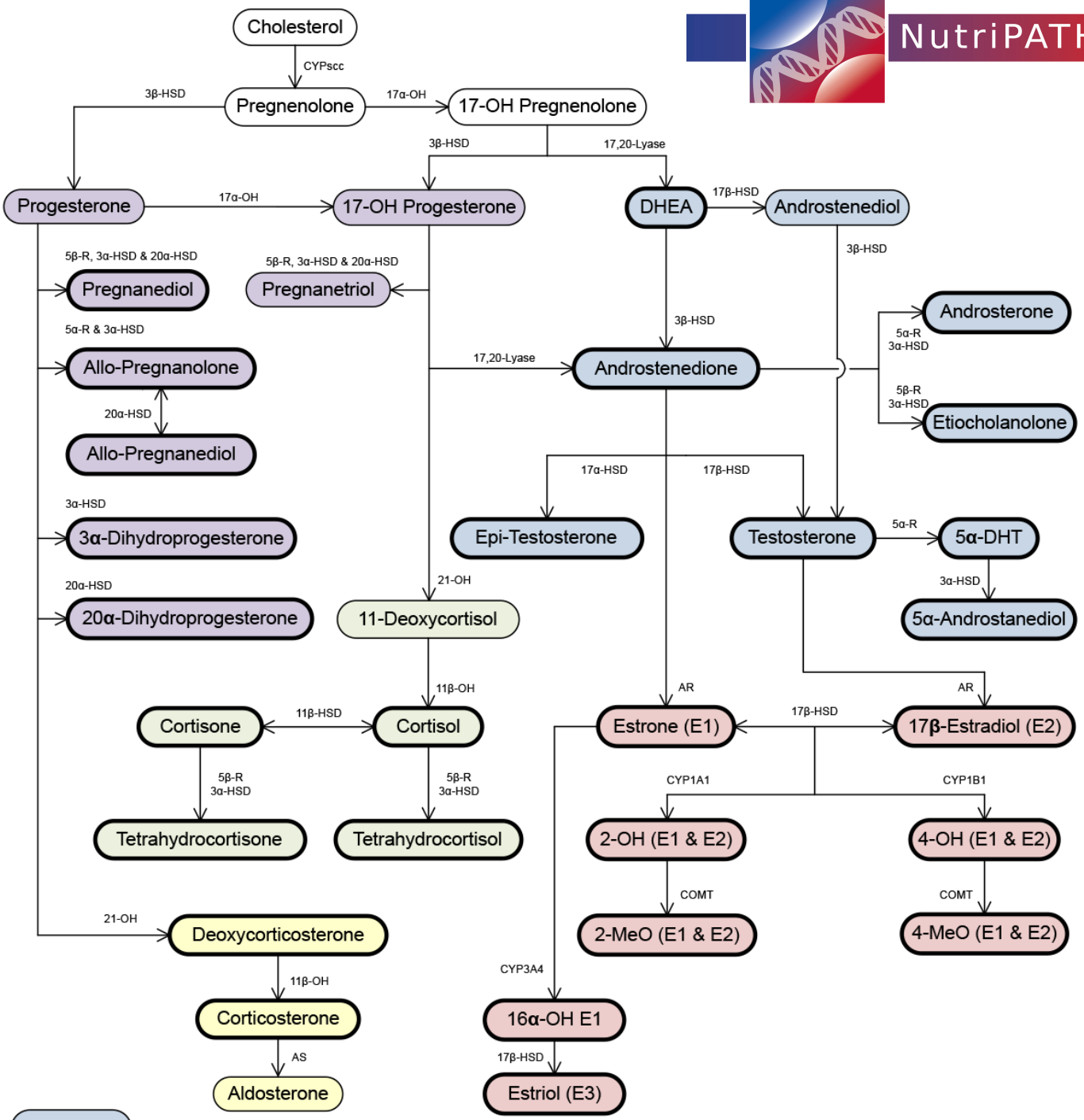
| TEST NAME | RESULTS \| 11/04/18 | RANGE |
|---|---|---|
| **Urinary Estrogens** | | |
| **Estradiol** | 2.07 H | 0.78-1.79 µg/g Cr Premeno-luteal or ERT |
| **Estrone** | 8.45 H | 2.27-5.22 µg/g Cr Premeno-luteal or ERT |
| **Estriol** | 1.56 | 0.78-1.98 µg/g Cr Premeno-luteal or ERT |
| **E3/(E1+E2)** | 0.17 L | >0.3 (> median value) |
| **2-OH Estradiol** | 0.98 H | 0.17-0.70 µg/g Cr Premeno-luteal or ERT |
| **2-OH Estrone** | 3.40 H | 0.70-2.54 µg/g Cr Premeno-luteal or ERT |
| **4-OH Estradiol** | 0.31 H | 0.10-0.18 µg/g Cr Premeno-luteal or ERT |
| **4-OH Estrone** | 0.76 H | 0.17-0.47 µg/g Cr Premeno-luteal or ERT |
| **16α-OH Estrone** | 1.21 H | 0.35-1.07 µg/g Cr Premeno-luteal or ERT |
| **2-OH (E1 + E2)/16-α-OH E1** | 3.60 | 1.29-5.49 Premeno-luteal or ERT |
| **2-MeO Estradiol** | 0.10 H | 0.03-0.08 µg/g Cr Premeno-luteal or ERT |
| **2-MeO Estrone** | 0.80 H | 0.26-0.68 µg/g Cr Premeno-luteal or ERT |
| **2-MeO E1/2-OH E1** | 0.24 | 0.21-0.38 Premeno-luteal or ERT |
| **4-MeO Estradiol** | 0.03 | <0.04 µg/g Cr |
| **4-MeO Estrone** | 0.04 | <0.04 µg/g Cr |
| **4-MeO E1/4-OH E1** | 0.05 | 0.05-0.13 Premeno-luteal or ERT |
| **4-MeO E2/4-OH E2** | 0.10 | 0.10-0.29 Premeno-luteal or ERT |
| **Bisphenol A** | 4.06 H | 1.11-3.74 µg/g Cr Premeno-luteal |

| TEST NAME | RESULTS \| 11/04/18 | RANGE |
|---|---|---|
| **Urinary Progestogens** | | |
| **Pregnanediol** | 1945 H | 465-1609 µg/g Cr Premeno-luteal or PgRT |
| **Allopregnanolone** | 11.39 | 2.23-14.87 µg/g Cr Premeno-luteal or PgRT |
| **Pgdiol/E2** | 948.78 L | 1000-1500 (Optimal Luteal Only) |
| **Urinary Androgens** | | |
| **DHEA** | 130.00 H | 15.82-129.17 µg/g Cr Premeno-luteal or DHEAT |
| **Androstenedione** | 7.54 | 3.93-13.53 µg/g Cr Premeno-luteal or ART |
| **Testosterone** | 3.66 | 1.22-3.97 µg/g Cr Premeno-luteal or ART |
| **Epi-Testosterone** | 3.67 | 2.01-4.66 µg/g Cr Premeno-luteal |
| **T/Epi-T** | 1.00 | 0.5-3.0 |
| **5α-DHT** | 1.76 H | 0.28-1.52 µg/g Cr Premeno-luteal or ART |
| **Urinary Creatinine** | | |
| **Creatinine (pooled)** | 0.66 | 0.3-2.0 mg/mL |

*<dL = Less than the detectable limit of the lab. **N/A** = Not applicable; 1 or more values used in this calculation is less than the detectable limit. **H** = High. **L** = Low.*

## Therapies

# The Steroid Hormone Cascade




## Enzyme Abbreviations

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

| SYMPTOM CATEGORIES | RESULTS \| 11/04/18 |
|---|---|
| **Estrogen / Progesterone Deficiency** | 5% |
| **Estrogen Dominance / Progesterone Deficiency** | 14% |
| **Low Androgens (DHEA/Testosterone)** | 2% |
| **High Androgens (DHEA/Testosterone)** | 1% |
| **Low Cortisol** | 5% |
| **High Cortisol** | 4% |
| **Hypometabolism** | 4% |
| **Metabolic Syndrome** | 0% |

| SYMPTOM CHECKLIST | MILD | MODERATE | SEVERE |
|---|---|---|---|
| Aches and Pains | ■ | | |
| Acne | ■ | | |
| Allergies | ■ | | |
| Anxious | ■ | | |
| Bleeding Changes | ■ | | |
| Blood Pressure High | ■ | | |
| Blood Pressure Low | ■ | | |
| Blood Sugar Low | ■ | | |
| Body Temperature Cold | ■ | | |
| Bone Loss | ■ | | |
| Breast Cancer | ■ | | |
| Breasts - Fibrocystic | ■ | | |
| Breasts - Tender | ■ | ■ | |
| Chemical Sensitivity | ■ | | |
| Cholesterol High | ■ | | |
| Constipation | ■ | | |
| Depressed | ■ | | |
| Fatigue - Evening | ■ | | |
| Fatigue - Morning | ■ | | |
| Fibromyalgia | ■ | | |
| Foggy Thinking | ■ | | |
| Goiter | ■ | | |
| Hair - Dry or Brittle | ■ | | |
| Hair - Increased Facial or Body | ■ | | |
| Hair - Scalp Loss | ■ | | |
| Headaches | ■ | | |
| Hearing Loss | ■ | | |
| Heart Palpitations | ■ | | |
| Hoarseness | ■ | | |
| Hot Flashes | ■ | | |
| Incontinence | ■ | | |
| Infertility | ■ | | |
| Irritable | ■ | | |
| Libido Decreased | ■ | | |
| Memory Lapse | ■ | | |
| Mood Swings | ■ | | |
| Muscle Size Decreased | ■ | | |
| Nails Breaking or Brittle | ■ | | |
| Nervous | ■ | | |
| Night Sweats | ■ | | |
| Numbness - Feet or Hands | ■ | | |


## Lab Comments

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

The parent estrogens estradiol (E2) and estrone (E1) are higher than reference ranges seen in premenopausal women. This is often associated with symptoms of estrogen imbalance (dominance) when progesterone is low (luteal insufficiency or anovulation) and the ratio of pregnanediol/estradiol is low. High estrogens occurs most commonly in the early teens and then again during the 10-15 or so years before menopause (perimenopause-usually about ages 35-50), when estrogens are produced at higher levels relative to progesterone and the ratio of progesterone (or pregnanediol in urine) is low relative to estradiol. If symptoms of estrogen dominance are/or become problematic consider means to lower the estrogen burden (diet consisting of more fiber and cruciferous vegetables, less red meat, weight reduction if problematic) and progesterone restoration therapy (assuming no contraindications) as this often helps balance symptoms of estrogen imbalance.

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

The 2-hydroxylated estrogens (2-OH-E2 and 2-OH-E1) are within/near mid to high-normal reference ranges; however, the 4-hydroxylated estrogens are above reference ranges. Higher levels of the 4-hydroxylated metabolites (4-OH-E1 and 4-OH-E2) have been associated with increased risk for breast cancer, particularly if they are not well methylated (see Methylated Hydroxyestrogens Below). High methylation of the 2- and 4-hydroxyestrogens indicates that these hydroxyestrogens are converted to inert metabolites that will not convert to estrogen quinones that interact with DNA, causing depurinating adducts that lead to mutations and higher cancer risk.

The hydroxylation of estradiol and estrone represent the first phase of metabolism and elimination of these estrogens via urine. Following hydroxylation at the 2-, 4-, or -16 position, the estrogens undergo further modification (methylation, sulfation, glucuronidation) that increases their solubility and excretion in urine. Before these urine estrogen conjugates can be tested by GC-MS/MS the sulfate and glucuronide groups must first be removed by enzyme hydrolysis.

Research and clinical studies show that the 2-hydroxylated estrogens (2-OH E2 and 2-OH E1) are a safer pathway of hydroxylation than the 4-hydroxyestrogens (4-OH E2 and 4-OH E1), the latter two of which bind to and damage DNA, leading to mutations that are associated with increased breast cancer risk. If either 4-OH-E2 or 4-OH-E1 are higher than reference ranges, as reported for this individual, this may indicate higher risk for DNA damage, mutations, and risk for developing breast cancer. However, this depends also on how well these potentially reactive estrogen metabolites are rendered inactive by methylation before they are converted to more reactive and dangerous estrogen quinones. 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.

2-hydroxylated estrogen metabolism, considered the safer pathway for estrogen metabolism, is increased with cruciferous vegetables and extracts of them. The most commonly used are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). Iodine also increases the 2-hydroxylation of estrogens, with a slight increase in 4-hydroxylation (Stoddard FR et.al. Int J Med Sci 5: 189-196, 2008). The more dangerous 4-hydroxylation pathway of estrogen metabolism is enhanced by exposure to environmental toxins, mostly petrochemical-based products, but also by heavy metals. These toxins mediate their action by inducing the cytochrome P450 enzyme 1B1, which is responsible for the formation of 4-OH-E2 and 4-OH-E1. Reactive Oxygen Species (ROS) formed from these environmental toxins further co-oxidize the catechol estrogens to more dangerous estrogen quinones.

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 2-hydroxylated estrogens (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. Newer research suggests that while higher levels of 16-hydroxy estrone may indeed be slightly associated with increased breast cancer risk in premenopausal women, higher levels are, paradoxically, associated with a decreased risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012). Overall, more recent studies have NOT shown the 2/16 ratio to be useful for predicting breast cancer risk.

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2-hydroxyestrogens are within normal reference ranges or high (beneficial). In contrast, methylation of the more toxic 4-hydroxyestrogens is low (considered higher risk). Adequate methylation of the hydroxyestrogens, and an associated high ratio of 4-hydroxylated estrogens to 4-methoxyestrogens (i.e. 4 MeO-E2/4-OH-E2 and 4-MeO-E1/4-OH-E1) is considered beneficial as this indicates the 4-hydroxyestrogens are rendered inert preventing them from oxidizing further to more dangerous 4-estrogen quinones that can form adducts with DNA, causing mutations that can lead to increased cancer risk.

The 2- and 4- hydroxyl estrogens are methylated by the enzyme Catechol-o-Methyl Transferase (COMT), which renders these catechol estrogens 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 of the hydroxyl (catechol) groups to quinones. Estrogen quinones, especially the 4-quinone of estradiol (4-Quinone-E2) and estrone (4-Quinone-E1) are highly electrophilic and bind to DNA, forming adducts that lead to permanent mutations. Many studies have shown that high urinary levels of these 4-quinones of estradiol and/or estrone are associated with increased breast cancer risk if the 4-hydroxylated estrogens are notinactivated by methylation, or the 4-quine estrogens are inactivated by glutathione sulfation. The 2- and 4-hydroxy estrogens are converted to their more dangerous oxidized quinone forms under oxidizing conditions in the cell, and this occurs more efficiently in the presence of oxidized lipids, especially those from trans-hydrogenated fats. These estrogen quinones, like all oxidized and electron-hungry molecules in the body are inactivated when bound to glutathione, the most ubiquitous antioxidant in the body. However, if glutathione is low, due to insufficient levels of minerals (selenium, iodine) and vitamins (C and E), the quinone estrogens are less likely to be detoxified (inactivated) and have potential to damage cells/DNA in close proximity to their formation (i.e. the breast cell/DNA). Neither the quinone estrogens nor their interaction with DNA is measured-only the precursor hydroxyl-estrogens and their methylated metabolites. Nevertheless, clinical studies investigating estrogen metabolites have shown that high levels of 4-hydroxylated estrogens (4-OH-E2 and 4-OH-E1) and/or low levels of their methylated forms are associated with increased breast cancer risk.

METHYLATION OF HYDROXYESTROGENS

The methylated form of 4-OH-E2 (4-MeO-E2) is lower than the reference range for a premenopausal woman. 4-OH-E2 itself is high, indicating poor methylation of this toxic catechol estrogen.

Methylation of 4-OH-E2 renders it inert, preventing it from oxidizing further to the more dangerous 4-estradiol quinone, a very reactive molecule that can form adducts with DNA, causing mutations that can lead to increased cancer risk. In this individual the 4-OH-E2 is elevated and is not well methylated (lower 4-MeO-E2). The 2- and 4-hydroxyestrogens 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). These inert methylated catechol estrogens are then excreted in urine. If methylation pathways are inadequate due to low levels of COMT (usually a result of gene polymorphisms), or lack of precursors of methylation (i.e. insufficient vitamins B6, B12, folate, betaine), the 2- and 4-hydroxyl estrogens may be oxidized further to more reactive 2- and 4-estrogen quinones. Estrogen quinones, especially the 4-quinone of estradiol is highly electrophilic and binds to DNA, forming adducts that lead to permanent gene mutations. Clinical studies have demonstrated that high urinary levels of 4-hydroxyestrogens of estradiol and/or estrone are associated with increased breast cancer risk.

The 2- and 4-hydroxy estrogens are converted to their more dangerous oxidized quinone forms under oxidizing conditions in the cell, and this occurs more efficiently in the absence of antioxidants (e.g. vitamins C and E, glutathione, etc.) and the presence of excessive levels of heavy metals and oxidized lipids, especially those from trans-hydrogenated fats. The 4-estrogen quinones are inactivated when bound to glutathione, the most ubiquitous antioxidant in the body. However, if glutathione is low, due to insufficient levels of minerals (selenium, iodine) and vitamins (C and E), the 4-quinone estrogens are less likely to be detoxified (inactivated) and have potential to damage cells/DNA in close proximity to their formation (i.e. the breast cell/DNA). Therefore, maintaining these nutrients at optimal level is important to preventing formation of the more dangerous 4-hydroxyestrogens, and increasing their methylation should they form.

BISPHENOL A (BPA)

Bisphenol A (BPA) is elevated. BPA is an endocrine disrupting chemical (EDC) derived from plastics used for making bottles, wraps for foods, and linings for food cans. BPA is not retained in the body for a prolonged period of time and is rapidly excreted into urine. High urinary levels of BPA indicate recent exposure to plastics that released excessive amounts of BPA into food or beverages consumed in the past 24-48 hr.

BPA acts as an EDC by binding to a activating both membrane and nuclear estrogen receptors in a manner similar to estradiol. Thus by mimicking the actions of endogenous estrogens, high levels of BPA can contribute to symptoms of estrogen dominance. High BPA levels have been associated with increased risks for many different health issues, including diabetes, breast cancer, and prostate cancer. When BPA levels are elevated, identification of its source and reducing exposure is worth considering.

PROGESTERONE METABOLITES (Pregnanediol-PgDiol and Allopregnanolone-AlloP)

Pregnanediol (PgDiol) is higher than reference ranges for a premenopausal woman (luteal phase). This is not uncommon in younger premenopausal women who tend to produce more progesterone during the luteal phase of the menstrual cycle, or in premenopausal women with luteal insufficiency and estrogen excess (estrogen dominance) who may be supplementing with exogenous progesterone, especially oral progesterone (none indicated). Topical progesterone supplementation has little impact on urinary PgDiol levels; therefore, the high PgDiol seen in these test results is unlikely from topical progesterone therapy.

The neuroactive steroid, AlloP, is within expected reference range for a premenopausal woman. High PgDiol and normal AlloP indicates lower levels of enzymes that convert progesterone to AlloP. One of these enzymes is 5-alpha reductase, the same enzyme that converts T to 5-alpha dihydrotestosterone (DHT), and DHEA/androstanedione to androsterone (see Steroid Hormone Cascade). AlloP is a neuroactive steroid meaning it is bioactive in the brain, where it binds to GABA receptors and, in most women, induces a calming effect (anxiolytic). In a small percentage (about 5%) of women high AlloP has a paradoxical effect in that it is anxiogenic, causing severe PMS-like symptoms, termed Premenstrual Dysphoric Disorder (PMDD) during the luteal phase of the menstrual cycle. Normally AlloP has calming, sleep-inducing effects.

ANDROGEN PRECURSORS (ANDROSTENEDIOL, DHEA)

Androstenedione and DHEA(S) are within expected reference ranges seen in premenopausal women.

In premenopausal women about half of the androstenedione is derived from the ovaries and the other half from the adrenals. At menopause, most of the androstenedione derives from the adrenal glands. DHEA is synthesized in the adrenal glands and is rapidly sulfated to DHEA-sulfate (DHEAS) to extend its half-life in blood. Androstenedione is converted into the androgens, testosterone and Epi-testosterone in near equal amounts in most individuals, or into estrone. More conversion to estrone occurs in individuals with higher amounts of adipose (fat) tissue, which contains high levels of aromatase, an enzyme that converts androgens to estrogens.

ANDROGENS AND METABOLITES

Testosterone (T) is within the expected reference range for a premenopausal woman. The more potent metabolite of T, 5-alphaa dihydrotestosterone (DHT) is higher than reference range, suggesting elevated expression of 5-alpha reductase enzyme. Individuals that over-express this enzyme in tissues, particularly the pilosebaceous glands (hair follicle) are more likely to loose hair on the scalp and have more problems with increased facial/body hair and acne when exposed to androgens like testosterone. 5-alpha reductase is also responsible for metabolizing progesterone to pregnane-type metabolites, which some scientists have suggested are more likely to stimulate the growth of breast tumors (see Wiebe-progesterone metabolites).

Androgens are important for strengthening structural tissues such as muscles, bone, connective tissue, and skin. They 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. Androgens are also precursors to the estrogens, estradiol and estrone. The most potent of the androgens is dihydrotestosterone (DHT), which is created from testosterone via 5a reductase. Testosterone itself is derived mostly from androstenedione and DHEA. 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.

Low androgens are associated with many different adverse conditions (bone loss, thinning skin, vaginal dryness, incontinence, cardiovascular disease, insulin resistance/metabolic syndrome, breast cancer) and symptoms (fatigue, low stamina, depression, memory lapses, loss of sex drive, hot flashes, allergies).

High androgens, as seen in these test results, particularly high DHT, is associated with increased facial and body hair, acne, loss of scalp hair, and oily skin and hair.

If symptoms of high androgens are problematic, consider the following: reduce androgen supplementation (assumes therapy with androgens such as testosterone or testosterone precursors like DHEA); evaluate precursor androgen levels (i.e. DHEA and androstenedione) and if high consider source (endogenous or exogenouus) as regards treatment strategy. High endogenous levels of these androgens and precursors is usually due to PCOS, adrenal hyperplasia, adrenal or ovarian tumors, each of which requires different clinical interventions (e.g. dietary modification, treatment for obesity/insulin resistance, 5-alpha reductase inhibotors to block excessive T to DHT conversion, surgical removal of benign or malignant tumors).. High levels of these androgens resulting from exogenous treatment with androgens (testosterone) or androgen precursors (DHEA) can be reduced by lowering or discontinuing supplementation.

EPI-TESTOSTERONE AND RELATIONSHIP TO TESTOSTERONE.

Epi-testosterone (Epi-T) and testosterone (T) are created in about equal amounts from androstenedione and DHEA. The ratio of T/Epi-T should be about 1 under normal circumstances, but normally ranges from about 0.5-2. When testosterone is supplemented the T/Epi-T ratio increases, which reflects an increase in the exogenous testosterone, but not Epi-T, which represents endogenous production.