Rocky Mountain Analytical
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Female Panel

Clinical Information for Professionals

Female Panel

The Female Panel is comprised of five major hormones. Interactions between these hormones are fundamental to health which means that imbalances may negatively impact health.

Estradiol (E2)

- Estradiol is needed for the proper function of progesterone receptors, and maintenance of the right balance between estrogens and progesterone is crucial for hormone health.
- High E2 interferes with proper thyroid function.
  - competes with T3 at T3-responsive genes and interferes with the tissue action of T3.
  - may increase Thyroid Binding Globulin levels, which binds up free T3 and T4 hormone, resulting in decreased tissue action of T3.
- Low estradiol levels post-menopause may be a consequence of adrenal dysfunction since post-menopausal production of estradiol comes via conversion from the adrenal hormone DHEA.

Progesterone

- Progesterone may enhance the sensitivity of estrogen receptors, which means a lack of progesterone could contribute to, or exacerbate, estrogen deficiency symptoms despite a normal E2.
- Too little progesterone relative to estradiol can result in estrogen dominant symptoms like weight gain at hip, breast tenderness, anxiety, fluid retention and fibrocystic breasts.

Progesterone to Estradiol Ratio (Pg to E2)

- The progesterone to estradiol ratio is only calculated when endogenous (unsupplemented) hormone levels have been measured. The most commonly observed ratio in regularly cycling women in the luteal phase is in the range of 23 to 57

Testosterone

- High testosterone and/or elevated DHEA-S may suggest the presence of polycystic ovary syndrome and/or insulin resistance and metabolic syndrome.
- Low testosterone levels post-menopause may be a result of adrenal dysfunction. After menopause, the adrenal hormone DHEA is the major source of testosterone (DHEA is converted to testosterone).

Cortisol

- Elevated cortisol can interfere with the action of progesterone and testosterone at gene regulatory sites. Consequently, women with normal progesterone and/or testosterone levels may exhibit signs of deficiency when cortisol levels are high. This is called a functional deficiency.
- High cortisol can induce the enzyme aromatase, which speeds the conversion of testosterone to estradiol; this can result in elevated estradiol levels, especially when DHEAS and/or testosterone are also elevated.
- Excess cortisol is catabolic for bone and also opposes the action of testosterone, which is anabolic for bone. Thus, significant bone loss may occur with elevated cortisol levels.
- Elevated cortisol in the evening has been associated with depression. High evening cortisol in breast cancer survivors has been associated with a poorer prognosis.
- Over time, high cortisol levels may progress to adrenal exhaustion and overall lower cortisol levels.

DHEAS

- DHEA is stored in the blood mainly in its sulphate form, DHEAS.
- Cortisol and DHEA have opposite effects on immune function and insulin regulation.
- High cortisol levels require more DHEAS to be released to balance effects of cortisol. Thus, chronically elevated cortisol can result in a deficiency of DHEAS.
- Low DHEAS levels may be associated with hypothyroidism and chronic illnesses such as lupus and rheumatoid arthritis.

Cortisol
DHEAS
Estradiol
Progesterone
Testosterone

Female panel provides an excellent overview of female hormone imbalance

Hormone	Clinical Considerations
Low Estradiol	• nutritional supplements - boron • progesterone supplementation - progesterone may facilitate estradiol receptor signaling and improve clinical effect of E2 • estrogen supplementation - transdermal is nearest to natural delivery from ovaries. Oral estrogens undergo metabolism in liver which can result in unwanted metabolites - to maintain balance, progesterone should always accompany estrogen supplementation, regardless of estrogen type, dose, route of administration or whether uterus is intact - use minimum dose required to relieve symptoms • lifestyle changes - weight gain (if currently underweight) • periodic monitoring of bone density in the face of low E2 may be advisable
Low Testosterone	• testosterone supplementation - transdermal testosterone: doses commonly range from 0.25 to 2 mg/day - oral testosterone: testosterone undecanoate is sometimes used one capsule every other day. Co-ingestion with 20 grams of fat helps decrease first pass metabolism. • periodic monitoring of bone density in women with low testosterone may be advisable
Low Cortisol	• assess diurnal cortisol via an Adrenal Function Panel or 4-point cortisol saliva test • nutritional supplements - adrenal support protocol (see Adrenal Function Panel Clinical Info Sheet) • cortisol supplementation - short term supplementation may be necessary in some cases (see *The Safe Uses of Cortisol* by William Jeffries, MD, FACP) • assess sleep: low morning cortisol is associated with insomnia

Hormone	Clinical Considerations
Low Progesterone	• nutritional supplements - vitex/chaste berry acts on dopamine receptors and decreases prolactin, which may help normalize luteal phase progesterone • progesterone supplementation - progesterone cream, oral micronized progesterone, or compounded sustained release micronized progesterone - use minimum dose required to relieve symptoms - women on birth control pills may benefit from progesterone cream supplementation • optimize thyroid function - low Pg may be symptomatic of low T3 as ovaries need T3 to secrete adequate progesterone. Progesterone supplementation may help optimize thyroid function
Low DHEA-S	• nutritional supplements - adrenal support protocol, particularly if low cortisol is also present • DHEA supplementation - oral, sublingual: minimum dose to relieve symptoms and achieve physiologic levels • low DHEA may be associated with hypothyroidism, chronic stress and/or chronic illness • the DHEAS level after DHEA supplementation may not increase as DHEA is broken down into metabolites

Hormone	Clinical Considerations
High* Estradiol	• prolonged excessive estrogen supplementation can lead to down-regulation of estrogen receptors and may result in deficiency symptoms even though measured levels are high • reduce dose of estradiol - when salivary estradiol levels are high and optimal clinical results have not been achieved - when saliva E2 levels are above or at high end of range and symptoms of excess (breast tenderness, migraines, fluid retention and weight gain at the hips) are present • estriol (E3) - is an end metabolite and bio-accumulation may occur. If clinical response is good, monitor E3 levels more frequently. If levels remain high and symptoms worsen, consider reducing dose • clinically stable for >6 months and no E2 excess symptoms or side effects: consider monitoring E2 more frequently • reduce estrogen synthesis - weight loss (fewer fat cells = less aromatase to convert T to E2 and androstenedione to E1) • progesterone supplementation to balance the effects of estrogen • nutritional supplements - vitamin B6 is a cofactor in estrogen metabolism - improve liver and bowel function to assist in estrogen elimination • check thyroid hormone levels: high estrogens can interfere with tissue action of T3
High* Progesterone	• prolonged excessive progesterone supplementation can lead to down-regulation of progesterone and estradiol receptors and possible deficiency symptoms even if measured levels are high • high endogenous progesterone is generally not problematic (less than 300 to 400 pg/mL). • reduce dose of progesterone - when saliva Pg levels are above or at high end of range and symptoms of excess are present: breast swelling, depression, excessive drowsiness • nutritional supplements - omega 3 fatty acid supplementation may prevent accumulation of testosterone

Hormone	Clinical Considerations
High* Testosterone	• prolonged excessive testosterone supplementation can lead to down-regulation of testosterone receptors and may result in deficiency symptoms even though measured levels are high • reduce dose of testosterone - when saliva testosterone levels are above or at high end of range and symptoms of excess are present: hirsutism, oily skin, acne • progesterone - if patient is on oral Pg and testosterone is high, consider switching to progesterone cream - progesterone cream may cause elevation of salivary testosterone due to conversion of progesterone to androstenedione and testosterone, although to a lesser extent than oral progesterone • consider investigating for polycystic ovary syndrome (PCOS) and/or insulin resistance as these conditions have a strong association with elevated androgens
High* DHEAS	• reduce dose of DHEA: small doses (less than 10 mg) of DHEA are generally effective in women • weight loss: elevated DHEAS is associated with central adiposity • nutritional supplements: adrenal support protocol • consider investigating for PCOS and/or insulin resistance due to strong link to excess androgens • institute measures to reduce insulin resistance: weight loss, exercise
High* Cortisol	• assess diurnal cortisol via an Adrenal Function Panel or 4-pt cortisol saliva test • nutritional supplements • adrenal support protocol (see Adrenal Function Panel Clinical Info Sheet) • assess sleep: difficulty sleeping may be a result of high bedtime cortisol • weight loss: elevated cortisol may be associated with weight gain • test for/treat metabolic syndrome if necessary

* Note that high saliva hormone levels may result if a woman has skin to skin contact with someone on transdermal hormones. For example, a women whose husband uses transdermal testosterone may report a high saliva testosterone level.

Progesterone-Estradiol Ratio

In women not supplementing with hormones, the progesterone-estradiol ratio may be helpful in detecting estrogen excess. A *relative* excess of E2 over Pg can occur even if both hormones are within normal limits (i.e E2 is on high end of normal and Pg is on the low end of normal).

- 95% of regularly cycling women not on hormones have a Pg to E2 ratio of between 23 and 57 (sampled one week prior to onset of menses).

Unfortunately, because of the variability in absorption from person to person, the Pg to E2 ratio is not useful when women are on topical progesterone and/or estrogen. In other words, the ratio of progesterone to estradiol is a useful index when hormones are produced endogenously, but the utility of the ratio with topical hormones has not been established.

Progesterone-Estradiol Balance

If symptoms of estrogen excess (e.g. breast tenderness) are present when an adequate amount of progesterone is given along with estrogen, then decreasing or discontinuing estrogen will generally address the problem. Sometimes switching from oral to transdermal progesterone alleviates estrogen excess symptoms. Occasionally, even when the measured level of progesterone is within range, supplementation with topical progesterone may be useful. If no hormones are being supplemented, then it is a question of addressing the endogenous imbalance: above or high end of range estradiol and/or below or low end of range progesterone. It is important to ensure that other hormones are within range as well; particularly cortisol and testosterone.

Post-Hysterectomy: Results from the Premarin™ only arm of the Women's Health Initiative Study indicate that unopposed oral conjugated estrogens carry an increased risk of stroke. Because there are progesterone receptors throughout the body, not just in the uterus, bio-identical progesterone should always be given with estrogens, even after a hysterectomy. Addition of bio-identical progesterone often allows the estrogen dose to be halved, and paves the way for gradual discontinuation of oral estrogens. Once off oral estrogens, a retest of estradiol levels can be performed. If estradiol levels are below range and symptoms are an issue, supplementation might be worth considering. However, in many cases, bio-identical progesterone is sufficient.

Progesterone Cream & Saliva Hormone Tests

The salivary progesterone level after topical progesterone application is mostly a qualitative measure. For example, one woman applies 50 mg of progesterone cream and gets a saliva hormone result of 3000 pg/mL. Another woman uses the same dose and tests the same number of hours after cream application, and gets a saliva hormone result of 10,000 pg/mL. The different levels are likely a consequence of the high lipid solubility of progesterone. The amount of progesterone absorbed may vary considerably depending on percent body fat. In other words, there is no scientific rationale to support a claim that a saliva progesterone level of 3000 pg/mL is better than a level of 500 pg/mL. Nevertheless, there is value in knowing whether the level is above or below range. Note, there is some evidence that salivary progesterone levels may reflect progesterone stored in fat after progesterone has been supplemented topically.

Low Progesterone: If the progesterone level is unexpectedly low and clinical response is lacking, perhaps a different carrier (cream or other base) may be needed. Patient compliance should also be investigated if suboptimal clinical results are seen and the progesterone level is below range. If the progesterone level is above range, it may be an indication of excess supplementation. Symptoms such as drowsiness, depression, fluid retention and breast swelling (in upper outer quadrants toward axillae) are possible signs of progesterone excess.

Progesterone cream and endometrial protection: There is minimal research to suggest that progesterone cream produces a quiescent endometrium when given with estrogens, and there is no human data correlating saliva progesterone levels with progesterone levels in uterine or breast tissue. Therefore, it's important to understand that maintaining a specific saliva progesterone level is no guarantee of endometrial protection, when progesterone is supplemented in conjunction with estrogens.

When To Test?

Hormone testing in **peri-menopausal** women with irregular periods generally shows an estrogen dominant state. In such cases, testing may not be necessary as it generally only confirms the suspected estrogen dominance. Testing in peri-menopause may be useful if new symptoms develop or symptoms are not alleviated by the addition of progesterone.

Our data shows that for the majority of **pre-menopausal** women, a single sample taken one week prior to menses is representative of their state of hormone balance, data that is supported by research conducted by Ishikawa. However, in the presence of cycle-specific symptoms, a **Month-Long Hormone Assessment** (E2 and Pg every 3 days) may provide more detailed information. This assessment also includes an average testosterone, DHEAS and cortisol measured from equal aliquots of saliva from all 11 saliva samples.