PROGESTERONE METABOLITES

POSTMENOPAUSE

Urinary Progesterone Metabolites in Postmenopausal Women Not Supplementing with Progesterone

The urinary progestogen metabolites included in our profiles encompass the primary urinary metabolite, pregnanediol (Pgdiol), and four other more minor metabolites that belong to the pregnane (Allo-pregnanolone, Allo-pregnanediol) and pregnene (3α-dihydroprogesterone, 20α-dihydroprogesterone) categories. In postmenopausal women the level of pregnanediol is expected to be much lower than in premenopausal women (mean values 81 and 1324 μg/g creatinine, respectively) with optimal luteal ovarian function (equivalent to about 10-30 ng/mL progesterone in blood and 100-300 pg/mL progesterone in saliva).

IMPORTANT NOTE: Topical progesterone raises urinary pregnanediol very little even with pharmacological dosing (50-300 mg), likely because progesterone and its metabolites are excreted primarily in bile/feces. In sharp contrast, oral progesterone therapy raises urinary pregnanediol to levels much higher than seen in premenopausal women (luteal phase), without raising blood, salivary, or tissue levels of progesterone very much. For these reasons, we suggest evaluating saliva or capillary blood (not venipuncture serum) to determine the bioavailable level of the active progestogen, progesterone.

In addition to Pgdiol, four other progesterone metabolites are tested, which are listed above. Research, mostly in tissue culture with breast cancer cells and a few animal models[1], with progesterone and pregnene and pregnane metabolites has revealed that breast cancer cells have surface membrane receptors that are distinct from the classic intracellular progesterone receptors (A and B subunits) that bind to progesterone and activate unique gene sites associated with controlling estrogen-stimulated cell proliferation and cell differentiation. In contrast to progesterone itself, the pregnane class of progesterone metabolites, which are formed mostly from 5α-reductase metabolism (the same enzyme class that converts testosterone to its more active metabolite, 5α-dihydrotestosterone), activate distinct surface membrane receptors and stimulate cell proliferation, increase invasive potential, and inhibit apoptosis (necessary for differentiation). In sharp contrast, the pregnene class of progesterone metabolites, represented in the progesterone metabolite profile as 20α- and 3α-dihydroprogesterone, have the opposite effect to inhibit cell proliferation, decrease invasion and angiogenesis, and promote cell differentiation (apoptosis). Therefore, knowing the relative direction of progesterone metabolism (pregnene or pregnane formation), provides a guide to potential risk of stimulating occult cancer growth when evaluating progesterone levels in premenopausal or postmenopausal women not using progesterone, and in women using exogenous progesterone (mostly oral because topically applied progesterone is not excreted in urine).

800.600.1636 | info@zrtlab.com | zrtlab.com

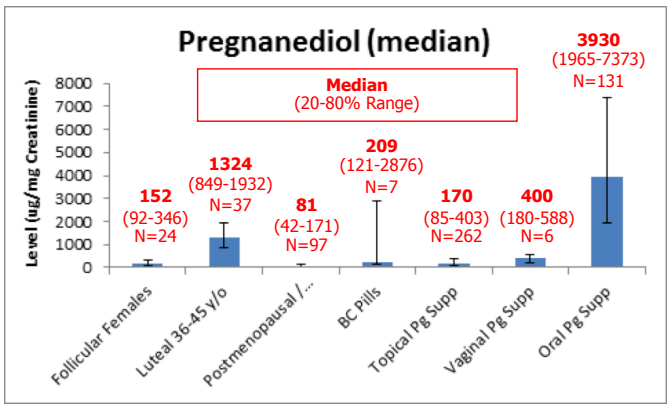
Revised 02.26.14

ZRT LABORATORY

Guide to Evaluating Progesterone Metabolites in Postmenopausal Women

Pregnanediol is the primary metabolite of progesterone, but because postmenopausal women make very little progesterone other than that produced by the adrenal glands, it is expected that pregnanediol will be much lower than luteal levels. However, it is still possible to evaluate the relative distribution of progesterone metabolites that fall into the pregnene and pregnane progesterone metabolite categories. If higher levels of pregnane metabolites are found relative to the pregnene metabolites, then it is possible that progesterone supplementation could be contraindicated. However, as regards the risk of stimulating occult cancerous breast cells this will depend on the progesterone dosage and delivery (e.g. oral vs. topical), the intracellular progesterone receptor level, and the relative contribution of other hormone-related breast cell growth agonists (e.g., estradiol) and antagonists (e.g., testosterone, progesterone) simultaneously present.

IMPORTANT NOTE: When topical progesterone is used at physiological (10-30 mg) or pharmacological (> 50 mg) dosing, very little pregnanediol or other metabolites are found in urine or venipuncture serum (see chart below). The small increase in urinary progesterone metabolites seen with topical dosing may be due to release of progesterone into the salivary glands and eventually in the gastrointestinal tract, where it would be converted to progesterone metabolites that find their way into urine, as with oral progesterone dosing. In stark contrast to urinary progesterone metabolites, physiological dosing (10-30 mg) with topical progesterone results in very high levels of salivary progesterone (range 300-3000 pg/mL, physiological range 50-300 pg/mL) but physiological levels of capillary blood progesterone (20-40 ng/mL). With topical physiological dosing progesterone is also found in physiological (luteal) levels in breast tissues in humans, and this dose of progesterone has been shown to inhibit in vivo estrogen-activated proliferation in human breast[2,3] and uterine epithelial cells. Thus, while urinary progesterone metabolites are a convenient way to evaluate overall endogenous ovarian production of progesterone in a premenopausal woman, this method will lead to inaccuracies in tissue uptake of exogenous progesterone supplementation, both topical (underestimation) and oral (overestimation).



References

1. Wiebe JP. Progesterone metabolites in breast cancer. Endocr Relat Cancer 2006;13:717-738.

2. Chang KJ, Lee TT, Linares-Cruz G, Fournier S, de Lignieres B. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995;63:785-791.

3. De Boever J, Verheugen C, Van Maele G, Vanderkerckhove D. Steroid Concentrations in Serum, Glandular Breast Tissue, and Breast Cyst Fluid of Control and Progesterone-Treated Patients. In: Endocrinology of Cystic Breast Disease, edited by A. Angeli, New York:Raven Press, 1983, p. 93-99.