TRANSDERMAL (TD) PROGESTERONE (Pg)

A Critical Review of the Literature and Available Data

MARK S. NEWMAN, M.S.
Founder and President
Precision Analytical Inc.

KEY POINTS AND BEST PRACTICES

Treatment/Dosing

- **TD Pg should not be used in peri/postmenopausal women with a uterus for either endometrial protection or symptom relief without endometrial surveillance. Clinicians may prefer oral or vaginal Pg in estrogen sufficient women as both have been proven to consistently protect the endometrium.**
- TD Pg can be considered for symptom relief in postmenopausal women without a uterus if not taking estrogen. If premenopausal women have modestly insufficient Pg, TD Pg may be used for symptom relief.

Laboratory Monitoring

- **There are no laboratory tests that have been proven to provide meaningful feedback regarding whether a particular dose of TD Pg is appropriate or effective.**

- Salivary and capillary blood spot testing ***cannot*** be used to monitor TD Pg therapy.
  - Salivary levels far exceed premenopausal levels on typical Pg doses and have been proven to be highly variable from day to day while on therapy.
  - Salivary values may remain elevated for months after the cessation of therapy.
  - Elevations in salivary and capillary blood spot have never been shown to correlate to a clinical outcome.

- Neither serum nor urine values increase linearly with increased dosing of TD Pg.
  - Serum Pg levels go up slightly, but not to luteal (premenopausal) levels, with typical doses.
  - Increasing dosing until luteal levels of serum or urine are achieved is not advisable.

NOTE: *This material is educational and not an endorsement for a particular HRT dose or route of administration.*

EXECUTIVE SUMMARY

Bioidentical hormone replacement therapy (BHRT) is the standard of practice in the functional medicine community. In the traditional medical community, BHRT is becoming more popular. The latter is multifactorial and includes more FDA-approved options, a less adverse side-effect profile, and patient demands for more "natural" options. FDA-approved BHRT includes: micronized oral estradiol, transdermal estradiol patches (Vivelle-dot), estrogen pellets, micronized oral and vaginal progesterone, as well as transdermal testosterone (Androgel), injectable testosterone, and testosteone pellets (Testopel). Similar to the above FDA-approved options, natural BHRT can be compounded. In the functional medicine community, the latter is common practice to "individualize care." Typically, the steroid hormone and patient preference determines the optimal delivery system (oral vs transdermal) to achieve the desired outcome.

All of the FDA-approved products have undergone large, randomized, placebo-controlled trials prior to their approval. This takes a large patient base, a long time, and a lot of capital. The functional medicine ecosystem has developed a large patient base over time; however, they have not had large research investors like pharmaceutical companies and/or large national organizational support. For example, the Postmenopausal Estrogen-Progestin Intervention (PEPI) trial[1] was a substudy of the Women's Health Initiative, a twenty-plus year study that was funded by the National Institutes of Health (NIH) and the National Heart, Lung, and Blood Institute (NHLBI). Whereas, the studies looking at BHRT are small studies with small sample sizes. Therefore, most of the current data that functional medicine clinicians rely on is extrapolated from the larger trials that occasionally included bioidentical formulations, or from small sample size studies.

When choosing BHRT it is important to address the following: [1] the treatment goal, such as symptom relief, endometrial protection, fertility issues, bone-health, etc.; and [2] the best formulation and length of time to limit any and all adverse consequences (increased cardiovascular and breast risk). In addition, how do we measure efficacy of therapy?

BHRT treatment efficacy has largely been determined using invasive technologies, including transvaginal ultrasound (TVUS) and endometrial biopsy. Other less invasive laboratory technologies continue to be studied to assess efficacy of therapy to afford patients additional options.

This brief review, using representative literature examples, will discuss whether using a transdermal delivery system is safe and which laboratory testing is best suited for monitoring bioidentical transdermal progesterone treatment.

LABORATORY TESTING

The traditional "gold-standard" for hormone monitoring is serum testing.[2] Recently, a 4-spot urine testing assay was compared to standard serum assays for estrogen and progesterone. The study documented excellent reliability, with urine estrogen and progesterone metabolite concentrations following serum levels.[3] However, the large randomized controlled HRT trials used TVUS and endometrial biopsy to measure efficacy of therapy.[4,5] This is especially true when evaluating progestin/progesterone

therapy to balance estrogen's endometrial effects in peri/postmenopausal women with an intact uterus.[4] Unfortunately, none of the existing studies included urine testing and only rarely included serum testing. Therefore, additional studies are necessary to correlate urine testing to clinical outcomes. When accomplished, DUTCH's 4-spot urine test will be an excellent cost effective, reliable, and clinically valid option to invasive TVUS testing, endometrial biopsy, and/or serum testing,

Urine metabolite testing is the "gold standard" for assessing congenital adrenal hyperplasia (CAH) treatment efficacy,[6] and is becoming the "standard of practice" in infertility clinics for cycle mapping and efficacy of progesterone therapy, instead of daily serum testing.[6,7]

Salivary testing, on the other hand, has been used for research purposes for many years.[8] Salivary testing's use in a clinical setting has been controversial and of limited value because of its greater variation over a 24-hour period when compared to serum testing, plus its difficulty in distinguishing a follicular and luteal phase timeframe.[9]

GENERAL INFORMATION

The majority of research involving progesterone has been on its role in balancing estrogen's effects. This estrogen-progesterone partnership, in addition to peri/menopausal symptom relief, has been studied for its use in endometrial protection and infertility, its role in breast cancer risk, and in osteoporosis prevention and treatment, to name a few.

This section has two purposes: [1] to demonstrate the controversies associated with TD Pg treatment and endometrial protection; and [2] to evaluate serum, saliva, and urine's clinical utility when monitoring TD Pg. In general, there is limited data using salivary testing with any of the bioidentical hormone formulations. Urine testing has generally followed serum trends and available data, which is also limited, is included.[3]

SERUM TESTING AND ENDOMETRIAL PROTECTION

Results vary when serum is used to monitor TD Pg. Bello, et al., in a preliminary study, showed that when an alcohol-base gel 100mg TD Pg dose was applied, luteal-phase plasma levels were achieved. This finding did not apply when a water-based TD

Pg gel was applied.[10] In several other studies, TD progesterone creams did not raise serum progesterone levels to the degree necessary for an antiproliferative endometrial effect (> 5ng/ml).[8] It is interesting and problematic to note that very few of the studies monitoring TD Pg using serum evaluated the endometrium to determine efficacy of therapy. These studies used "generally accepted" serum progesterone levels (> 5ng/ml).[8] In the three studies where endometrial biopsies were performed, Leonetti, et al.[11] documented an antiproliferative effect in all study subjects (37), with no documented serum levels; Wren, et al.[12] in 27 study subjects, noted low serum levels and no antiproliferative changes; and Landes, et al.[13] found an atrophic endometrium in twenty-eight out of forty (70%) study subjects, but did not obtain serum levels.

Based on these and other studies, it is hard to recommend TD Pg in peri/postmenopausal women with a uterus. In fact, Leonetti, et al., despite all subjects having an atrophic endometrium, stated: "because of the short duration and limited number of participants in our study, we do not recommend PC [progesterone cream] as an alternative progestin in HRT at this time. A longer trial will be needed before recommending PC as a safe option in HRT."[9] Further studies using alcohol-based gel formulations, serum levels, and endometrial biopsy are warranted to ascertain its effectiveness for endometrial protection.

However, in premenopausal patients who are not anovulatory and have serum or urine results documenting luteal phase endogenous progesterone levels, transdermal progesterone may be a reasonable choice to relieve vasomotor symptoms. Caution: if there is any reason to suspect a need for endometrial protection, TD Pg should not be used.[14] Instead, PO or vaginal progesterone would be a better choice.

SALIVA TESTING AND ENDOMETRIAL PROTECTION

In the functional medicine community, without much supportive evidence, salivary hormone testing is commonly used to assess baseline TD Pg hormone levels and efficacy of hormone therapy. The advantages of salivary hormone testing are: it's non-invasive, it's usually stress free, it's relatively easy to perform at home, and you can obtain repeated real-time sampling.

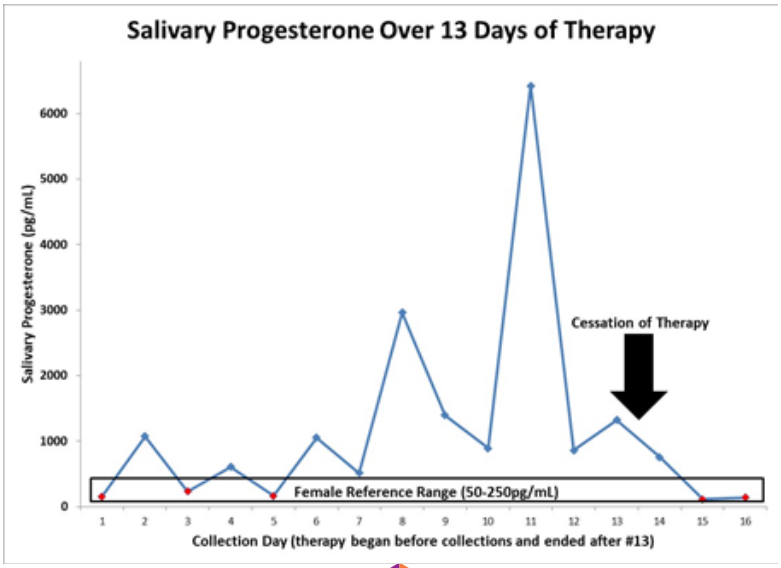
Yet, there are disadvantages that outweigh these benefits.[6] In one of the most comprehensive studies, Wren BG, et al.[12] evaluated 27 postmenopausal women on TD Pg cream, comparing serum and salivary levels. These authors found that there was significant

TREATMENT VALUES OVER 14 DAYS		
Patient ID	Lowest	Highest
A	6	104
B	10	111
C	11	360
D	4	144
E	2	192
F	5	129
G	13	377
H	82	927
I	173	1256
J	0	319
K	4	247
L	4	61
M	1	977
N	6	412
O	6	489
P	2	66
Q	1	28
R	4	81

variability in salivary progesterone levels when compared to serum. The salivary levels were at least 10-fold higher than the serum and, when compared to baseline levels, the TD Pg levels were 16.8-7,000 times higher. Yet, despite these high salivary levels, there was no endometrial protection.[12] This study was the longest (48 weeks) of its kind evaluating TD Pg's protective effects. Based on these results, TD Pg should not be used in postmenopausal women with a uterus. [SEE CHART TO THE LEFT]

Similar to Wren BG, et al.[12] Lewis JG, et al.[15] also documented high salivary gland tissue levels and stated "caution is necessary when interpreting these salivary findings." In individual salivary collections (done very carefully to eliminate contamination potential), results as high as 47,000pg/mL were seen, whereas, baseline levels were just above 100pg/mL. This study confirmed what has been seen in other studies (very high salivary levels and low serum Pg levels). By collecting samples over the course of 8 weeks, this group also reported highly variable salivary levels while on therapy.

To further investigate salivary progesterone reproducibility, DUTCH had a single patient collect saliva samples while using transdermal progesterone 50mg and 2mg Biest. The patient ceased therapy after day 13. Three of the values fell within the premenopausal range, while other values went as high as >6,000pg/mL. This degree of variability is consistent with the other studies. [SEE FIGURE BELOW]



Similar to previous studies, Stanczyk FZ[10] noted that with TD Pg there is insufficient data to draw reliable conclusions regarding endometrial protection. He commented on a study by Du JY, et al., where 10 postmenopausal women were randomized to 80mg TD Pg water-based cream or oil-based gel for 14 days and then crossing over after a 14-day washout. These results, consistent with other studies comparing TD Pg serum and saliva, showed that salivary[12,15] and capillary blood spot levels were supraphysiologic when compared to those seen in serum or whole blood. The author noted that these salivary and capillary blood spot Pg levels were in excess of the normal ranges for both pre- and postmenopausal women. He concluded that when applying topical gels or creams, salivary and capillary blood spot levels increase dramatically, "thus confirming the distribution of progesterone to tissues despite very low serum progesterone levels."[10]

The latter needs some clarification. Stanczyk is correct, but his conclusion only applies to the salivary gland. High TD Pg salivary tissue levels do not necessarily translate into high endometrial tissue levels. There has been no study assessing either salivary or capillary blood spot progesterone levels and endometrial protection. Therefore, given the current state of the evidence, neither salivary testing, nor capillary blood testing, should be considered a reliable measure of luteal phase levels and should not reassure any clinician of endometrial protection. Additionally, studies have shown that after discontinuing common doses of TD Pg, salivary levels may remain high for months, questioning the validity and clinical utility of these values.[16] While at the same time providing clinicians with false reassurances.

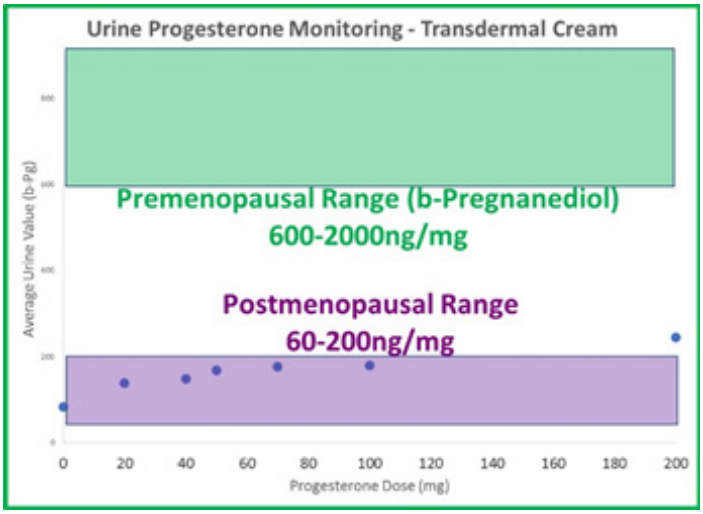
URINE TESTING AND ENDOMETRIAL PROTECTION

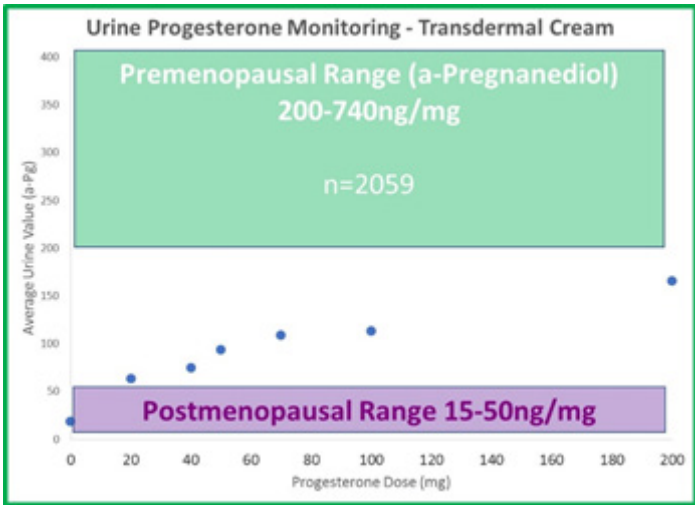
The data on TD Pg urinary monitoring is limited. Carey BJ, et al.,[17] in a study involving post-menopausal women, showed that after a single TD Pg (40mg) dose, serum Pg levels were low with wide variability. But by day 42, serum progesterone levels and urinary pregnanediol-3-glucuronide levels increased but did not approach luteal levels. Transdermal progesterone 40mg is thought to be equivalent to 45mg vaginal progesterone, which does provide endometrial protection. The discrepancy is probably secondary to local vaginal delivery effects, the "uterine first-pass" phenomenon.

Recently, as noted above, Newman M, et al.[3] also documented a robust serum-urine correlation in patients treated with various TD Pg doses. Alpha-pregnanediol and beta-pregnanediol are indirect progesterone measures and have been shown to correlate with serum Pg.[3]

More than 2000 patient results show urine concentrations that elevate above baseline (0mg) but do not approach luteal levels even with 200mg of TD Pg, similar to the pattern seen with serum testing.

The DUTCH test approximates endogenous Pg levels with a slight potential addition from TD progesterone therapy. This occurs in both premenopausal and postmenopausal women. In fact, when treating premenopausal women, clinicians can accurately assess whether ovulation is occurring and if adequate Pg is being made, especially for TD Pg doses <50mg.





The author has tested 10 different urinary progesterone metabolites (as well as progesterone itself) following TD therapy. It does not seem likely that rapid metabolism using an alternate pathway is in any way an explanation for low urinary values. All progesterone metabolites tested to date have responded similarly to therapy.

CLARIFYING RESEARCH NEEDS

There is a need for definitive randomized, placebo-controlled trials to establish with more certainty TD Pg's effects on the endometrium, as well as to determine the most reliable, valid, and clinically useful monitoring tool (serum vs urine vs saliva). Additionally, clarifying differences between delivery systems (water-based gels, alcohol-based gels, and creams) would be helpful to determine the most effective and efficient means of accomplishing treatment goals.

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