Progesterone Use as Hormone Replacement Therapy: Myths, Facts, and Solutions
by Gary Huber, DO

Winston Churchill famously quoted, "Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing had happened." Hopefully as scientists and academics we are willing and able to identify truth when it shows itself. I want to share with you my soft stance on the use of progesterone. I resist hard stances because I never know what future research may reveal and I hope to remain flexible in my thinking. The purpose of the following discussion is to shed light on some of the myths related to hormone therapies and add facts to facilitate a confident and logical decision-making process in the discussion of endometrial cancer avoidance. Which hormone therapies best protect the endometrium from cancer risk? Given the complexity of hormone receptors, metabolites, and function, it is difficult to engage in discussion without including some related comment on breast cancer; but the primary target for this paper is endometrial hyperplasia and cancer. Interestingly, many of the conclusions arrived upon in this discussion will apply equally to breast cancer risk.

The most efficacious and safest way to protect the endometrium is with topical progesterone.

Here are the assertions I wish to demonstrate in this discussion:

1. Progestins differ greatly from progesterone in form and function, but both serve to protect the endometrium from estrogen stimulation and proliferation.
2. Progestins did not perform better than progesterone and carry far too much overall health risk to be considered for use in long-term therapies.
3. Topical progesterone has been shown to effectively reduce estrogen's mitogenic influence on endometrium.
4. Oral progesterone is also protective to the endometrium, but excessive oral progesterone is short lived and increases pregnanes and thus breast cancer risk.
5. Topical progesterone achieves higher cellular and blood levels of progesterone than oral progesterone.
6. The most efficacious and safest way to protect the endometrium is with topical progesterone.
7. Breast cancer will be diagnosed in one out of every eight women while uterine cancer occurs in only one out of every 3,700 women. Uterine cancer rates are currently 27 cases per 100,000 women.1 A woman between the age of 45 to 65 years, is more than twice as likely to die from cancer than heart disease. Breast cancer is the leading cause of death in women 45-65 years old, while uterine cancer ranks much lower in the seventh position.2

Consequently, treating a woman with any modality to protect her endometrium that puts her breast at risk is not viewing the larger picture. I want to explore how we can best protect endometrium and breast tissue as we help women move through menopause.

Let's Be Clear

Progesterone is NOT progestin. It is alarming how many scientific articles confuse the two and even lump them into the same category as if they share the same physiologic effect. Let's compare:

• Progesterone is needed in order for a woman to conceive a child, maintain pregnancy, and is produced at exceedingly high levels, roughly 400 mg/day in the third trimester. By contrast, progestins cause birth defects and prevent pregnancy.3
• Progesterone is breast protective and reduces risk for breast cancer while use of progestins increases risk of breast cancer by 26%.4-12
• Progesterone promotes cognitive function and calming neuro-steroids (allopregnanolone) while progestins increase risk of Alzheimer's by 100%.3,13

• Progesterone benefits heart health while use of progestins increase risk of heart attack by 28% and adversely affects coronary function in young women.12,14,15,16

Let's agree that from a sheer physiologic standpoint these are very different elements and we need to be cautious in our vocabulary and thinking when reading medical literature that constantly confuses the two. We would hope that our endocrinology experts would know this distinction, yet endless articles published in endocrinology journals continue to list "progesterone/progestin" and speak of "progesterone" in the title when it was in fact progestins used in the studies. This generates tremendous confusion for both practitioners and patients. The following studies are just a small sampling of articles that make medical claims yet confuse progestins with progesterone; but any remedial search of the literature will expose hundreds more. In "Progesterone Action in Endometrial Cancer, Endometriosis, Uterine Fibroids, and Breast Cancer," the authors consistently list "progesterone/progestin" speaking of the two as interchangeable.17 In "The impact of micronized progesterone on breast cancer risk: a systematic review" the authors state micronized progesterone in the abstract but then go on to discuss Provera and the PEPI trial without making a distinction.4

Hormone Physiology

A few basic physiology points need to be made clear, and I do believe the following points are universally agreed upon in the medical literature. Estrogen is the mitogenic factor leading to pathologies of the uterus and breast, including endometrial cancer, endometriosis, uterine fibroids, and breast cancer.17 Estrogen stimulates, whereas progesterone inhibits, endometrial growth. Progesterone inhibits epithelial proliferation by blocking the production of mitogenic mediators in the stroma.18 Progesterone can bind the receptor but also has paracrine effects whereby it has antiproliferative effects via "Hand2" to impact epithelial cells even without binding the progesterone receptor. Progesterone receptor expression is driven by estradiol presence and is expressed in both endometrial epithelial and stromal cells but not in all cells or all the time. In fact, as few as 30% of the cells may be expressing receptors at any one time. Progesterone antagonizes estrogen-driven growth in the endometrium, and insufficient progesterone action strikingly increases the risk of endometrial cancer.

In the adult mammary gland, the progesterone receptor (PR) is not expressed in all cells; rather, 7–10% of the epithelial cells are PR-positive, and these cells are usually not proliferating.19-21 The majority of human breast cells that were proliferating were PR-negative.22 Consequently, we know that autocrine and paracrine effects are in play when dealing with breast and endometrial physiology.

Oral vs Topical Progesterone

This question creates confusion for many clinicians. If we look at the simple physiology and metabolism of the two different routes of administration, then this confusion quickly clears. Orally administered progesterone is quickly and thoroughly metabolized by both the prehepatic gut microflora and then the hepatic first pass metabolism, such that very little unadulterated progesterone makes it to the breast and uterine tissues. In studies by Adlercreutz, Nahoul and Levine, we consistently see that oral progesterone is quickly converted to metabolites and that blood and tissue levels never reach significant levels.23-25 Given that topical and vaginal delivery methods bypass the early gut and liver metabolism, true progesterone as measured in the blood stream by LC-MS is robustly present. Early studies of progesterone's movement utilized radio immune assay (RIA) techniques that have in recent years been shown to be inaccurate as these RIA techniques can't distinguish metabolites such as pregnenes and pregnanes from true progesterone.24

Chang showed that when radiolabeled progesterone was given topically and then measured in breast tissue biopsy that high levels had indeed been found despite little to none being seen in the blood stream.8 In fact, he noted that only 0.1% of the injected dose appeared unmetabolized in the bile. Miles et al administered topical vaginal progesterone versus IM injections of progesterone, then

measured blood and endometrial biopsy that showed superior tissue delivery using vaginal progesterone over IM prog.26 The study by Levine and Watson is the most compelling evidence as he administered either 90 mg of vaginal progesterone or 100 mg of oral and then measured blood values by LC-MS.24 The vaginal progesterone gel dramatically outperformed the oral, generating a C-max reading of 10.51 ng/ml compared to the oral progesterone's mere 2.2 ng/ml. Not only was the gel greater in peak concentration, it also produced a long-term effect lasting many more hours than the oral dose. The area under the curve was 133 ng-h/ml for the vaginal gel and only 3.46 ng-h/ml for the oral dose.

Based upon these findings, we have seen clearly that aggressive metabolism of orally administered progesterone could leave the uterus and breast tissue unprotected. Topical applications either to skin or vaginal mucosa have both proven to be effective delivery tools with satisfactory tissue levels. Only a neophyte to hormone replacement therapies would advocate that oral progesterone is needed to protect the endometrium. But let's review the voluminous studies to date to gain perspective here.27-42

We also have to acknowledge that there are dozens of studies exploring the use of oral progesterone to protect the endometrium during use of estradiol replacement therapy. These studies range across a wide array of doses for both estradiol and progesterone, oral and topical, leaving us with a mixed picture of success. We will address those studies momentarily.27-42

Exploring Progesterone's Metabolites

We have already seen that using oral progesterone leads to rapid breakdown and poor tissue levels so the trend by some has simply been to increase the oral dose to create a larger pool of progesterone. This immediately creates a second problem as large doses of oral progesterone alter the natural metabolism of progesterone and generate increasingly large pools of pregnane metabolites. A review of Wiebe's work will offer a clear picture.43-45 He has demonstrated that enzymes for progesterone's breakdown exist in all types of cells and tissues and is not limited to the gut and liver. The enzyme 5-alpha-reductase will rapidly metabolize progesterone to pregnanolone and pregnanediol, the "pregnane" metabolites. These pregnanes are known as neuro-steroids and do offer a calming influence to the brain; but when their production outpaces pregnenes then this ratio drives breast cancer risk. Studies using various breast cell lines have shown that 5aP (pregnane) and 3aHP (pregnene) have opposing actions in terms of cell proliferation and adhesion; 5aP stimulates cell proliferation (through increased mitosis and decreased apoptosis) and cell detachment, whereas 3aHP suppresses cell proliferation (through decreased mitosis and increased apoptosis) and detachment. This effect has been noted in multiple breast cell lines regardless of estrogen and progesterone receptor sensitivity or receptor presence. In breast cancer cell lines, we consistently measure pregnanes at high levels relative to low pregnene levels.

From my experience in over hundreds of hormone replacement cases, when urinary progesterone metabolites are measured it is rare that any women can tolerate more than 100 mg of oral progesterone without aggressively producing excess pregnane metabolites. This is a major concern as I pointed out above that pregnanes put the breast at risk and breast cancer is already thousands of time more likely to occur than endometrial cancer. It just doesn't hold up to logic that we would attempt to protect the endometrium with a strategy that places the breast at greater risk—especially when topical progesterone approaches work better and with less risk. For a simple video explaining interpretation of urinary hormone metabolites, please visit my website at www.huberpm.com to watch "Estrogen Lab Interpretation – Assessing Risk." Here is a link: https://www.huberpm.com/videolibrary.aspx.

Oral Progesterone Use in Endometrial Studies

There are dozens of studies exploring the use of oral progesterone to protect the endometrium, and we see a range of effects depending on dose; but a few consistent findings shine through.27-42 First

of all, oral progesterone can provide endometrial protection; but consistently the studies show that at lower doses such as 50 to 100 mg of oral progesterone there is still risk of endometrial proliferation. To be fair, even studies of progestins are not perfect and will display a small percentage of proliferative change. As doses ascend to 400 mg of oral progesterone, that risk expectantly decreases; but none of the studies employing these high progesterone doses extended their study to include examination of urinary metabolites. If they had, there is strong suspicion that we would have seen excessive pregnane:pregnene ratios, thus a risk to breast tissue which is unacceptable.

Another surprising trend in many of these studies is the use of excessive estradiol dosing. Let's look at the Jondet study from 2002 where 336 postmenopausal women were given 1.5 mg of topical estradiol daily for 24 days per month and then either a progestin (10 mg) or oral progesterone (200 mg) for 14 days per month.35 Endometrial biopsy at the end of 18 months of treatment did not show any cases of hyperplasia but did reveal some proliferative endometrium in a small percentage from both groups. But I want to expose the fact that this is a huge and unusual dose of estradiol. We know that it is the stimulatory effects of estradiol that potentially drives endometrial change and proliferation, so why would a study choose to give a dose that is 10 times physiologic? In a normal cycling female, the amount of estradiol produced over four weeks is roughly 3 mg. In standard hormone replacement therapy, we often give an average dose of 250 mcg of estradiol daily for 24 days which equates to roughly 6 mg. So why would we offer 1.5 mg daily for 24 days netting a total of 36 mg!! That is an enormous estradiol burden. It's also puzzling why they would offer high-dose estradiol for 24 days yet only provide protective progesterone or progestin for a mere 14 days. That reflects the very definition of "estrogen dominance," a state in which we expect to see adverse effects from hormone replacement. It's not surprising that there was some breakthrough proliferative change seen; in fact, the surprise is that there wasn't a higher percentage.

By contrast, the Moyer study using more sensible lower dosed estradiol patches over five years didn't report any hyperplasia or carcinoma and showed reduced rates of endometrial growth by reducing rates of mitosis with lower dosed hormones.37 DiCarlo et al used a 50 mcg estradiol patch with oral (100 & 200 mg) progesterone versus vaginal (100 & 200 mg) progesterone and reported no occurrence of hyperplasia.46 Interestingly they also reported that there were fewer bleeding occurrences in those taking progesterone vaginally. This points again to the superiority of topical progesterone application as it avoids first pass breakdown. In a follow up study by DiCarlo, they applied the same topical estradiol patch but this time to women taking three different progestins versus oral progesterone (200 mg).47 He followed 100 women through 12 monthly cycles; but again we see use of estradiol on a daily basis yet progesterone or progestin only given for 11 days. Again, this represents estrogen dominance, not in daily dose but in imbalance in daily exposure, and they witnessed bleeding episodes as monthly predictable cycles 73.6% of the time. They also saw additional irregular bleeding 8.3% and spotting occurrence 10.2% of the time. This represents breakthrough bleeding of some type in >92% of the time. Personally, my patient base wouldn't tolerate this. It is not the intended goal of hormone replacement therapy to generate a monthly cycle. It's interesting that oral progestins failed at a higher rate than the oral progesterone at controlling endometrial proliferation. I have to point to the low usage of the progesterone/progestin treatment arm as it was only available 11 days out of 28 while estradiol was applied daily. Would these results be more acceptable if progesterone were more consistently available throughout the month rather than just 11 days? The evidence suggests that it would.

So many of the studies exploring this topic used high-dose estradiol, which is hopefully something we have come to learn is unnecessary and dangerous. The Darj study used oral estradiol 2 mg/day while the Holst study used 3 mg of topical estradiol gel.29,34 It is common to see doses ranging from 1 to 3 mg daily for at least three weeks per month while limiting the progesterone to poorly absorbed oral doses given just 10 days per cycle. The general finding was that higher doses of oral progesterone were more protective than lower doses and more consistently produced an atrophic endometrium, but even doses of 400 mg orally did not completely halt proliferative changes from occurring. When compared to topical progesterone, there was no benefit seen and some assumed risk for breast pathology.

Endometrial Cancer

What factors consistently drive hyperplasia and proliferation of the endometrium?

• Excessive estradiol dose or excessive number of days of estradiol without the protective presence of progesterone.
• Lack of progesterone tissue levels due to rapid metabolism of oral dosing.
• Progesterone doses that are too low or too brief.

Other external factors that contribute to this paradigm are the non-hormonal factors such as obesity, plastics, and lifestyle. I feel that we all too often get caught up in our search for the perfect hormone regimen but overlook the obvious. Studies by Sjostrom & McCawley have shown that women who lost 20 Kg had a 38% reduction in cancer rates that included endometrial cancer.48,49 Obesity creates a deepening state of unopposed estrogen.50,52 Fatty tissue generates a greater amount of 5-alpha reductase converting more of the testosterone in local tissue to estrogen. We also know that 5-alpha reductase converts progesterone into pregnane metabolites.

Lastly, we have to acknowledge that toxins within our environment are creating much of this cancer risk. Exposure to glyphosate, phthalates, BPA, and metals have all been identified as endocrine disruptors.53-55 Every single hormone-related medical problem or fertility issue in both men and women can be generated or exacerbated by exposure to BPA and plastics. So, while you attempt to micromanage your patient's estradiol and pregnane level, she is guzzling soda pop from plastic bottles, choosing chips over cruciferous vegetables, and gaining weight. The battle has to be taken beyond the lab result and into the mind and homes of our patients.

FAQs

1. Do women need progesterone post hysterectomy? Absolutely. Progesterone plays a key role in brain, bone, and cardiac function. Progesterone is breast protective and any woman choosing to use estradiol post hysterectomy will be healthier with progesterone to counterbalance the effects of estrogen.

2. Topical progesterone use – vaginal vs oral troche vs topical. Progesterone applied to any mucosal membrane, oral or vaginal, will absorb with roughly twice the efficiency as skin application. Topical progesterone moves largely via diffusion and lymphatics so there will be a disproportionality high concentration of the hormone near the site of application. Skin application allows us to spread this effect over a broader area by applying it to different sites to allow distribution more evenly to brain, breast, and pelvic structures.

3. Typical dosing. Topical progesterone cream use can range from 10 to 80 mg depending on indication, age of patient, and personalized metabolism. For more information on this please feel free to contact my office for treatment protocols and guidance at help@huberpm.com or see our website for discussions at www.huberpm.com.

4. Is oral progesterone safe to use? Yes, but stick to lower doses of 50 to 100 mg as it is rare that women can tolerate a dose above 100 without producing excessive pregnanes. If you use higher doses, then be sure to monitor urinary pregnane and pregnene levels. I recommend monitoring urine metabolites in every hormone patient. See my discussion of quinone estrogens and management of estrogen metabolism on my website www.huberpm.com in the video section. I review estrogen metabolism and lab interpretation. https://www.huberpm.com/videolibrary.aspx.

5. Urine metabolites are great for assessing "risk and metabolites," but it is not the proper tool for assessing tissue levels or making dose adjustments. When assessing tissue levels, blood spot and

saliva are the reliable approaches. Only a small amount of your hormones leaves the body by urine as the gut is the primary pathway of elimination so checking urine will not give you a reliable picture. It is similar to magnesium, which can be measured in the blood; but it only represents 2% of your total body burden of magnesium in the serum and so is not accurate for assessing body status.

I trust that this discussion has offered a rational insight to help your practice. If you have further questions then please feel free to contact me at help@huberpm.com. Allow me to close with another famous quote by Maslow who once prophetically stated, "If your only tool is a hammer, then every problem looks like a nail". My hope is that we can all remain flexible in our thinking and always leave the door open for new ideas. Our patients are counting on it.

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Biography

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