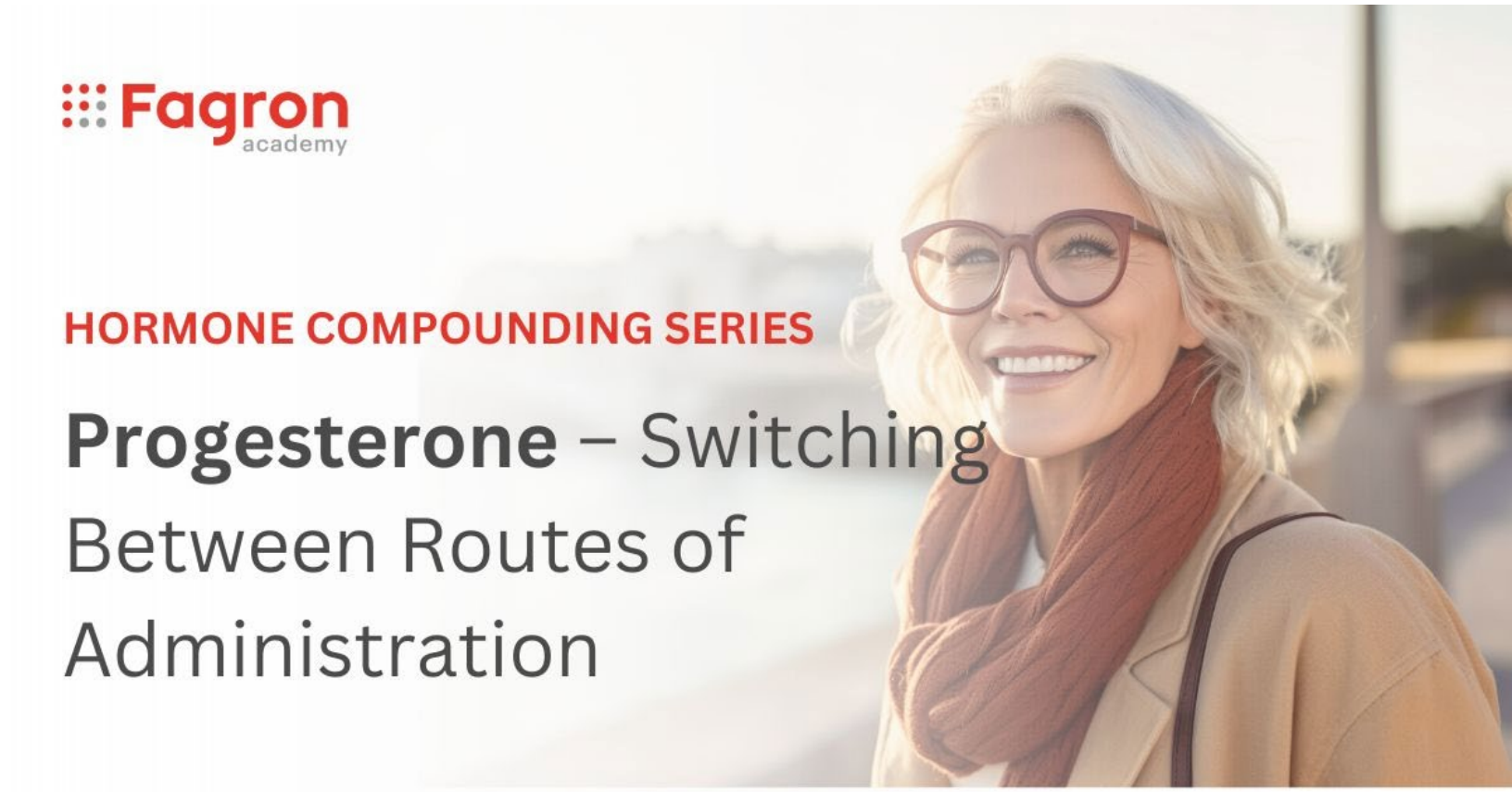

HORMONE COMPOUNDING SERIES

Progesterone – Switching Between Routes of Administration

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The previous blog post on estradiol discussed the history of hormone replacement therapy in women, the impact of the Women's Health Initiative, and information on switching between routes of administration for estradiol. Progesterone is often prescribed in conjunction with estradiol treatment in menopausal or postmenopausal women with an intact uterus for the prevention of endometrial hyperplasia and resultant endometrial cancer that is associated with estrogen treatment alone in this population.1 Though synthetic progestins with enhanced oral bioavailability such as medroxyprogesterone acetate are available, progesterone micronized is recommended as first line for endometrial protection given the enhanced risk of coronary heart disease (CHD) and breast cancer associated with this progestin as compared to progesterone.2

In addition to this need for progesterone supplementation for protection from endometrial hyperplasia, there is data to suggest that progesterone alone or alongside estradiol can play a role in management of vasomotor symptoms. Progesterone can play an important role in sleep and in restoring a narrowed thermoneutral zone toward normal.3,4 One randomized, placebo-controlled, parallel design trial in perimenopausal women evaluated 300mg oral progesterone (once daily at bedtime) vs placebo over a four-month period. Women in the progesterone group reported significant decreases in night sweats and daytime vasomotor symptom intensity as well as improved quality of sleep.4 Some data suggests potential benefit for other routes of administration as well. One placebo-controlled trial of menopausal women on 20mg transdermal progesterone cream daily for a year found patients in the treatment group reported significant improvement in vasomotor symptoms over placebo.5 Another randomized controlled trial of placebo compared to 5, 20, 40, or 60mg transdermal progesterone daily found a trend toward greater vasomotor symptom improvement with escalating progesterone dose.6

Why Switch Between Routes?

Progesterone is currently commercially available as oral capsules, vaginal gels, and as an injectable, though, the injectable product and vaginal product are not indicated for prevention of endometrial hyperplasia in women taking HRT. Patients who wish to try transdermal or buccal progesterone products would need to consider compounded options. In terms of switching between oral, vaginal, and transdermal routes of administration, patients may switch due simply to preference, for example, patients may dislike potential leakage associated with a vaginally administered product. Patients may also switch due to adverse event profile or desired effect of progesterone. Clinically significant levels of progesterone may be achieved via the oral, vaginal, or transdermal route, however, different pharmacokinetic profiles and different metabolic processes may result in different adverse event profiles via these various routes.

Evidence suggests that the mild sedative like effects of progesterone that may be important for its benefit for improving sleep quality may be in part related to key metabolites such as allopregnanolone, a metabolite produced when progesterone is taken orally. Allopregnanolone is a modulator of GABAA receptors and has been found to produce sedative-like effects in animal studies.7 Alternative routes of administration, such as the vaginal route produce lower levels of these metabolites that may be partially responsible for sleepiness associated with oral progesterone. While somnolence and dizziness may be adverse effects of oral or vaginal progesterone, studies suggest that oral progesterone has a higher rate of these adverse effects as compared to vaginal progesterone.17,19 Currently, little data is available on the incidence of somnolence and dizziness of progesterone transdermally vs orally, but the lower Cmax and smoother pharmacokinetic profile as well as lack of first pass metabolism may result in lower incidence of these adverse effects via the transdermal route.8 If sleepiness is an adverse effect, we might consider alternatives to the oral route, alternatively, if the patient benefits from this effect of progesterone as it helps to improve sleep quality in patients who have been suffering from nighttime vasomotor symptoms and poor sleep quality, the switch to an oral product may be desired.8

Another adverse event that could contribute to switching between routes is breakthrough bleeding or spotting. Some studies have noted 10-fold higher concentrations of progesterone in the uterus after vaginal vs oral administration despite higher plasma levels being noted with oral use.20 This may be a contributing factor as to why some studies note a 20-50% incidence of breakthrough bleeding with continuous oral progesterone HRT regimens in the first 6 months of therapy, compared to some data on vaginal progesterone that suggests less than 20% of patients receiving continuous vaginal progesterone experienced bleeding in the first 6 months of treatment.21,22,23

Dosing considerations for switching between routes of administration

When a patient is switched from one route of administration to another, finding the correct dosing can be a challenge. Frequently, dosage adjustment and monitoring may be needed to find the correct and efficacious dose upon switching. Though set guidelines for switching between routes of administration in terms of how to convert dosing are not available, there is limited data comparing progesterone via various routes of administration. For example, progesterone administered vaginally results in higher serum levels and a longer half-life of serum progesterone. One study found progesterone 100mg inserted vaginally resulted in a maximum serum level of 5ng/mL after 6 hours, whereas another study noted 100mg progesterone given orally resulted in serum levels between 1.5-2.2ng/mL after 1-2 hours followed by a rapid return to baseline after 4-6 hours.8 It should be noted that serum levels are not always a good marker for adequate progesterone therapy depending on goal of treatment. Some studies have noted that vaginal progesterone results in much higher uterine progesterone concentrations at lower systemic serum levels as compared to oral progesterone.20

Pharmacokinetic data, though it can give us an idea of general profile of and extent of absorption, can be difficult to interpret given the activity of various metabolites, but one study on vaginal progesterone dosing for

prevention of endometrial hyperplasia treated women with 45, 90, or 180mg every other day and found all concentrations prevent hyperplasia.8,9 Oral progesterone dosing of 200mg/day in a cyclical pattern or 100mg daily has also been found to prevent endometrial hyperplasia.2 For patients who are also using progesterone for control of vasomotor symptoms or sleep, a consistently taken oral dosage form may be preferred over a cyclical approach or vaginal use.

Limited data on buccal use suggests superior progesterone absorption but with a pharmacokinetic profile that may be more similar to oral use as opposed to transdermal or vaginal use. One study of 100mg buccal progesterone found that serum levels rose quickly to 8ng/mL within 1.3hrs before continuing to decline to 1.5ng/mL after 8 hours.8 This peak is about 3.5-5x higher than noted for oral progesterone, though, at this time specific studies on progesterone buccally for protection against endometrial hyperplasia are not available.

A few studies have also evaluated transdermal progesterone. One small study of 6 women evaluated progesterone starting at 30mg per day before escalating to twice daily use (60mg per day) found serum levels to be 1.6-3.3ng/mL after two weeks of dosing. The study did not explicitly compare this to oral progesterone, but did conclude that percutaneous progesterone application would likely be a safe and effective route of administration.10 Another study evaluated 12 postmenopausal women and compared oral and transdermal dosing. Women were given 200mg progesterone capsules orally for 12 days or progesterone cream 40mg twice daily for 12 days. Evaluations of blood samples over 12-24 hours were collected after 12 days of treatment and the study noted no significant difference in overall bioavailability between these doses via these separate routes of administration.11 With regards to transdermal progesterone and whether or not it provides protection from endometrial hyperplasia. One small study in 26 women looking at transdermal micronized progesterone at 40mg per day compared to medroxyprogesterone acetate 2.5mg orally per day in combination with estrogen treatment found that in the transdermal group 81% of women were atrophic and 19% were proliferative compared to 73% atrophic and 27% proliferative for the oral MPA group. This 12-week study concluded that transdermal progesterone had a similar impact on the endometrium as compared to standard oral therapy.12 However, another study evaluating the same dose of transdermal progesterone in 41 women reported 32% had evidence of insufficient endometrial protection after 48 weeks of use with 1mg estradiol transdermal daily.13,14 This discrepancy may be the result of different vehicles used to deliver progesterone as well as interpatient variability as both studies were small. Currently, there is no consensus on a transdermal dose of progesterone to provide endometrial protection.12

A note on oral progesterone: impact of release rate and micronization on bioavailability

Progesterone is often dosed orally, however, not all types and forms of progesterone can be considered equal. Micronization can play a huge role in bioavailability of progesterone. Micronization of progesterone to particle sizes less than 10 microns drastically increases the surface area and improves absorption of the drug. Suspending progesterone in oil can also enhance progesterone bioavailability.15 One study comparing progesterone milled, micronized, milled in oil, micronized in oil, or micronized in enteric coated capsules found that while all products did significantly increase serum progesterone, progesterone micronized in oil resulted in the highest progesterone absorption, followed by micronized, then micronized enteric coated, then milled in oil, with the milled powder coming in with the lowest absorption rate.16

In addition to particle size and vehicle being key considerations for oral progesterone, release rate can also be an important factor. Some studies suggest that slow-release progesterone type dosage forms may result in fewer adverse effects as compared to immediate release progesterone.17 Specifically, slow-release progesterone has shown reduced propensity for causing drowsiness and dizziness sometimes associated with oral progesterone as compared to immediate release dosage forms.17,18

Interested in compounding transdermal or vaginal progesterone? Check out our recent stability study published in the International Journal of Pharmaceutical Compounding: International Journal of Pharmaceutical Compounding (ijpc.com). If you'd like to learn more about HRT for women, check out our upcoming Webinar Understanding HRT for Women: A Practical Guide to Interpretation of Lab Results.

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