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ORAL PROGESTERONE (OMP): Best Practices

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Clinical Recommendations for OMP Dosing

A key reason for prescribing OMP is endometrial protection in women with a uterus. OMP protects the endometrium from estradiol's (E2) proliferative effects. The OMP dose MUST balance E2's proliferative effects. Therefore, the OMP dose is dependent on the E2 dose. The evidence supports that both OMP 100mg/d and 200mg/d protect the endometrium. Continuous OMP provides more complete endometrial protection compared to sequential OMP.

Research has proven that 200mg/d, combined with a standard dose TD E2, i.e., a 0.05mg/d patch, protects the endometrium. The OMP dose is dependent on the E2 dose. Lower OMP doses (100-200mg/d) may be used when prescribing ultra-low or low-dose TD E2, i.e. 0.014mg/d or 0.025mg/d, respectively. In fact, when OMP 50mg was combined with either oral estradiol 0.5mg/d in a single capsule, the endometrium was protected with both doses.

In addition to protecting the endometrium in women with a uterus, OMP is an important physiologic partner to estradiol in decreasing morbidity and improving a woman's quality of life. Listed below are comorbidities where OMP is either helpful or has a neutral effect.

- Breast Cancer: OMP 200mg, when added to TD E2, DOES NOT increase breast cancer incidence. TD E2 and OMP may be continued safely for > 10 years with ongoing surveillance. There is indirect data that OMP 100mg does not increase breast cancer incidence.
- Vasomotor Symptoms (VMS): OMP 300mg/d, without TD E2 preparations, relieves VMS, including severe VMS. Lower OMP doses have not been extensively tested.
- Cardiovascular Disease (CVD): All commonly used OMP doses (100mg/d, 200mg/d, and 300mg/d) are safe and do not negatively affect the vascular tree, and specifically the coronary arteries. OMP does not increase Deep Vein Thrombosis (DVT) or pulmonary embolism (PE) risk.
- Cognition: OMP 200mg/d is safe; it neither adversely affects, nor improves cognitive function.

This material is educational and not an endorsement for a specific HRT dose or route of administration

Laboratory Assessment of OMP

OMP works via increasing systemic progesterone (Pg) levels AND through the clinical impact of Pg metabolites. These metabolites, like α-pregnanolone, are created in supraphysiological levels when Pg is taken orally. The clinical effects, such as biopsy documented endometrial protection, have been correlated to OMP dosing but have not been standardized to any testing modality or Pg level.

Serum and saliva should never be used for OMP monitoring for two reasons:

1. OMP is typically dosed around bedtime, peaks in 1-4 hours, and is back to baseline within 8 hours; an AM sample is meaningless and may lead to overdosing.
2. While typical serum and saliva tests (immunoassays) are accurate when patients are not taking OMP, they dramatically overestimate Pg values when taking OMP (metabolites cross-react).

Urine testing can be used to measure metabolism patterns (α-pregnanediol and ß-pregnanediol).

- Because much of OMP's clinical impact comes from its metabolites (alpha metabolites are particularly helpful with sleep disturbances), urine metabolite testing is helpful.
- Urine testing shows which pathways predominate (alpha pathway or less active beta pathway).
    - ◊ Metabolism patterns vary significantly between patients, and their consideration may be helpful. For example, patients preferring the less active beta pathway may not get adequate relief from sleep disturbances with typical OMP dosing.
    - ◊ Some in vitro research implies alpha metabolites may increase breast cancer proliferation.

EXECUTIVE SUMMARY

Precision Analytical (PA)'s goal is for you to use this OMP brief review as a guide when determining which hormone regimen is best for your patient. Extrapolate when you can, rationalize when you must, but always individualize care. Remember, results take time, and the goal is always to "do no harm." The OMP story, like the transdermal estradiol (TD E2) story, is always evolving.

The large RCTs which studied synthetic hormones should not be used to guide direct patient care decisions. The evidence presented in this summary provides clinically relevant information. PA's comprehensive oral micronized progesterone (OMP) review can be obtained to dig deeper into the literature.

Oral Micronized Progesterone (OMP) is NOT a Synthetic Progestin (SP)

Much of the medical literature on progesterone (Pg) or Pg-like compounds is contradictory. This is a result of researchers confusing the synthetic progestins' effects with natural Pg's effects. Correct terminology is critical. The terms progesterone, progestogen, and progestin are commonly interchanged in the medical, scientific, and public literature, which contributes to misconceptions about these compounds and their clinical benefits and risks.[1]

We encourage you to read each study carefully, regardless of its title. Throughout this review, authors have referred to "progesterone" when in fact the study drug was medroxyprogesterone (MPA). In other studies, the term "progestin" was used when the drug used was OMP. When the term "progestogen" is used, the study or review could be referring to either, or both!

Guidelines

In 2017, Cobin and Goodman, updated the American College of Endocrinology Position Statement on Menopause and stated that "[w]hen the use of progesterone is necessary, [oral] micronized progesterone is considered the safer alternative over MPA for both breast and endometrial protection."[2]

Transdermal Progesterone (TD Pg) DOES NOT Provide Endometrial Protection

Topical Pg, excluding vaginal application, does not provide adequate endometrial protection, the primary indication for Pg treatment. Blood or tissue concentrations are insufficient for TD Pg to be used for endometrial protection until well-planned, randomized, placebo-controlled, double-blind studies (RCTs) are performed with endometrial histology.[2,3,4]

Serum Pg increases to some degree with oral and vaginal Pg,[5] but TD Pg has not been shown to reach luteal levels in serum. Urine testing, which measures Pg indirectly by way of its metabolites,[6] tends to follow similar Pg patterns seen when monitoring TD Pg with serum testing. Saliva testing is reported to overestimate tissue levels[3] and neither saliva nor capillary blood spot results have been correlated with endometrial histology.

Most experts will not recommend TD Pg for endometrial protection until further clinical trials are performed using TD Pg with TD E2.[7,8,9]

Compounded OMP Never Studied

There are no outcome studies evaluating compounded OMP. This does not mean it is not effective; many key opinion leaders (KOLs) prescribe compounded OMP, with presumed clinical success. In reviewing the scientific literature, all studies used FDA-approved OMP preparations, PROMETRIUM or UTROGESTAN (Europe).

ENDOMETRIAL HYPERPLASIA/CANCER, BREAST CANCER

Endometrial Hyperplasia

OMP is necessary to protect the endometrium. The goal is for OMP to balance estradiol's proliferative effects. Barring any contraindications to MHT, there is robust data documenting that OMP 200mg/d protects the endometrium.[4,9,10,11,12] OMP 100mg has also been successfully used to protect the endometrium;[12,13] Ongoing surveillance is necessary.

Endometrial Cancer

OMP 200mg, when added to TD E2, does prevent endometrial cancer.[4,9] Continuous therapy offers the most complete protection; however, if sequential therapy is opted for, 12-14 days is necessary.[11] OMP 100mg also protects the endometrium, however this data is not as robust as the evidence in the OMP 200mg/d studies.[4,12,13,42] Keys to preventing endometrial hyperplasia and endometrial cancer are: ensure treatment compliance and balance the TD E2 proliferative dose with a protective OMP dose.[12]

- OMP 200mg, including PROMETRIUM, prevents both endometrial hyperplasia and endometrial cancer
- If sequential: 12 -14 days a must
- Continuous OMP 100mg probably protects the endometrium
- A continuous regimen offers more complete endometrial protection
- Key: treatment compliance is necessary to prevent endometrial hyperplasia and cancer

Breast Cancer

Combined MHT with OMP is not associated with any increase in breast cancer risk, even when treatment is continued for ≥ 10 years.[14,15,16] Time from menopause onset to treatment initiation has no impact on women using estradiol with OMP.[17] OMP 200mg/d for twelve days, the KEEPS regimen, did not increase breast cancer when combined with CLIMARA (0.05mg/d) or PREMARIN (0.45mg/d).[14] Lower doses have not been studied. However, it is reasonable to believe that OMP 100mg, if it balances E2's endometrial proliferative effects, will not increase breast cancer. The OMP dose is dependent on the TD E2 dose.

As of this writing, it is important to remember that OMP is the only delivery system that ensures breast safety. The data on vaginal Pg is scarce and long-term data on TD Pg is non-existent.[14]

- PROMETRIUM 200mg/d x 12d/month with CLIMARA 0.05mg/d DOES NOT increase breast cancer
- OMP must balance TD E2's endometrial proliferative effects

COMORBIDITIES AND OMP

Osteoporosis

E2 and Pg are both necessary to obtain and maintain bone mineral density (BMD). Normal ovulatory cycle lengths (12-14 days) are necessary to prevent bone loss. HPA axis dysfunction is thought to be a root cause of secondary amenorrhea or oligomenorrhea. In adolescents and premenopausal women with ovulatory defects, OMP 300mgs at bedtime days 14-27 will restore ovulation, build bone, and decrease osteoporosis and fracture risk. In perimenopausal women with high fluctuating E2 levels, OMP 300mg is reasonable, but has not been studied. In postmenopausal women (PMP) women (natural and surgical), OMP along with TD E2 prevents osteoporosis.[18,19,20] The optimal OMP dose to prevent osteoporosis has not been studied.

- OMP 300mg QHS days 14-27 restores ovulation in adolescents and premenopausal women with short luteal cycles, oligo/amenorrhea
- OMP doses to prevent osteoporosis in perimenopausal and PMP women have not been studied
- HPA axis dysfunction is a root cause

Vasomotor Symptoms (VMS)

OMP 300mg as sole therapy is safe and effective for PMP women, one to eleven years after menopause, with VMS, including moderate to severe VMS.[21,22,23] Lower OMP doses have not been studied. However, it is plausible that lower OMP doses, if they balance TD E2's endometrial effects, when combined with TD E2, may have synergistic effects in relieving VMS. The two together may allow for lower E2 doses and less E2 tissue exposure. If OMP treatment is discontinued, symptoms recur, but there is no rebound or significant VMS increase when compared to baseline.[23]

- OMP 300mg as sole therapy improves VMS
- Lower doses not studied

Cardiovascular Disease (CVD) and Cognition

The available literature documents that OMP is safe for the CV system[24,25,26] and does not increase venous thromboembolic (VTE) risk (DVT, PE)[27,28]

All commonly used OMP doses, 100mg/d, 200mg/d, and 300mg/d, are safe and do not negatively affect the coronary arteries.[24-26] In addition, these commonly used OMP doses do not increase DVT or PE risk.[27,28]

OMP 200mg is safe and neither adversely affects nor benefits cognitive function in women, even PMP women > 10 years since their last menstrual period.[29-32]

OMP 100mg, 200mg, and 300mg:
- Are safe for the CV system
- Do not increase DVT, PE
- Neither help nor harm cognition

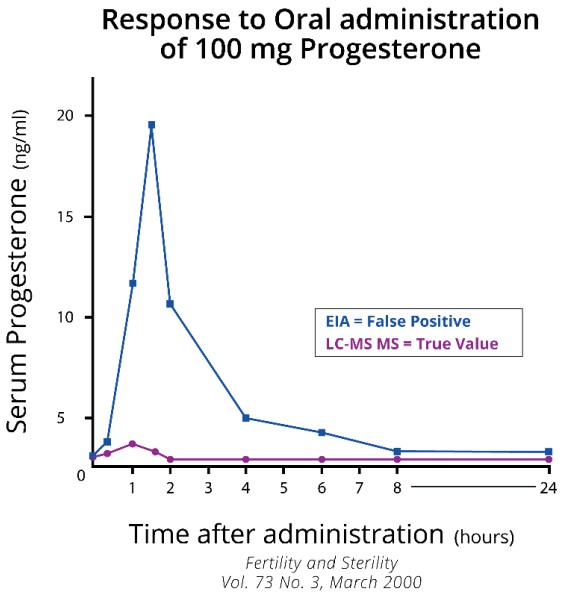
LABORATORY TESTING FOR ORAL PROGESTERONE (OMP) MONITORING

Serum and Saliva Testing

There are two fatal flaws in using serum or saliva testing that prevents their success when monitoring OMP: Kinetics and Assay Accuracy.

Kinetics

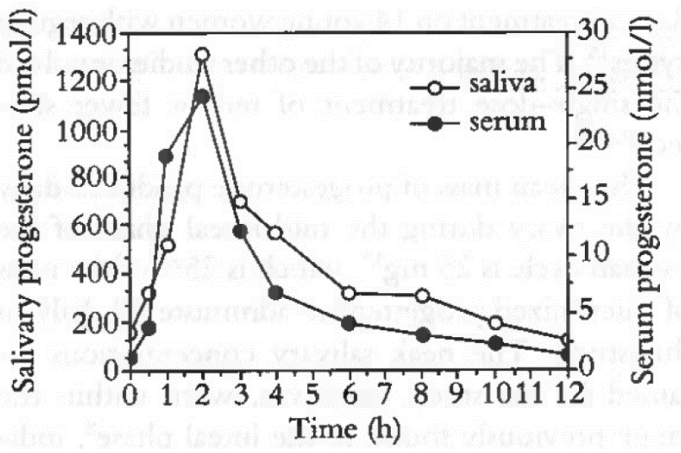
OMP's up-and-down patterns do not lend itself to successful monitoring. OMP is typically taken at bedtime (because it tends to help with sleep disturbances). Research shows that serum and saliva levels peak within 1-4 hours and return to baseline within approximately 5-8 hours.[33-35] When the most accurate testing (LC-MS/MS) is used, values return to baseline as quickly as within two hours (see graph).[5]



The speed of Pg's rise and fall makes this testing impractical. Relevant values exist only during the time the patient is sleeping, making an AM serum or saliva result clinically misleading.

Assay Accuracy

OMP undergoes extensive first-pass metabolism, creating high concentrations of Pg-like metabolites.[33] Typical serum or saliva assays are immunoassays, which cross-react with these metabolites.[35] When patients are not on hormones, these tests are accurate. Below you can see the impact of OMP when tested using an enzyme immunoassay (EIA) versus an LC-MS/MS assay.



The EIA result is artificially elevated when compared to the more accurate LC-MS/MS value. Two hours after treatment, accurate serum Pg results are back to baseline while the EIA value is erroneously over 10ng/mL (a value comfortably, but inaccurately in the luteal range).[5,36]

Because of their inaccuracies, immunoassays, are inappropriate for OMP monitoring in blood.

Salivary immunoassay patterns have been shown to parallel serum results (see graph on page 6),[36] therefore the same issue likely makes salivary testing inaccurate as well.

Serum or salivary progesterone can be successfully used to assess Pg levels in a non-supplementing woman; however, any potential OMP dose adjustment based on serum or salivary values should not be considered. *If patient dosing is adjusted by targeting luteal levels in serum or saliva, dosing mistakes are the rule, not the exception.* Endometrial protection cannot be assumed based on any lab values.[37]

Progesterone Metabolite Urine Testing

Progesterone is not measured directly in urine. It is typically measured by its phase 1 metabolite, β-pregnanediol. β-pregnanediol levels have been shown to correlate with serum Pg.[6,38] In addition to β-pregnanediol, the DUTCH Test® also measures the other primary Pg metabolite, α-pregnanediol. Precision Analytical has recently published data (endogenous Pg) showing excellent agreement between these Pg metabolites and serum Pg. These metabolites are excellent surrogate markers for endogenous Pg when patients are NOT on Pg therapy.[6]

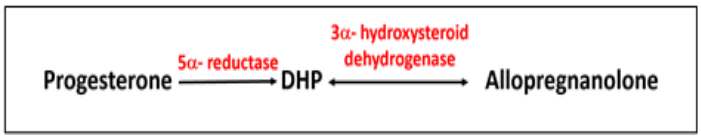
Are Pregnanediol Metabolites Useful Markers When OMP is Prescribed?

When OMP is taken, Pg urine metabolites increase well beyond premenopausal levels. This is expected. Oral hormones, including Pg, because of extensive first-pass metabolism, flood the urine with metabolites that never pass into the systemic circulation.[39] These metabolic products (Pg metabolites) do not reflect circulating Pg. These urinary Pg metabolites do not reflect actual progesterone tissue exposure. This does not mean that urine testing has no value; it means that the test's clinical utility is somewhat complicated. To understand the value of metabolites, we must explore the uniqueness of oral Pg's clinical impact.

How Does Oral Progesterone Create a Clinical Impact?

Circulating Pg and its metabolites combine to create Pg's overall effect in protecting the endometrium. OMP is unique because it creates supraphysiological metabolite levels which help in combatting sleep disturbances. In general, all the alpha metabolites are thought to be more active compared to their beta counterparts.[39,40]

Urine testing can assess which pathway predominates for an individual patient. Pg, when metabolized by 5α-reductase Type 1, becomes 5α-dihydroprogesterone (DHP). This reaction is irreversible. Then 3α-hydroxysteroid dehydrogenase (HSD) converts DHP into allopregnanolone. This reaction is reversible. Similarly, Pg is also metabolized by 5β-reductase to similar metabolites, i.e., 5β-DHP, that have less biological activity. See the diagram below.[39,40]



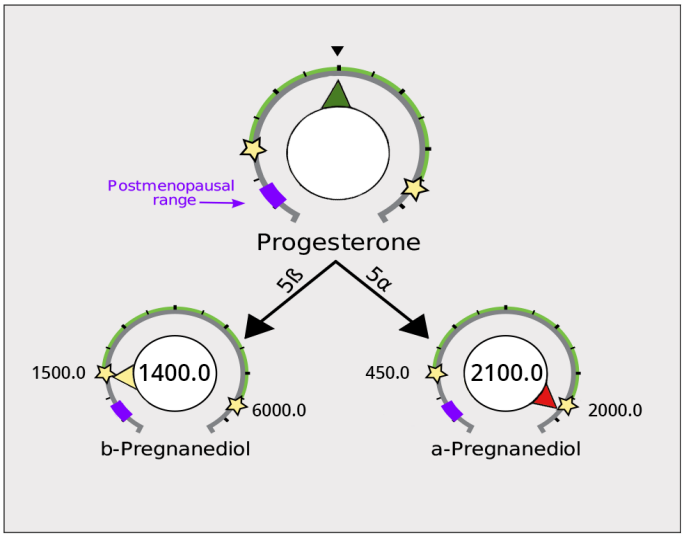
OMP metabolism is a complex, multistep process that needs consideration when dosing OMP. With oral administration, Pg metabolism begins when Pg comes in contact with intestinal microflora containing the 5b-reductase enzyme. Then the intestinal mucosa, which expresses the 5α-reductase enzyme, continues to metabolize OMP.

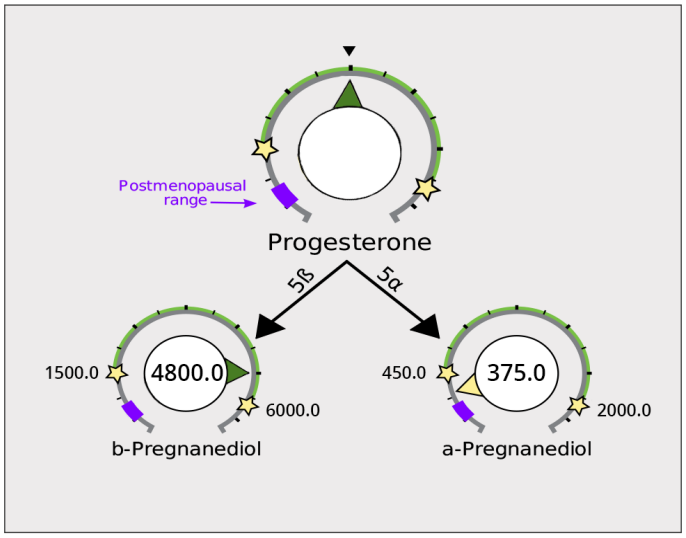
Within the intestinal wall, the conjugation process begins, and via the enterohepatic circulation the liver continues Pg metabolism and conjugation. In a woman, liver cells mainly express 5b-reductase and 3α- and 20α-hydroxylase activities, along with glucuronide conjugation.[41] Therefore, gut health and detoxification are important considerations when dosing OMP.

The two patient results below represent two different extremes in metabolite patterns. The first patient (on the left) metabolizes OMP down the alpha pathway towards α-pregnanediol.

The second patient (on the right) prefers the less active beta pathway. It is very likely that circulating levels of the more active metabolites, i.e., α-pregnanolone, are much higher in the patient on the right. This should be considered when dosing OMP.

While alpha metabolites may have an increased impact with respect to sleep disturbances, some research suggests they may also have proliferative effects.[39,40] For this reason, excessive levels of these active metabolites may be undesirable as it relates to minimizing breast cancer risk.





CONCLUSION

OMP plays a key role in clinical practice. OMP has been extensively studied, and it is well documented that continuous OMP 100mg/d and 200mg/d either using a sequential regimen (12-14 days/month) or a continuous regimen balances estradiol's endometrial proliferative effects without invasive testing. Like OMP, vaginal Pg protects the endometrium; however, there is limited evidence. Contrary to OMP and vaginal Pg, TD Pg cannot be reliably used to protect the endometrium.

We look forward to future research investigating the viability of lower OMP doses when using low dose estradiol therapy. When monitoring OMP, urine metabolite testing holds promise and shows clinical utility but needs further investigation and clinical correlation. Serum and saliva testing, on the other hand, do not appear to hold any promise for clinical utility with OMP therapy and should not be used to monitor therapy.

Remember, women spend approximately one-third of their lives in menopause, so it is important to get the OMP dose and laboratory assessment correct to limit all adverse events.

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