Progesterone Administration in Postmenopausal and Hysterectomized Patients

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Progesterone (P4) helps balance estradiol (E2) in the body, making its use in hormone replacement therapy (HRT) just as important as E2. Conventional HRT wisdom seems to claim that since progesterone's main role is to protect the uterus from estrogen dominance, no further P4 treatment is needed once a woman completes menopause because estradiol levels significantly decrease.[1] Along with this idea, some believe that progesterone is unnecessary to supplement after women undergo a hysterectomy.

While progesterone is known mostly for its effect on the uterus,[2] P4 receptors are located in other parts of the body outside of the uterus as well, and have various effects on other tissues. Newer studies reveal additional effects of progesterone for bone health,[3] hot flashes,[4] and even sedation with implications for treatment of mood disorders.[5] Progesterone may also be helpful for women who have undergone a hysterectomy. Therefore, evidence suggests that because progesterone has receptors and can exhibit its effect on other parts of the body, P4 can have beneficial effects even in postmenopausal women or women without a uterus.

BONE HEALTH

Clinical evidence suggests that endogenous progesterone plays a role in postmenopausal bone health. For instance, three *in vitro* studies revealed progesterone's effect at increasing osteoblast levels and its ability to promote osteoblast maturation and differentiation.[6,7,8] Studies also suggest that progesterone may have a beneficial role in postmenopausal osteoporosis when administered in combination with an antiresorptive agent such as estradiol or conjugated equine estrogen (CEE).[3]

Additionally, there is evidence that combination estradiol and progesterone therapy has a greater effect on bone density compared to E2 alone, even in women who have undergone a hysterectomy. Therefore, healthcare professionals treating hysterectomized women, who are at high risk for osteoporosis, might consider combining progesterone with their prescribed regimen if the patients are only on estradiol treatments.[9]

HOT FLASHES

Estradiol therapy alone is a well-known treatment for hot flashes in postmenopausal women, but progesterone is also administered in combination with E2 in treating and preventing symptoms of hot flashes. However, progesterone therapy alone may have unique individual effects at treating hot flashes. One study showed that megestrol (P4 derivative) 20 mg by mouth twice daily decreased hot flashes by 85% in four weeks.[10] Another study using progesterone cream (20 mg) applied on the skin daily for one year improved or resolved vasomotor symptoms (hot flashes) significantly versus placebo.[11]

SEDATING EFFECTS

Progesterone can also have significant effects on sleep, and researchers appear to have a better grasp of its effects on sleep compared to estradiol.[5] When progesterone is administered intravenously, it has direct sedative qualities, stimulating benzodiazepine receptors, which then stimulate the production of the non-rapid eye movement (NREM) related GABA receptors.[12] Progesterone has anxiolytic effects by acting as a GABA agonist, although the exact mechanism remains unclear.[13] Progesterone metabolites, including allopregnanolone and pregnanolone, act as agonists at the $GABA_A$ receptor, resulting in sedative effects.[14,15]

One study compared micronized progesterone 100 mg and 400 mg oral capsules to vaginal 400 mg suppositories. The results showed that postmenopausal women given progesterone 100 mg and 400 mg orally induced a hypnotic state, while subjects assigned to 400 mg vaginal suppositories did not experience sleepiness.[16] This implies that orally administered progesterone may be effective at promoting sleep in postmenopausal women.

MOOD & DEPRESSION

The estradiol-progesterone ratio may also be a key factor in properly treating mood disorders in some female patients. A small study by Dr. Bronson found that a deficiency of progesterone may be a primary factor in mid-life anxiety patterns. This study observed that some patients with high estrogen levels and low progesterone levels "exhibit[ed] extreme rage, followed by conciliatory, self-defeating demeanor."[17] This behavior pattern may have a pharmacological basis because one of the largest concentrations of progesterone receptors is in the limbic area

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of the brain, which is the center of emotion possibly related to rage, anger and violence as described by some physiologists.[17,18,19] And as previously stated, progesterone has a calming effect as described by its action on GABA receptors in the brain. This suggests that a P4 deficiency may lead to varying levels of anxiety, depending on the degree of estradiol-progesterone imbalance.

Related to mood disorders and anxiety, premenstrual syndrome (PMS) and postpartum depression both can occur from an abrupt dip in progesterone levels. One study found that both conditions were treated effectively with progesterone in some patients, especially as prophylaxis treatment for PMS and postpartum depression.[20] Combined with Dr. Bronson's study, this seems to imply that progesterone can be an effective treatment for anxiety in perimenopausal women. Dr. Bronson's observational study found that treatment was most effective at higher progesterone doses (400-600 mg daily) administered topically, with most women treated reporting significant improvements in their emotional health.[17,18] However, large, randomized, controlled trials are needed to substantiate progesterone's effectiveness at treating mood disorders and depression.

CONCLUSIONS

Adding progesterone to estradiol or using P4 alone for HRT in postmenopausal women with or without an intact uterus may improve their quality of life by mitigating or preventing vasomotor symptoms or postmenopausal bone loss, addressing sleep issues, and potentially improving mood. Further research using progesterone alone in women with postmenopausal symptoms is needed to further assess its individual effects. However, progesterone receptors are widespread throughout the body outside of the uterus and have a plethora of effects when supplemented with P4. Because of this, progesterone might be considered an important part of HRT for women who have completed menopause or who have undergone hysterectomy. Any HRT should be preceded by appropriate diagnostic evaluation by a practitioner.

If you have any questions, contact the PCCA Pharmacy Consulting Department at 800.331.2498.

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