# Progesterone Is Important for Transgender Women's Therapy—Applying Evidence for the Benefits of Progesterone in Ciswomen

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**Background:** Although the 2017 Endocrine Society Guidelines for gender dysphoria stipulated that cross-sex hormone therapy (CHT) achieve gonadal steroid levels equivalent to those of a cisperson of the chosen sex, for transgender women (male-to-female gender dysphoria), current gonadal therapy is usually estradiol. Accumulated evidence indicates that normally ovulatory menstrual cycles are necessary for ciswomen's current fertility, as well as for later-life bone and cardiovascular health and the prevention of breast and endometrial cancers.

**Evidence Acquisition:** Extensive past clinical experience with transgender women's CHT using estradiol/estrogen combined with progesterone/medroxyprogesterone and pioneering the addition of spironolactone. Comprehensive progesterone physiology research plus a brief review of transgender women's literature to assess current therapy and clinical outcomes, including morbidity and mortality.

**Purpose:** To emphasize that both ovarian hormones, progesterone as well as estradiol, are theoretically and clinically important for optimal transgender women's CHT.

**Evidence Synthesis:** It is important to add progesterone to estradiol and an antiandrogen in transgender women's CHT. Progesterone may add the following: (i) more rapid feminization, (ii) decreased endogenous testosterone production, (iii) optimal breast maturation to Tanner stages 4/5, (iv) increased bone formation, (v) improved sleep and vasomotor symptom control, and (vi) cardiovascular health benefits.

**Conclusions:** Evidence has accrued that normal progesterone (and ovulation), as well as physiological estradiol levels, is necessary during ciswomen's premenopausal menstrual cycles for current fertility and long-term health; transgender women deserve progesterone therapy and similar potential physiological benefits. (*J Clin Endocrinol Metab* 104: 1181–1186, 2019)

The recent Endocrine Society clinical practice guidelines for "gender dysphoric/gender incongruous persons" advise clinicians to "maintain sex hormone levels within the normal range for the person's affirmed gender" (1). Every normal, fertile, menstrual cycle in cisgendered women (whose gender identity as women aligns with their female sex assigned at birth) ideally produces progesterone, as well as estradiol ($E_2$). Therefore, rather than being treated with daily $E_2$ and an antiandrogen, as is the current clinical practice, to follow guidelines, we need to prescribe oral micronized progesterone (referred to in this article as progesterone) as an

Abbreviations: BMD, areal bone mineral density; CHT, cross-sex hormone therapy; CVD, cardiovascular disease; DHT, dihydrotestosterone; E, estrogen; $E_2$, estradiol; EPT, estrogen-progestin therapy; ET, estrogen therapy alone; MPA, medroxyprogesterone acetate; $P_4$, progesterone (the hormone); PR, progesterone (the hormone) receptor; RCT, randomized controlled trial; T, testosterone; VTE, venous thromboembolism.

at least cyclic component of treatment of all transgender women (gender dysphoric men to women). With the addition of progesterone to $E_2$ therapy, we will highly likely be able to decrease the prevalence of the two health risks that are now documented to be higher than the general population of women or men in transgender women, as currently treated: cardiovascular diseases (CVDs) (2–5) and low bone density and fracture (3, 6). Thus, the purpose of this Perspectives article is to detail the potential benefits, and unlikely adverse effects, of the addition of progesterone treatment to transgender women's endocrine therapy.

I came to this perspective on treatment of transgender women from my experience as the endocrinology lead in a Gender Dysphoria Clinic in the 1980s and early 1990s. We then pioneered the addition of spironolactone (antiandrogen), to estrogen (E) for transgender women (7). As guidelines now say (1), we were treating with oral E (it was before transdermal $E_2$ therapy became available) plus medroxyprogesterone acetate (MPA; as it was also before oral micronized progesterone became available). My perspective is shaped by the prioritization of disease prevention over its treatment, the dictum that clinicians should aim to "do no harm" and that the consideration of physiological-first principles and high-grade evidence leads to improved patient care.

Before a discussion of progesterone's importance for transgender health, it is first necessary to understand the physiological roles and partnership of $E_2$ and the hormone progesterone ($P_4$) in enhancing ciswomen's health. The "job" of $E_2$ is to cause important cell growth that manifests as initial and continued cellular proliferation (8). By contrast, although $P_4$ in cell culture causes proliferation for a few days, it then transforms into its primary, maturational role that includes inhibition of the proliferative effects of $E_2$ (8). Both $E_2$ and $P_4$ act, not just in the pelvic and sex organs, but also in every tissue of ciswomen's bodies during the entire span of their reproductive years. Balanced levels of these ovarian hormones during the 30 to 45 years of menstrual life appear sufficient to decrease the risk for many diseases that may otherwise present during the years of menopause (beginning a year after the final menstruation) and aging when both gonadal steroid levels are normally low.

That cyclic $P_4$ is necessary for ciswomen's fertility is well recognized (9); it is less well appreciated that within regular, normal-length cycles, $P_4$ levels and ovulation are quite variable between cycles within-woman and between women (10). This variability provided the opportunity to "see" the adverse health effects (e.g., on changes in bone density) of subclinical ovulatory disturbances (anovulation or short/insufficient luteal phases within regular cycles) (10, 11). Perhaps because of cumulative and daily life stressors, approximately one-third of regular, normal-length menstrual cycles in ciswomen, ages 20 to 49, are without sufficient $P_4$ (12). Normal ovulation and regular menstruation during the premenopausal years in ciswomen are necessary to prevent bone loss, based on a meta-analysis of prospective observational studies (10) and are associated with a decreased incidence of heart disease within 10 years of menopause onset (13) and with potential breast cancer prevention (14, 15). Progesterone "area under the curve" levels across the menstrual cycle exceed those of integrated menstrual cycle $E_2$ levels in ciswomen's ovulatory cycles because progesterone is produced in nanomoles per liter and $E_2$ in picomoles per liter quantities (15). For metabolic and antiandrogen effects [to suppress LH and gonadal testosterone (T) and inhibit the conversion of T to dihydro-T (DHT)], I suggest that transgender women's progesterone be given daily rather than cyclically, at least until orchiectomy and always at bedtime, because of its sleep-enhancing effects (as subsequently discussed).

Gonadal steroids have sex-specific actions (16); thus, the application of data from progesterone actions in women to the care of those who were biological men before they became transgender women requires evidence. In general, that evidence is available, although sometimes from data using MPA, which usually acts through the $P_4$ receptor (PR). Progesterone suppresses LH and T in men (17), it inhibits conversion of T to DHT in men (18), it has bone formation-stimulating effects and increases areal bone mineral density (BMD) in men (17), and it also improves sleep based on a randomized controlled trial (RCT) in men (19). There is also clinical evidence that breast maturation occurs on progesterone in men (7). As the fundamental endothelial system appears similar in men and women, progesterone likely will improve the cardiovascular system as well (20).

When E or $E_2$ treatments are prescribed for transgender women, I believe it is important to use physiological dose $E_2$, delivered transdermally (either as a gel or patch). Transdermal $E_2$ is effective at enlarging breasts and increasing feminizing subcutaneous fat, increasing sex hormone-binding globulin (although less than oral $E/E_2$) and thus, decreasing free (active) T. However, transdermal $E_2$ carries less increased risk for venous thromboembolism (VTE) (21). Knowing what we now know about risks for VTE in transgender women (5), I believe that $E_2$ should not be given orally. I also believe that higher $E_2$ doses (arbitrarily, more than double physiological) carry increased risks (note that the mean dose in the large Goodman study was 4 mg of oral $E_2$, where a physiological ciswoman dose is 0.5 to 1.0 mg/d) (5). Given the recent evidence that "low doses" of

conjugated equine E (0.625 to 1.25 mg/d), with or without cyproterone acetate, lowered androgen, LH, and follicle-stimulating hormone levels into ciswoman ranges (22), it is not clear why higher $E/E_2$ doses are commonly used for transgender women's cross-sex hormone therapy (CHT). Both oral $E/E_2$ and higher doses are associated with an increased risk of VTE and pulmonary embolism in transgender women (2, 5, 23), and the recent paper also showed increased ischemic stroke (5). These are life-threatening, adverse effects that can be devastating for a transgender woman and therefore, when possible, using transdermal $E_2$ and lower doses, should be avoided.

## Oral Micronized Progesterone's Benefits for Transgender Women

There are at least six discrete clinical reasons why I believe, based on my clinical experience and the literature, that progesterone is likely to be beneficial for transwomen. [Note that here, I am discussing desired effects that are unique to progesterone and not present in synthetic progestins (24) that also carry a range of adverse effects distinct from progesterone.] I will briefly outline each of these with available supporting evidence, while also referring to CHT-treated transgender women's health risks (3), occurring when they are typically $E/E_2$ plus antiandrogen treated (4).

### More rapid feminization

Progesterone competes for the 5-alpha reductase enzyme that converts T into DHT (18), the hormone that masculinizes skin and hair follicles. Thus, progesterone decreases the masculinizing effects of DHT on unwanted male-pattern hair. My impression is that the slowness of improvement to feminine in facial and head hair is likely why transgender women may seek higher doses of $E/E_2$. In my clinical experience, feminization occurred more rapidly with $E_2$ and antiandrogens plus progesterone than with $E_2$ and antiandrogens alone. Obviously spironolactone or cyproterone acetate play major roles in feminization by acting as direct androgen receptor blockers (7).

### Progesterone suppression of gonadal androgen production

Progesterone feeds back to the hypothalamus slowing the pulsatility of LH and lowering average LH levels (25), thus decreasing gonadal T production. Again, this is an action of $P_4$/progesterone to assist antiandrogen therapy in achieving a feminine shape and secondary sexual characteristics.

### Progesterone plus $E_2$ leads to optimal breast maturation and size

Along with elimination of facial and male pattern body hair, one of the important goals of transgender women is to develop mature and physiological breasts (that are classified as Tanner stage 5) (26). However, currently, the majority seeks breast augmentation surgery (3), because $E/E_2$ plus antiandrogen therapy means the areola stays small ($\leq$2.5 cm, $\leq$1 inch) and masculine, and breasts remain Tanner stage 3 (27). $P_4$ is necessary for the ductal branching within the breast (and hence, for lactation) (28) and eventual maturation leading to the enlargement of the normal ciswoman's areola diameter of $\geq$3 cm (7). Currently reviewed evidence (29, 30) is inadequate to assess the breast effects of transgender women's CHT, because breast size, not areolar diameter (the primary difference between Tanner 3 and 5 stages) (26), has so far gone unreported except by one research group (7). The areolar size changes in puberty and during development of ovulatory menstrual cycles, as well as in transgender women on CHT, require further study.

### Progesterone adds to $E_2$ in increasing BMD

Lower BMD is, after CVD, the second major health risk identified in transgender women on long-term CHT (4). It is unknown yet whether low BMD is related to fractures, as there is only one case report of osteoporotic fractures in a transgender woman (6). She was a nonsmoker but had a strong osteoporosis family history (6), which in ciswomen, is related to more rapid bone loss (31).

Progesterone increases bone formation by activating a specific PR on bone-forming osteoblast cells, causing them to increase the number of mature osteoblasts (32) and to increase the process of creating collagen bone matrix that is subsequently mineralized (33). A recent meta-analysis assessed BMD change in RCT data in postmenopausal ciswomen directly (without regard to hysterectomy status) randomized to E therapy alone (ET) vs E-progestin therapy (EPT) (34). Results showed highly, significantly greater spine BMD gain (+0.68%/year) with EPT than with ET alone ($P = 0.00001$) (29). Note that RCTs of progestins that do not act through the osteoblast PR were excluded in this meta-analysis; thus, progesterone would have the same or greater effects as MPA in these studies (34). A recent review showed evidence that progesterone can prevent and treat osteoporosis in ciswomen (35).

Use of cigarettes and/or intake of excess amounts of alcohol are known lifestyle risks for osteoporosis. These habits commonly involve addictive brain processes and seem more common in trans- than ciswomen. Progesterone has also shown benefits for addiction (36).

## Progesterone improves sleep and hot flushes/flashes (vasomotor symptoms)

Short sleep durations may occur because of emotional distress (often evoked by gender conflicts), extremely stressful work, alcohol excess, inactivity, and other reasons. Short sleep (≤6 hours) is associated with negative metabolic changes and CVD, as well as an increased risk for depression. All of these reasons for, and consequences of, disturbed sleep may be increased in treated transgender women (3, 4).

Progesterone (300 mg at bedtime) significantly improves deep sleep, decreases the time to fall asleep, and decreases midsleep wakening based on placebo-controlled randomized trials in both cismen (19) and ciswomen (37). Progesterone must be given at bedtime to avoid daytime drowsiness because of its sleep-promoting effects. The 300-mg progesterone dose maintains the $P_4$ blood level in the ciswoman's luteal phase range (the desired goal) for the full 24 hours (38).

Progesterone, in a dose of 300 mg at bedtime, also effectively treats menopausal hot flushes/flashes, based on a systematic review (39), and a placebo-controlled RCT in menopausal ciswomen (40). Because the discontinuation of ET (as usually occurs before any transgender surgeries) may sometimes trigger vasomotor symptoms (41) and because progesterone effectively treats them, continuing progesterone therapy during the surgical process (as it is not implicated in VTE) (21) may make that process less physiologically and symptomatically stressful.

## Progesterone improves cardiovascular physiology

Heart attack and CVDs are currently increased in treated transgender women (2–4), although a recent large case control study showed increased VTE and ischemic stroke but not acute myocardial infarction (5). Both $E_2$ and progesterone improve endothelial function through the endothelial nitric oxide system. Progesterone, intra-arterially, to achieve luteal-phase levels, significantly increased flow-mediated dilatation and was not different from physiological intra-arterial $E_2$, although $E_2$ effects were not significantly different from vehicle (20). This endothelial action, plus the fact that progesterone does not increase the risks for VTE (21), may assist in preventing the CVD seen in some long-term CHT-treated transgender women (2–5). Finally, a comprehensive review suggested that balanced, normal premenopausal $E_2$ and ovulatory progesterone levels were related to preventing acute myocardial infarction within the first 10 years of the onset of menopause in ciswomen (13).

Thus, there are at least six reasons why progesterone will likely add to the effectiveness of $E_2$ (ideally delivered

transdermally for improved safety) (21) and anti-androgens, such as spironolactone, in the treatment of transgender women. However, we live in a culture that emphasizes the benefits of E and often blames $P_4$/progesterone, perhaps because progesterone is often wrongly conflated with progestins (24). Thus, there are clinical concerns that $P_4$/progesterone treatment raises about potential adverse effects that I will briefly address in this next section.

## Potential Progesterone-Related Adverse or Unwanted Effects

These concerns about potential progesterone-related adverse effects fall into three main categories: (i) concern about negative effects on cardiovascular health, (ii) about negative emotional/moods, and (iii) risks for breast cancer.

### Progesterone and cardiovascular effects

The assumption that progesterone causes adverse cardiovascular effects is primarily because of CVD related to androgenic progestins. However, there are no long-term RCT data on progesterone and cardiovascular effects and no progesterone therapy studies in which the primary outcomes are acute myocardial infarction, stroke, VTE, or heart failure. In part, at least, this is because oral micronized progesterone has only been available for a couple of decades. However, progesterone shows no signal for increased coagulation (21, 24). Progesterone has substantial random-ordered, positive endothelial effects compared with vehicle and $E_2$ (20), but similar results did not reach significance in a 3-month RCT in menopausal ciswomen for which the endothelial function data were underpowered (42). In that same 3-month RCT, progesterone caused no changes in weight, waist circumference, blood pressure, inflammation, coagulation, or lipids (except a substantial but clinically unimportant lowering of high-density lipoprotein cholesterol) (42).

### Progesterone and mood effects

In a premenstrual symptom crossover RCT in cycling ciswomen, 300 mg progesterone was given at bedtime premenstrually for 10 days/cycle; it showed significantly improved anxiety and had no negative mood effects (43). Another placebo-controlled progesterone clinical trial also showed no negative mood effects (44). Likewise, in an observational study in 62 healthy ciswomen, 20 to 40 years old, serum $P_4$ levels and ovulatory status were not related (positively or negatively) to daily diary records of frustration, depression, and anxiety (45). Therefore, although it is a common belief that progesterone causes

negative mood changes, controlled trial and prospective observational evidence for this assumption is lacking.

### Progesterone and breast cancer risk

E (E or $E_2$) with MPA increased the risks for breast cell proliferation and breast cancer, but there is increasing evidence that the opposite may occur with progesterone (15, 46). The large French E3N Prospective Cohort Study of menopausal therapy in ciswomen by its component characteristics showed no increased risk for breast cancer in women on $E/E_2$ with progesterone, although the same study showed a significantly elevated risk with ET or EPT (14). The combined evidence suggested that progesterone would protect against the rare risk of breast cancer in transgender women treated with E.

### Conclusion

Oral micronized progesterone, a fundamental ovarian steroid, molecularly identical to the natural hormone, should be added to $E_2$ for transgender women based on physiology and emerging evidence of the importance of progesterone with $E_2$ for ciswomen's bone and likely cardiovascular health. Progesterone will probably prevent at least some of the negative cardiovascular system and bone health effects reported in transgender women on current long-term, $E/E_2$-only, or $E/E_2$ antiandrogen CHT. Progesterone will also aid antiandrogen effects through different pathways than spironolactone or cyproterone acetate and may promote feminine physiological breast maturation, while also aiding disturbed sleep and perhaps decreasing anxiety. It may also facilitate transgender women's acceptance of physiological (rather than high) $E_2$ doses ideally delivered transdermally. Evidence is mounting that ciswomen's lifelong health is enhanced by sufficient $P_4$ (normally ovulatory) within regular estradiol-sufficient monthly menstrual cycles. I believe it is time that we now follow current guidelines and provide transgender women with these $P_4$ or progesterone benefits in their CHT.

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