Hormone Therapy for Transgender Women 101

This is intended to be a comprehensive introduction to transfeminine hormone therapy and everything one needs to know to achieve a basic understanding of the subject. For non-conventional hormone therapy in transfeminine non-binary people, see here.

Video adaptation of this thread here by u/aria_Bennett. Spanish version of this thread here by u/keylanaomi (slightly outdated). Vietnamese version of this thread here by u/CaptainGlover1.

Introduction

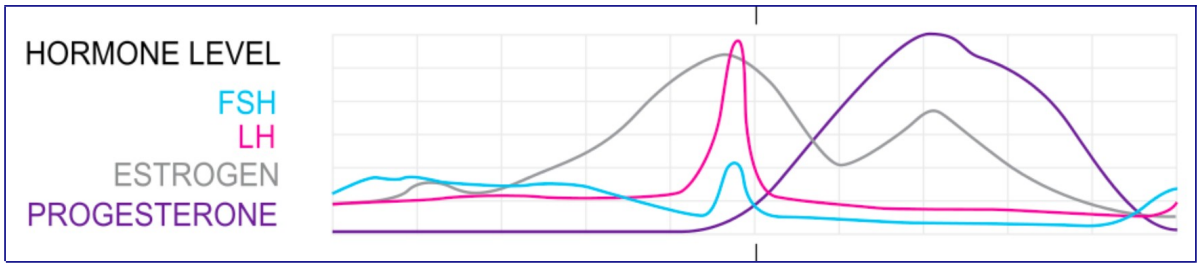
The goal of hormone therapy for transfeminine people, otherwise known as male-to-female (MtF) hormone replacement therapy (HRT) or feminizing hormone therapy (FHT), is to produce feminization and demasculinization both of the body and of the mind. Medication therapy with sex hormones and other sex-hormonal medications is used to mediate these changes. Sex hormones include the estrogens (E), progestogens (P), and androgens. A person's hormonal profile is a consequence of the type of gonads they are born with. Natal men have testes, which produce high levels of androgens and low levels of estrogens, while natal women have ovaries, which produce high levels of estrogens and progestogens and low levels of androgens. Consequently, transfeminine people, such as transgender women, are given estrogens, progestogens, and/or antiandrogens (AAs)—medications that oppose androgens—to correct their sex-specific hormonal profile from male to female.

Hormones, effects, and levels

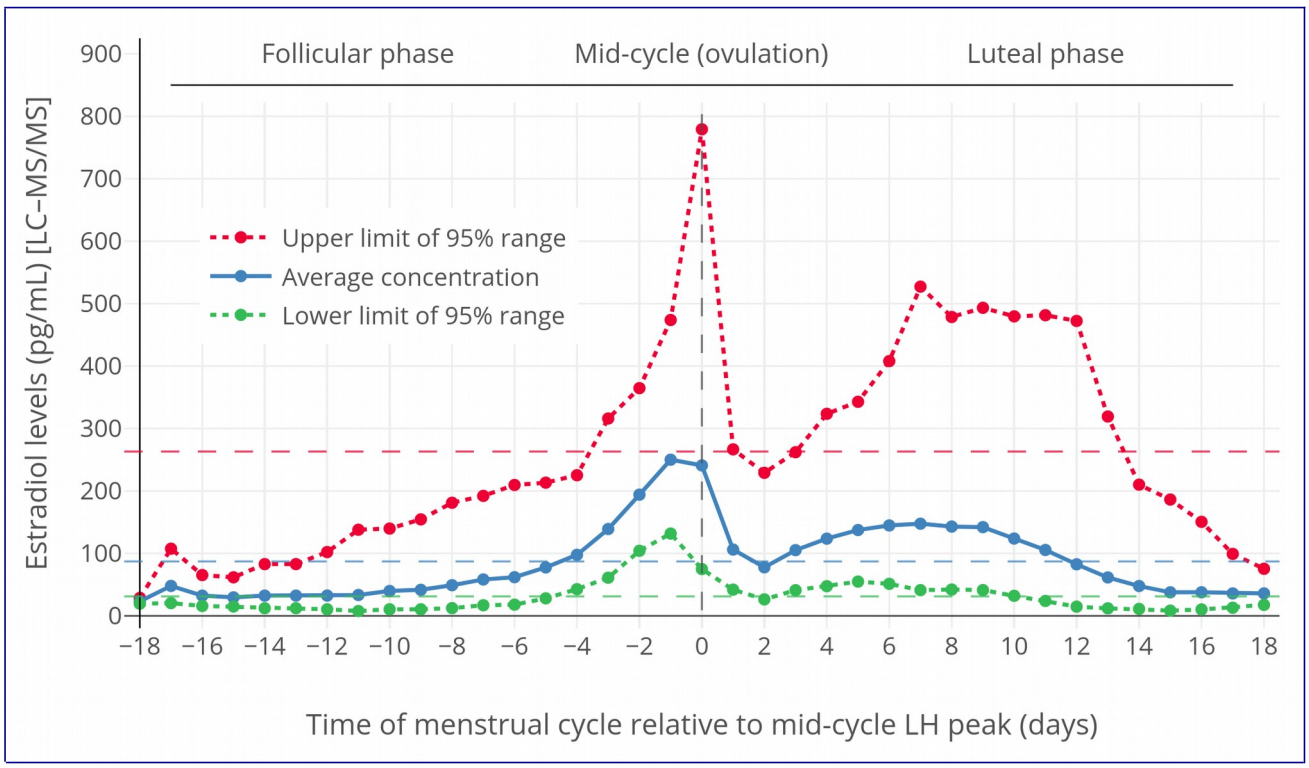
The major estrogen in the body is estradiol (E2), the main progestogen is progesterone (P4), and the major androgens are testosterone (T) and dihydrotestosterone (DHT). The sex hormones are responsible for and determine secondary sex characteristics. Estrogens cause feminization, including breast development, a feminine pattern of fat distribution (concentrated in the breasts, hips, thighs, and buttocks), widening and rounding of the pelvis (in those who have not yet undergone epiphyseal closure), and other changes (Wiki). They are also the major hormones responsible for sexual desire in women (Cappelletti & Wallen, 2016). Progestogens have essentially no known role in feminization or pubertal breast development. An involvement in breast size/shape is controversial and unsupported at present (Wiki; Reddit). Progestogens instead produce effects in the female reproductive system and oppose the actions of estrogens in certain tissues like the uterus, among other effects (Wiki). Androgens cause masculinization, including growth of the penis, general enlargement of the body, broadening of the shoulders and chest, enlargement of the rib cage and torso, muscle growth, voice deepening, a masculine pattern of fat distribution (concentrated in the stomach and waist), and facial/body hair growth (Wiki). They also produce pronounced sexual desire and arousal (e.g., spontaneous erections), cause oily skin, acne, seborrhea, scalp hair loss, and body odor, and inhibit breast development caused by estrogens. In addition to their effects on the body, sex hormones have general effects in the brain, which influence cognition, emotions, and behavior, as well as important effects on health, both positive and negative.

Sex-hormone levels are tested with blood work in transfeminine hormone therapy to make sure that the hormonal profile has been properly modified by the medications the transgender woman is

given and hormone levels are within female ranges. As such, it is useful to have knowledge of normal sex hormone levels. Hormone levels vary substantially but in a predictable manner during the normal menstrual cycle in cisgender women, as shown in the following graphs (Wiki-Graph, Wiki-Graph):



The normal menstrual cycle in human premenopausal females.



Estradiol levels across the menstrual cycle. The horizontal dashed lines are the mean integrated levels across the entire cycle.

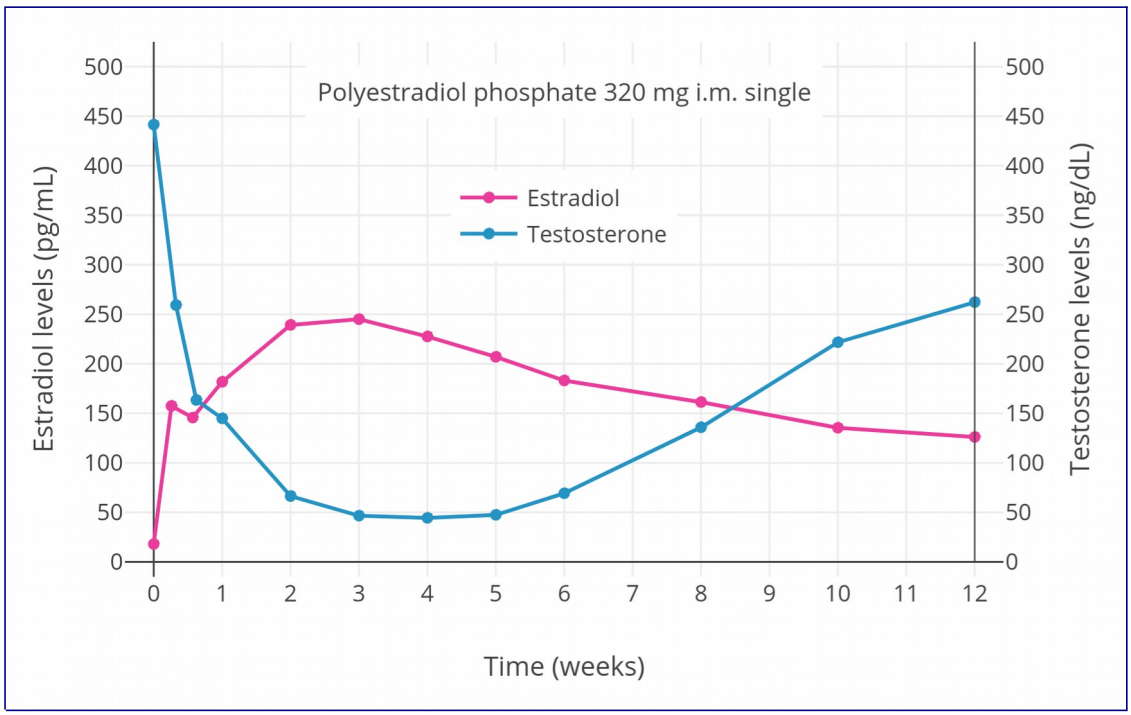
The menstrual cycle consists of the follicular phase (first half; days 1–14), mid-cycle (middle of the cycle; days 8–16 or so), and the luteal phase (latter half; days 14–28). Estradiol levels are relatively low and progesterone levels are very low during the follicular phase; estradiol levels briefly surge and trigger ovulation during mid-cycle (day 14 or so); and estradiol and progesterone levels are high during the luteal phase. The following table provides ranges for hormone levels as determined with state-of-the-art blood-work methodology (LC–MS) (Jameson et al., 2015):

Hormone	Group	Time	Range
Estradiol	Women	Menstrual cycle	6–373 pg/mL
		Follicular phase	6–182 pg/mL
		Mid-cycle	44–373 pg/mL
		Luteal phase	18–219 pg/mL
	Men	N/A	≤29 pg/mL

Hormone	Group	Time	Range
Progesterone	Women	Menstrual cycle	≤0.3–22 ng/mL
		Follicular phase	≤0.3 ng/mL
		Mid-cycle	0.1–1.5 ng/mL
		Luteal phase	6.7–22 ng/mL
	Men	N/A	≤0.4 ng/mL
Testosterone	Women	Menstrual cycle	5–45 ng/dL
	Men	N/A	250–1100 ng/dL

Mean estradiol levels are about 100 pg/mL in women and 25 pg/mL in men, while mean testosterone levels are about 30 ng/dL in women and 600 ng/dL in men. Based on these values, testosterone levels are on average about 20-fold higher in men than in women. In addition to the values in the table, the average levels of testosterone in women with symptoms of androgen excess (e.g., facial/body hair growth) due to polycystic ovary syndrome (PCOS) (affects around 5% of women) are about 60 ng/dL (Goodman & Cobin, 2012). As such, even testosterone levels that are marginally elevated relative to normal female levels can produce excessive androgenic effects in women. The goal of transfeminine hormone therapy is to achieve both estradiol and testosterone levels within the normal female range, although it is not necessarily problematic if estradiol levels are above typical mean female levels. In fact, this is often warranted in transfeminine hormone therapy to help suppress testosterone levels.

In addition to their general effects in the body and brain, estrogens, progestogens, and androgens have antigonadotropic effects. That is, they suppress the gonadotropin-releasing hormone (GnRH)-induced secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), from the pituitary gland in the brain. The gonadotropins signal the gonads to make sex hormones and to supply the sperm and egg cells necessary for fertility. If gonadotropin levels are sufficiently suppressed, then the gonads will no longer make sex hormones and fertility will cease. About 95% of the amount of sex hormones in the circulation is made by the gonads. At sufficiently high levels, estrogens and androgens are able to maximally suppress testosterone levels by 95% in cisgender men and transfeminine people (Wiki), while progestogens are able to maximally suppress testosterone levels by about 50 to 70% (Reddit). Levels of estradiol of over 200 pg/mL can suppress testosterone levels by about 90% (to ~50 ng/dL), while levels of estradiol of about 500 pg/mL can suppress testosterone levels by about 95% (to ~20 ng/dL) (Wiki). The antigonadotropic effects of high doses of estrogens and progestogens are commonly taken advantage of in transfeminine hormone therapy to shut down gonadal testosterone production. A combination of an estrogen and a progestogen can be used to achieve maximal suppression of testosterone levels at lower doses than would be necessary if an estrogen or progestogen were used alone (Wiki). The following is an example of suppression of testosterone levels by estradiol therapy (Wiki-Graph):



Estradiol and testosterone levels after a single intramuscular injection of 320 mg polyestradiol phosphate (a form of estradiol) in men. Testosterone levels decreased by about 90%.

Hormonal medications

The estrogens that are used in transfeminine people are estradiol and estradiol esters. Examples of estradiol esters include estradiol valerate (EV), estradiol cypionate (EC), estradiol enanthate (EEn), and estradiol benzoate (EB). They are prodrugs of estradiol (i.e., are converted into estradiol in the body) and have identical biological activity, but have longer durations when used by injection. This allows them to be administered less often. Other, non-bioidentical estrogens such as ethinylestradiol (EE; found in birth control pills) and conjugated estrogens (CEEs; Premarin) are resistant to metabolism in the liver and have disproportionate effects on estrogen-modulated liver protein synthesis, resulting in a greater risk of blood clots, cardiovascular issues, insulin resistance, and other health problems (Wiki). For this reason, as well as the fact that high doses of estrogens are needed to suppress testosterone levels in gonadally intact transfeminine people, these estrogens should ideally never be used as the estrogen component in transfeminine hormone therapy. Progestogens include progesterone and progestins (synthetic progestogens) such as medroxyprogesterone acetate (MPA; Provera, Depo-Provera) and norethisterone. There are dozens of progestins (Wiki). Bioidentical progesterone may be safer than progestins health-wise, and hence may be the preferred progestogen for use in transfeminine hormone therapy. However, there is also indication that non-oral progesterone may share the health risks of progestins (Reddit).

Aside from estrogens and progestogens, there is another class of hormonal medications used in transfeminine hormone therapy known as antiandrogens (AAs). These medications nullify the effects of androgens in the body. They work by a variety of different mechanisms of action and include antagonists of the androgen receptor (AR) (directly block the effects of androgens), antigonadotropins (suppress gonadal production of androgens), and androgen synthesis inhibitors (inhibit the enzyme-catalyzed synthesis of androgens). Examples include:

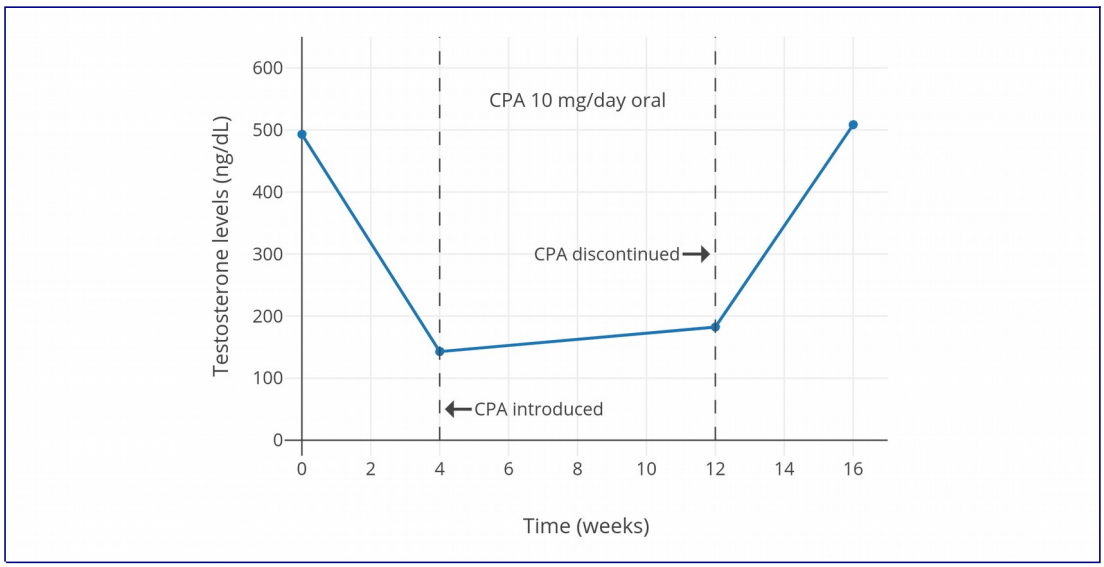
- AR antagonists: steroidal antiandrogens (SAAs) like spironolactone (Aldactone) and cyproterone acetate (CPA; Androcur) and nonsteroidal antiandrogens (NSAAs) like bicalutamide (Casodex).
- Antigonadotropins: estrogens, progestogens, and GnRH agonists and antagonists (GnRHa) like leuprorelin (Lupron) and elagolix (Orilissa).
- Androgen synthesis inhibitors: 5α-reductase inhibitors (5α-RIs) like finasteride (Propecia) and dutasteride (Avodart).

Although estrogens and progestogens are antigonadotropins and hence are functionally antiandrogenic, they are not usually referred to as "antiandrogens". Instead, the term "antiandrogen" is most commonly reserved to describe other antiandrogens, especially AR antagonists like spironolactone, CPA, and bicalutamide.

Spironolactone and bicalutamide work by directly blocking the effects of androgens. They do not suppress testosterone levels (Wiki; Reddit; Wiki), and their antiandrogenic efficacy is limited by this fact; relatively high doses by weight of these pure AR antagonists are required for adequate prevention of the effects of testosterone, especially in the context of high testosterone levels (see here and here for bicalutamide). However, pure AR antagonists like spironolactone and bicalutamide can be very useful when testosterone levels are incompletely but markedly suppressed (e.g., <150 ng/dL). Because pure AR antagonists do not work by lowering testosterone levels, blood work is less useful for them. Spironolactone has antimineralocorticoid side effects and has a rare risk of potentially life-threatening high potassium levels in those with specific risk factors (Wiki). Monitoring of blood potassium levels during spironolactone therapy is advisable in those with risk factors for high potassium levels, but appears to not be necessary in people without such risk factors (Plovanich et al., 2015). Risk factors for high potassium levels include old age, kidney disease, and other potassium-elevating drugs and supplements.

Bicalutamide is a more potent, selective, and efficacious AR antagonist than spironolactone and has fewer side effects, including no antimineralocorticoid effects or hyperkalemia risk. It has almost no side effects in women (Erem, 2013; Moretti et al., 2018). Bicalutamide also does not adversely interact with estradiol. The medication has a small risk of liver function abnormalities and rare instances of liver failure (Wiki) and lung disease (Wiki). Liver monitoring is advisable during bicalutamide therapy. Bicalutamide has mostly been used to treat men with prostate cancer, but has also been used to treat other androgen-dependent conditions and is becoming increasingly used in transfeminine people (Wiki; Reddit). Due to its various advantages over spironolactone, it is possible that bicalutamide may eventually supersede spironolactone as an antiandrogen in transfeminine people.

CPA works both by blocking the effects of androgens and, due to its very potent progestogenic activity, by suppressing levels of testosterone, as shown in this graph (Wiki-Graph):



Testosterone suppression with 10 mg/day CPA in men. Levels decreased by ~60–70% (from ~500 ng/dL to ~150–200 ng/dL).

The suppression of testosterone levels by CPA strongly improves its efficacy as an antiandrogen; relatively low doses of CPA may be able to maximally suppress testosterone levels in combination with low to moderate doses of an estrogen (Wiki). CPA may have some risk of mood issues (Wiki). It also has a risk of elevated liver enzymes and rare incidences of liver damage, blood clots, and non-cancerous brain tumors (Wiki; Reddit). Monitoring of liver function and prolactin levels, which allow for detection of liver problems and one of the relevant types of brain tumor, is advisable during CPA therapy. The side effects and risks of CPA may be minimized by using the lowest fully effective dosage, which is far lower than what is often used clinically (Reddit). CPA is notably not approved for use in the United States, but is available in most other countries.

5α-RIs work by preventing the potentiation of testosterone into its several-fold more potent metabolite DHT in certain tissues like the skin, hair follicles, and prostate gland. Because of this, they have antiandrogenic efficacy that is limited to the treatment of scalp hair loss, excessive facial/body hair growth, and enlarged prostate. They are inappropriate as general antiandrogens in transfeminine people as they have little or no influence on the effects of testosterone elsewhere in the body. If a 5α-RI is used, dutasteride is a more complete and efficacious 5α-RI than finasteride, and is preferred. 5α-RI may have a small risk of depression (Wiki). GnRH agonists and antagonists work by completely blocking the effects of GnRH, and thereby abolish gonadal sex hormone production. They are like a reversible gonadectomy, and are the ideal antiandrogens for use in transfeminine people. Unfortunately however, they tend to be prohibitively expensive for most (e.g., ~US$10,000 per year without insurance). An exception is buserelin (Suprefact), which has become available online at very low cost (Reddit). Provided that an estrogen is taken in combination to prevent sex hormone deficiency, GnRH agonists and antagonists have essentially no side effects or risks.

An estrogen can be used alone at high doses to suppress testosterone levels into the female or castrate range (~5–50 ng/dL). Alternatively, an estrogen can be used at lower doses that result in more physiological estrogen levels in combination with appropriate doses of an antiandrogen (e.g., bicalutamide), a secondary antigonadotropin (e.g., a progestogen like CPA), or a GnRH agonist/antagonist. Their addition to estrogen therapy can suppress or block the remaining testosterone that isn't suppressed by estrogen therapy alone. Higher doses of estrogens may have a

greater risk of adverse health effects such as blood clots and cardiovascular issues, so the use of lower and more physiological doses of estrogens may be optimal (Getahun et al., 2018; Wiki; Wiki). However, it should also be noted that the absolute risks of health complications with high-dose estradiol are low, and are much smaller than those of non-bioidentical estrogens like conjugated estrogens and ethinylestradiol. They are also likely confined mainly to people with specific risk factors, including those who are of old age, who smoke, and who are obese, among others. In addition to potential health risks however, there is indication that high doses of estrogens may compromise breast development (Reddit; Reddit).

Routes, doses, and levels

Estrogens, progestogens, and antiandrogens are available in a variety of different formulations and for use by a variety of different routes of administration. Estrogens are usually used in transfeminine people by oral administration (swallowed) or by a parenteral (non-oral) route such as sublingual administration (held and absorbed under the tongue), transdermal administration (applied to and absorbed through the skin), or by injection, including intramuscular injection (IM; injected into muscle) or subcutaneous injection (SC; injected into fat) (Wiki). Parenteral routes, although less convenient than the oral route, are preferred, because oral estradiol results in excessive levels of estradiol in the liver and has a disproportionate impact on estrogen-modulated liver protein synthesis (Wiki). Particularly at the high doses of estrogens required to suppress testosterone levels in transfeminine people, this may increase the risk of health issues like blood clots and cardiovascular problems (Getahun et al., 2018). The health concerns of estradiol are largely allayed if it is taken parenterally at reasonable doses. Oral estradiol also has issues with bioavailability and often achieves low estradiol levels, which can limit its estrogenic efficacy and can result in inadequate testosterone suppression (Wiki; Leinung et al., 2018; Leinung, 2014).

Estradiol tablets can be taken sublingually instead of orally. The sublingual route has about 5-fold increased bioavailability compared to the oral route, but has a very short duration and should be taken in divided doses multiple times throughout the day to maintain high estradiol levels (Wiki). Transdermal estradiol patches can be used, but two to four high-dose patches may be required to achieve estradiol levels sufficient for full testosterone suppression in transfeminine people, at least with estrogen monotherapy (Wiki). Likewise, transdermal estradiol gel can be used, but many pumps or packets are required to achieve adequate estradiol levels. For parenteral estradiol esters, either intramuscular or subcutaneous injection can be performed. Subcutaneous injection is easier, less painful, and more convenient than the intramuscular route, and is preferred. Injections of estradiol esters can easily achieve high levels of estradiol, and last for days to weeks, depending on the estradiol ester in question. An injection of the polymeric ester polyestradiol phosphate (PEP; Estradurin), which in contrast to other estradiol esters should always be administered by intramuscular injection, lasts for months. However, the availability of PEP is very limited, with its use mostly restricted to the Nordic region of Europe (Wiki).

Progesterone can be used by the oral or rectal route or by intramuscular or subcutaneous injection (Wiki), while progestins are usually used by the oral route. Levels of progesterone with the oral route have been found using state-of-the-art assays (LC–MS) to be very low (<2 ng/dL at 100 mg/day) and inadequate for satisfactory progestogenic effects (Wiki; Reddit). In accordance, even high doses of oral progesterone showed no antigonadotropic effect in cisgender men (Wiki), which is in great contrast to progestins and parenteral progesterone. Additionally, oral progesterone is excessively (>90%) converted into potent neurosteroid metabolites like allopregnanolone, and this

can result in undesirable alcohol-like side effects such as sedation, cognitive/memory impairment, and mood changes (Wiki; Wiki). As such, while inconvenient, parenteral routes are greatly preferred for progesterone as well. Conversely, there are no issues with the oral route for progestins. Progesterone by injection has a relatively short duration and must be given once every one to three days. Antiandrogens are usually used by the oral route, but GnRH agonists and antagonists must be injected subcutaneously or intramuscularly one to three times per day or once every one to six months (depending on the formulation), surgically implanted once a year, or used as a nasal spray two to three times per day. However, an oral GnRH antagonist known as elagolix has recently been introduced for medical use (Reddit).

This table provides recommended dosages of medications used in transfeminine hormone therapy for transfeminine people who have or have not undergone gonadectomy:

Medication	Type	Route	Dosage
Estradiol	Estrogen	Oral	2–10 mg/day
		Sublingual/buccal	0.5–2 mg 1–4x/day
		Transdermal (patches)	50–400 µg/day
		Transdermal (gel)	2–6 mg/day
Estradiol valerate	Estrogen	Oral	2–10 mg/day
		Sublingual/buccal	0.5–2 mg 1–4x/day
		IM/SC injection	2–10 mg/week
Estradiol cypionate	Estrogen	IM/SC injection	2–10 mg/week
Estradiol benzoate	Estrogen	IM/SC injection	1–5 mg 2x/week
Estradiol enanthate	Estrogen	IM/SC injection	4–20 mg/2 weeks
Polyestradiol phosphate	Estrogen	IM injection	40–240 mg/montha
Progesterone	Progestogen	Oral	100–300 mg 1–2x/day
		Rectal (capsules, suppos.)	100–200 mg 1–2x/day
		IM injection	25–75 mg/1–3 days
		SC injection	25 mg/day
Progestins	Progestogen	Oral; IM/SC injection	Various
Cyproterone acetate	Progestogen	Oral	5–12.5 mg/day (total)b
Spironolactone	Antiandrogen	Oral	100–200 mg 1–2x/dayc
Bicalutamide	Antiandrogen	Oral	12.5–50 mg/dayc
Finasteride	5α-RI	Oral	0.25–5 mg/day
Dutasteride	5α-RI	Oral	0.5 mg/day
GnRH analogues	GnRH modulator	Parenteral (various)	Various
Buserelin	GnRH agonist	Nasal spray	400 µg 3x/day
Elagolix	GnRH antagonist	Oral	150–200 mg 1–2x/day

^ a In the case of polyestradiol phosphate, a loading dose of 320 mg for the first one or two injections can be employed to reach steady state estradiol levels more quickly. b For CPA, half of a 10-mg tablet to one full 10-mg tablet per day (5–10 mg/day) *or* a quarter of a 50-mg tablet every other day or every day (6.25–12.5 mg/day). c For the pure AR antagonists, spironolactone and bicalutamide, it is assumed that testosterone levels are substantially suppressed (≤200 ng/dL).

After removal of the gonads, antiandrogens can be discontinued, and, if applicable, doses of estrogens and/or progestogens can be lowered or adjusted to approximate the physiological effects

of normal female-range levels of estradiol and/or progesterone. Normal average production of estradiol in premenopausal women is about 6 mg per month (Rosenfield et al., 2008).

It should be noted that there is high variability between individuals in the levels of estradiol achieved during estradiol therapy. That is, estradiol levels during treatment with the same dosage of estradiol can differ widely between individuals. This variability is greatest with the oral and transdermal routes. As such, the doses of estradiol recommended are not absolute and should be individualized in conjunction with blood work on a case-by-case basis. It should also be noted that estradiol levels can vary considerably from one blood test to another, most importantly with the sublingual and injected routes. However, this variation is predictable, and can be minimized with proper timing of blood tests. High variability between individuals is also applicable to progesterone, but is less applicable to progestins and antiandrogens.

For levels with different formulations, routes, and doses, see the table here for estradiol and here for progesterone (only LC–MS and RIA + CS assays for oral progesterone). For time–concentration graphs with all of the different routes, see the graphs here and here.