RANDALL CHILDREN'S HOSPITAL
LEGACY EMANUEL

Gender Care Center
Estrogen Information

Hormone therapy can help transgender people feel more comfortable in their bodies, changing their bodies to align more with their gender identity. Like with other medical treatments, there are risks and benefits. This information is to help patients and families understand the medical care available to work with their treatment team to make the best decisions for what is right for them.

What is a hormone?

Hormones are chemical messengers that are made in one organ (a gland) and have an effect somewhere else. There are many different glands in the body (thyroid, pituitary, adrenal, testicles, pancreas and others) that produce many different hormones (thyroid, LH, FSH, growth hormone, cortisol, testosterone, insulin and others) that have a wide range of effects on the human body. Hormones are responsible for growth, puberty, overall metabolism, blood sugar regulation, hunger, thirst among other body functions. A hormone must bind to a receptor on a cell for specific actions to occur. All hormones are highly regulated by the body.

What about sex hormones?

Sex hormones regulate the development of puberty and the changes that result from it. They are mainly produced by a person's sex organ (ovary or testicle), although some are made in one's adrenal gland. These hormones produce the changes we associate with puberty such as facial and body hair, breast growth and bone strength, among others.

There are 3 categories of sex hormones:

1. Androgens: testosterone (produced in testicle), dihydrotestosterone (DHT, active form of testosterone, testosterone is converted to this near the organs it effects by an enzyme); other androgens that are produced in the adrenal gland
2. Estrogens: estradiol (produced in ovary)
3. Progestin: progesterone (produced in ovary)

What is Gender Affirming Hormone or Estrogen Therapy?

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Gender affirming hormone therapy refers to taking medicine to change the level of sex hormones in your body. Changing these levels will affect features that are associated with sex and gender. Estrogen therapy can help make the body look and feel less masculine and more feminine.

What Medicines (or hormones) are Involved:

Estrogen

Estrogen is the main hormone responsible for promoting feminine physical traits, like breast development, soft skin and curves. It works directly on tissues in the body (for example, breasts will develop, fat will redistribute). Estrogen will eventually suppress testosterone production by the testicles. Most commonly we give estrogen by a patch (transdermally), as this way it is delivered through the skin, and avoids passing through the liver. We can also administer it by taking a pill under the tongue (sublingually) or by injection.

Androgen Blockers

These medicines work by blocking testosterone from having its effect by stopping it from binding to its receptor. The result is slowing the growth of facial hair and helping stop spontaneous erections. Androgen blockers tend to have a mild feminizing effect when used alone. They are often used in conjunction with estrogen, as estrogen can work better when testosterone effect is blocked.

The most common form of androgen receptor blocker we use is called Spironolactone. This is actually a diuretic (makes people pee) that has a side effect of blocking testosterone. When on this medication, one needs to drink fluids. Our team will monitor electrolyte levels and blood pressure. Another androgen blocker is called Biclutamide. With this medication, the liver needs to be healthy. There is little long-term information on Biclutamide.

In addition to the changes mentioned above, some individuals will experience breast development while on an androgen receptor blocker. It is presumed, although not confirmed, that this breast development is permanent.

Progestins

There are mixed opinions about using progestins for feminizing hormone therapy. If used, they are introduced later in one's transition for final breast changes and nipple development. They have possible risks of depression, fatigue and weight gain, so these must be discussed with a provider prior to starting.

What is a typical dose?

Feminization therapy doses differ from person to person as bodies respond to hormones differently. Often this is because of genetics that are inherited from families. Providers prescribe what best fits based on individual medical history and desired outcomes. Our team will also work with each individual/family based on insurance coverage around the best path forward.

Everyone's journey is different. Each body absorbs, processes and responds to sex hormones differently. Some people show more changes than others on a similar dose and changes may happen more quickly in some than others. There is no way to predict how each individual will respond before starting estrogen. Taking more hormone than the prescribed dose will not speed up the process. It can actually slow down changes as excess estrogen in the body can be converted to testosterone as well as increase health risks. We encourage each patient and family to bring up any concerns around dosage with their medical provider.

Some people, as part of their transition, have an orchiectomy (removal of testicles). For those individuals, androgen receptor blockers or pubertal suppression are no longer needed.

People born with testicles will not be able to produce the amount of estrogen needed to see feminization of effects estrogen, so for those who desire the feminizing impacts of estrogen, they will need to take estrogen for the rest of their life. This is also important for bone health.

Changes and Timeline:

- **Androgen Receptor Blockers without Estrogen:** Typically taking Spironolactone or Biclutamide without estrogen has small effects. Most changes that happen from blocking testosterone are reversible and will go back to the way it was before for those that stop taking the medication.

Average Timeline	Effect
After 1 to 3 months	• Decreased sex drive • Fewer erections, or difficulty getting them • Decreased ability to make sperm and ejaculatory fluid
Gradual (usually takes at least 2 years)	• Slower growth of facial or body hair • Slowed / stopped male patterned balding • Variable breast growth (presumed permanent)

- **Estrogen:** Taking estrogen is stronger than an androgen receptor blocker alone. Estrogen works on cells in the body that have estrogen receptors. Eventually, taking estrogen will have an indirect effect of suppressing testosterone production.

Average Timeline	Effect
After 1 to 3 months	• Softening of skin • Less muscle mass, more body fat • Redistribution of body fat to breasts and hips • Possible decrease in sex drive • Fewer erections, or difficulty getting them • Decreased ability to make sperm and ejaculatory fluid
Gradual changes (max effect in 2 years)	• Breast and nipple growth (quite gradual and can continue on adult maintenance doses) • Slower growth of facial and body hair • Slowed or stopped male pattern baldness • Smaller testicles

A note on breast changes: It can take 2 years or more for breasts to reach their maximum size. As with all people, there is quite a range in how large breasts will grow. In many cases they will not get over an A or B cup size. For those unhappy with their breast size after 24 months or more of estrogen, surgical augmentation can be considered. The implants have the best outcome with as much growth as possible from hormones prior to placement.

Medical provider visits: As doses are being increased and adjusted, the medical provider sees each patient every 3-4 months. The appointment will discuss changes noticed on treatment and how things are going. Labs will be needed 2-3 times a year to help adjust.

What Changes are Permanent?

Breast growth and Fertility.

Breast growth from estrogen (and if there is significant growth from an androgen receptor blocker) is permanent and will not go away after an individual stops taking estrogen. Nipple change is also permanent.

Both the androgen blockers and estrogen decrease sperm production. Long-term effects on fertility is not fully understood. For those that stop taking medication, the ability to make sperm may or may not come back. Again, given the newness in this field, we strongly recommend the use of protection (condoms) if having sex with a person with a vagina/ovaries for birth control. In addition, hormone treatment is not protection against any sexually transmitted infections.

For patients that are considering sperm preservation, we recommend doing so before starting hormone therapy. Preservation can still occur for patients that are taking hormones. Those patients would need to stop estrogen therapy for a time to preserve before returning to hormone care. Our team can refer you to our colleagues at OHSU to discuss these options and pricing (Gender-Clinic-Fertility-Preservation-Handout.pdf (ohsu.edu)).

What will not change on Estrogen Therapy?

- Penis
- Pubic Hair
- Chromosomes
- Adams' Apple: Once this is formed during puberty, it will not go away.
- Bone Structure: taking estrogen will not change the bone structure once changes have happened. The distribution of the fatty tissue in the face may change altering the appearance to become more feminine but the bones themselves will not change.
- Voice pitch: (how high or low your voice is) will not change. Speech or voice therapy can help train individuals to speak in a higher pitch. Some people have surgery on their vocal chords or surrounding cartilage to try to make their voices sound lighter.
- Height: Once someone is done growing, there is no way to change height with hormones.
- When taking estrogen, the hair follicle does not produce hair as frequently as before taking estrogen. However, the hair does not permanently go away unless someone has either electrolysis or laser hair removal.

Other things that will not change:

Body image: often hormone therapy significantly improves gender dysphoria as the body becomes more congruent with gender identity. However, for those that body dysphoria does not improve with hormone care, it may be beneficial to speak to a mental health therapist or other community support around these feelings.

Mental Health: as stated above, often hormone therapy significantly improves gender dysphoria as a person's body becomes more in line with their gender identity. Life can still present with emotional and social challenges, stress and other factors that can contribute to

mental health struggles. We recommend having an established mental health provider through the transition process for ongoing support. Other supports, like groups, community, and peers to rely on can be helpful.

What are the risks of taking feminizing hormones?

As treating transgender youth is such a new practice, long-term effects of using estrogen and androgen receptor blockers is not known. Knowledge of using estrogen and these medications comes from use in adult patients, as well as in individuals with different medical conditions requiring hormone therapy. Transgender medicine is an ongoing field of study and more will be known the longer it is practiced. There may be long term health risks we simply do not know about yet.

We try to create the safest hormone regimen with our patients by measuring levels and watching for the side effects we know about. The biggest thing in preventing risks of feminizing hormone therapy is to avoid smoking. Smoking increases the risk of blood clots and heart disease by itself. When estrogen is taken, this risk increases substantially. Even the occasional smoker is at increased risk.

- Liver Health
  Typically, estrogen is processed by the liver, especially if taken orally. There is a chance that taking hormones over a long period of time can put a strain on the liver, leading to liver disease. We check your liver function at the initiation of therapy and at regular intervals afterward.

- Blood Clots
  Taking estrogen increases the risk of blood clots. **Blood clots** can cause death, lung damage (clot in the lungs), brain damage (stroke), heart attack, or chronic problems with veins in legs. The risk of blood clots is MUCH higher for smokers.

  The risk of clots is lowered by:
  - Taking Estrogen by skin patch or under the tongue
  - Using lower doses of estrogen

- Changes in Fat Storage
  Estrogen changes the way body uses and stores fat. Taking estrogen can increase deposits of fat around internal organs, which is associated with an increase risk for diabetes and heart disease. It can also increase risk of gallstones. Patients on treatment need to see a medical professional right away for:
  - Pain in chest, leg or abdomen
  - Leg swelling
  - Headaches with vomiting

- High Blood Pressure
  Estrogen can also cause high blood pressure. We monitor blood pressure at every visit. Watching diet, active level and not smoking will all help blood pressure.
- Galactorrhea and Prolactinoma
  When breasts grow, there can be a milky discharge from the nipples. This is called galactorrhea. This is caused by estrogen stimulating the production of the hormone prolactin, which stimulates the breast ducts to make milk. We check levels of prolactin regularly, and especially for those experiencing galactorrhea, to monitor for very high levels that may indicate a small tumor on the pituitary gland that produces prolactin. This is called a prolactinoma. These lesions are not usually life threatening, but they can cause visual disturbances and headaches. They can be treated medically or, rarely, surgically.
- Breast Cancer
  It is not known if taking estrogen causes an increased risk of breast cancer. There have been cases of people who have developed breast cancer after hormone therapy for gender affirming care. The risk of breast cancer is higher for those that:
  - Have a family history of breast cancer
  - Have been taking estrogen or progestin for more than 5 years
  - Are 50 years or older
  - Are overweight

- Kidney Health (Spironolactone only)
  Spironolactone affects the balance of water and salt in the kidneys. If the amount of water and salt gets out of balance, low blood pressure may result. Rarely this imbalance can lead to high levels of potassium in the blood, causing changes in heart rhythm that can be life threatening. We check blood for potassium levels and kidney function on a regular basis when on Spironolactone.
- Skin rash
  Occasionally the patches for estrogen can be irritating and cause a rash. We want to know when this happens for our patients.

What needs to happen for patients to start gender affirming hormone care?

As per the World Professional Association for Transgender Health (WPATH) and Endocrine Society Guidelines, a mental health professional needs to write a letter of readiness prior to starting pubertal blockers, androgen blockers or gender affirming hormone care. The mental health questionnaire (MHQ) on our website can also be used. Here is a possible sequence of events:

1. Some patients and families work with Gender Care Center Behavioral Health Clinician, around the WPATH letter over 2-6 sessions, and some individuals work with an outside mental health provider. For those working with an outside therapist, we ask that the patient either bring this letter or MHQ to an appointment or send via MyHealth, or have the mental health provider either fax, mail (ensure you have a copy), or secure e-mail. We will need this on file before beginning gender affirming care. We will ask you to sign a release of information (ROI) so that our team is able to follow up with your outside mental health provider as needed.
2. Appointment with Medical Provider: review of goals, treatment, side effects and timelines, physical exam if indicated. Sometimes the initial medical appointment is focused on establishing care and asking questions of the provider. We don't require the WPATH letter or assessment to be complete before an initial provider appointment. We just need that before starting gender affirming treatment.
3. Labs will be obtained after first appt with Medical Provider for those ready to move forward with gender affirming medical care, a bone age x-ray may be obtained. If the provider is concerned about bones, a dexa scan for bone health may be ordered.
4. Once labs come back, and if all looks normal, our nurse will call you with the treatment plan. They will also call in a prescription for the treatment and you can start it at home. We have each patient and their parent/guardian/caregiver sign an informed consent form, covering topics in this handout prior to prescribing estrogen.
5. Patients see their provider approximately every 3-4 months in the first year, and then every 6 months after. In these appointments, we will:
    - Ask questions about overall health
    - Check vital signs (pulse, blood pressure, weight, height)
    - Ask about physical and emotional changes after treatment has been initiated
    - Ask about signs and symptoms of the side effects mentioned above
    - Recommend timing of blood tests and dose adjustments

Resources:

Excellence for Transgender Health

www.transhealth.ucsf.edu

Estrogen Therapy : Brief Description

Estrogen: Typically given in a patch form, applied 2x a week

I Physical Effects:

A. Breasts may take years to develop, and are a permanent change from taking estrogen
B. Testicles: will eventually produce less testosterone
    - sperm may not mature, leading to reduced fertility
    - ability to make sperm may or may not come back
    - testicles may shrink by 25% (may be permanent, unknown)
    - decrease in erections, wet dreams, but still may happen
C. Non-permanent changes: may reverse if stop taking estrogen
    - Softer skin, decreased acne
    - decreased muscle mass
    - fat redistribution
    - curvy figure
D. Estrogen **will not change** hair growth, voice pitch, Adams apple once they have developed

II Medical Risks

Estrogen *may* increase risk of

- blood clots (pulmonary embolism, stroke, heart attack, leg vein pain)
    - THIS RISK IS GREATLY INCREASED WITH SMOKING
- liver dysfunction
- breast cancer
- heart disease, cholesterol levels
- increase in frequency of migraine headaches
- increase blood pressure
- increase gall stones
- prolactin producing brain tumors

Breasts may take years to develop, and are a permanent change from taking estrogen

Testicles: will eventually produce less testosterone

- sperm may not mature, leading to reduced fertility
- ability to make sperm may or may not come back

- testicles may shrink by 25% (may be permanent, unknown)
- decrease in erections, wet dreams but still happen
- decrease in libido

Non-permanent changes: may reverse if stop taking estrogen

- softer skin, improved acne
- decreased muscle mass
- fat redistribution

Estrogen will not change hair growth, voice pitch, Adams apple once they have developed

Androgen receptor blockers: Block binding of testosterone to it's receptor

- **May be used alone, or before/during estrogen therapy**
- **May eventually suppress testosterone production**
- **Once testosterone is suppressed with estrogen, these agents may be stopped**

I. Spironolactone

Affects balance of water and salt in the kidneys, diuretic (makes you pee more often). Side effect is blocking testosterone receptor.

- increase in amount of urine produced, increase frequency of urination – good fluid intake is important
- reduces blood pressure
- increases thirst
- rarely, causes high levels of potassium which can change heart rhythm
- may have small amount of breast development
- levels of sodium and potassium are monitored regularly, as well as testosterone

II Biclutamide

Strong anti-androgen used in prostate cancer

- Can cause liver changes in up to 3%, must have normal liver function to start
- Very little long-term data
- 85% develop breasts in 6 months on therapy