Seattle Children's Gender Clinic Gender-Affirming Hormone Protocols

These protocols were created by providers at Seattle Children's Gender Clinic, with input from Crystal Beal, MD, using a combination of multiple resources, including the Endocrine Society, WPATH, and UCSF guidelines for gender-affirming care, and common practices in our clinic.

These protocols are meant to be used as examples to guide management of gender-affirming hormones. Gender affirming care, like much of healthcare, is optimized when it is patient-centered focusing on each individual's and family's specific health needs and desired health outcomes. *Treatment should be adjusted based on the goals and needs of the individual patient.*

All of the medications listed are prescribed as off-label use for gender-affirming care.

Contents:

Revised 02/2023

Puberty Blockers

GnRH agonist formulations and dosing:

- Histrelin implant (Supprelin, Vantas)
    - Dosing: 50 mg per implant
    - Approved to last 1 year, shown to be effective for longer in some studies
    - We recommend replacing the implant every 1.5 years, as leaving it in longer can lead to more complicated removal due to breakage of the implant
    - Vantas no longer being produced as of Oct 2021
- Leuprolide injections (Lupron IM, Eligard SC)
    - Dosing: 22.5 mg IM/SC q3 months.
    - Other dosing options: 11.25 mg q3 months (Lupron only), 30 mg q3 months (Lupron only). Monthly and 6 monthly formulations are also available.
    - Dose titration: Increase dose if continued pubertal progression AND labs showing puberty not suppressed. It is very rare that this is needed on the 22.5mg q3 month dose.

    *Lupron depot adult formulation or Eligard SC is most frequently used as it comes in the effective desired dose (22.5mg) versus the Lupron peds-depot which comes in 11.25mg and 30mg.

Risks:

- Local site reaction (10-15%). Patients may experience aching discomfort at the site for a few days after the injection
- "Menopausal symptoms" if starting later in puberty with no additional exogenous hormones. Symptoms include hot flashes, night sweats, fatigue, mental cloudiness
- Potential mood changes
- Potential increased pubertal changes x1 months before suppression: including chest/breast tenderness and menstrual bleeding in patients with ovaries, spontaneous erections or increased sex drive in patients with testicles
- Fertility preservation options may be limited for youth who are earlier in puberty
    - Puberty blockers alone do not impact fertility.
    - If puberty blockers are started prior to the completion of puberty, and then gender-affirming hormones are added, fertility preservation options may be limited. The degree to which fertility is impacted depends on where a patient is in puberty prior to initiation of puberty blockers.
    - For patients who are interested in fertility preservation, this should ideally be completed prior to starting puberty blockers.
    - Sperm banking and egg harvesting may not possible until Tanner stage 3-4. Cryopreservation in earlier puberty stages is not widely available
    - Patient, family, and provider should balance possible loss of fertility against further advancement of non-reversible pubertal changes

- Limitations of future surgery options
    - Patients AMAB may require peritoneal or intestinal vaginoplasty instead of penile skin inversion if puberty blockers are started in early puberty
- Potential decreased bone mineral density
- Decreased growth velocity to prepubertal range and potential effects on final adult height
- Case reports of sterile abscesses, anaphylaxis, and increased seizure frequency
- Case reports of prolonged QT (in older adult men)

Baseline evaluation:

- Labs: Ultrasensitive LH (sometimes called "pediatric assay"), FSH, endogenous sex steroid (estradiol or total testosterone), vitamin D 25OH.
    - Labs are best done in the morning (before 9am) especially in early puberty when there can be diurnal secretion of LH and estradiol/testosterone.
    - Ultrasensitive LH >0.3 mIU/mL is generally considered to be a marker of puberty starting, but this may vary based on the lab assay used (check the lab reference ranges for Tanner stage)
- Imaging:
    - DXA scan is recommended by the Endocrine Society. Not a requirement in our practice, but emphasis should be placed on those patients with risk factors for low bone mineral density (primary bone disease, inflammatory bowel disease, irritable bowel disease, cerebral palsy, inactivity, disordered eating, alcohol use, tobacco use, Depo Provera, glucocorticoids, or a history of nontraumatic fractures)
    - Consider bone age x-ray to determine starting bone age and how much growth potential is remaining especially if the patient has pre-existing growth concerns

- Consider EKG if there is a family history of prolonged QT or sudden cardiac death, patient is on QT prolonging medications (listed below), or has symptoms of prolonged QT such as syncope. In patients with a history of structural heart disease or arrhythmias their case should always be discussed with their primary cardiologist before initiating treatment.
    - In theory, the highest risk population is AMAB with adult levels of testosterone that are suddenly dropped. There have not been reports of prolonged QT in children or individuals AFAB.
    - Common QT prolonging medications:
      Antibiotics: azoles, macrolides (azithromycin, erythromycin), fluoroquinolones (ciprofloxacin, ect)
      Antidepressants: sertraline, fluoxetine, venlafaxine, amitriptyline, imipramine, citalopram
      Antipsychotics: haloperidol, ziprasidone, quetiapine, thioridazine, olanzapine, risperidone
      Others: methadone, sumatriptan, ondansetron, diphenhydramine

Follow up labs:

- Use standard LH for monitoring. Ultrasensitive/pediatric LH should only be used for initial labs to determine if the patient has started puberty.
- There are no clear cut offs for lab monitoring but below serve as general guidelines. Your lab may have different values. Always interpret in the context of clinical puberty progression.
- Histrelin implant: obtain random labs 1-3 months after placement: LH, estradiol or total testosterone (based on sex assigned at birth)
    - Goal LH < 3, estradiol < 20, testosterone < 30
- Leuprolide injections: obtain stimulated labs 1 hour after 2nd injection: LH, estradiol or total testosterone
    - Goal LH < 4, estradiol < 20, total testosterone < 30
    - If unable to obtain stimulated labs, can check random levels in between injections and use goal values listed above for histrelin implant
    - Stimulated labs mimic a leuprolide stimulation test, and results are interpreted differently than random levels
- Check labs once after starting pubertal suppression, then repeat if there is any clinical pubertal progression. Endocrine Society guidelines recommend checking labs every 6-12 months, but we often will repeat labs only if there is concern for clinical progression.
- If labs are abnormal:
    - If LH is mildly elevated and estradiol/testosterone is low, monitor for pubertal progression clinically
    - If significantly elevated LH and/or elevated sex steroid, monitor more closely for clinical pubertal progression and repeat labs in 3 months

Consider repeat DXA every 1-2 years if low BMD at baseline or on GnRH agonist for longer than 2 years without additional hormone therapy

- Consider repeat bone age every 1-2 years if concerns about linear growth

<u>Additional considerations:</u>

Timing of starting blockers:

- Earliest time to start is Tanner stage 2 (Tanner 2 breast buds or >4cc testicles AND ultrasensitive LH >0.3 mIU/mL)
- Latest time to start is 2 years post-menarche for patients AFAB. In patients who are >1 year post-menarche, there is a higher risk of hot flashes. Consider using menstrual suppression instead of puberty blockers after this time if pubertal changes seem to be complete.
- Can be started as late as Tanner 5 (post pubertal) for AMAB if preferred over androgen blocker

Dosing:

- We start the same starting dose for everyone.
- Increase dose if there is continued pubertal progression and labs showing puberty is not suppressed

Changing formulations:

- If switching from injections q3 months to implant, implant should be placed within 3 months of last injection

Discontinuing blockers:

- There is no consensus for when to discontinue after starting gender-affirming hormones
- People with ovaries: Testosterone suppresses estrogen production. Can discontinue blockers when testosterone level >100 and/or on testosterone for >3-6 months. Some may choose to continue blockers until Testosterone is at adult levels (400-700).
- People with testicles: Estradiol does NOT suppress testosterone completely. When Estradiol is at adult levels (>100), can consider either continuing puberty blockers or transitioning to spironolactone until orchiectomy

References:

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- Bangalore Krishna K, et al. Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium. Horm Res Paediatr. 2019;91(6):357-372.
- Hembree, Wylie C et al. "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline." The Journal of clinical endocrinology and metabolism vol. 102,11 (2017): 3869-3903. doi:10.1210/jc.2017-01658

Testosterone

Formulations and dosing:

Subcutaneous

Testosterone cypionate 200 mg/mL

- 1 mL vials. Vials are labeled as single use, but are often reused for multiple injections.
- Contains cottonseed oil
- Preferred formulation due to more availability
- Can be administered IM or subQ at same dosing, we recommend subQ due to easier administration (typically using 25G 5/8" needle with 1 mL syringe). SubQ is off label and may confuse the pharmacy but is well supported in the literature.
- Also available in 100 mg/mL concentration in a 10mL vial, but we do not use this in our clinic to keep consistency and avoid dosing errors

Testosterone enanthate 200 mg/mL

- 5 mL vials.
- Contains sesame oil
- Can be used if there is local reaction/allergy to cypionate. Dosing is equivalent.
- Can be administered IM or subQ at same dosing, we recommend subQ due to easier administration.

Initial dosing:

Lower dose – 20 mg (0.1mL) every week (patient on puberty blockers or younger age 13.5-14 years old)

Standard dose - 30 mg (0.15mL) every week (ages 15-16)

Higher dose – 40 mg (0.2mL) every week (ages 17-18)

Dose titration – Increase by 10-20 mg every 3-6 months. Max adult dose 100 mg weekly.

- We usually recommend weekly (instead of every 2 weeks) dosing for more consistent hormone levels.

Example dosing titration for patient starting at low dose:

- 20 mg every week x3-6 months
- 30 mg every week x3-6 months (this dose is typically continued until at least age 15)
- 40 mg every week x3-6 months
- 50 mg every week x3-6 months
- Continue to increase by 10 mg every 3-6 months as desired based on physical and emotional effects and testosterone levels
- Adult testosterone levels can be reached with dosing anywhere from 50-100 mg weekly
- Younger patients typically increase by 10 mg every 6 months, older patients increase by 10-20 mg every 3 months (if desired)

Transdermal Gel

Androgel 1% gel pump or packet

- 1 pump = 12.5 mg
- Packets are available in 25 mg/packet or 50 mg/packet
- 1% gel is preferred for WA state medicaid

Androgel 1.62% gel pump or packet

- 1 pump = 20.25 mg
- Packets are available in 20.25 mg/packet or 40.5 mg/packet

Formulation specific side effects:

- Potential for skin irritation and sensory processing intolerance
- Variable absorption and testosterone levels achieved
- May transfer to other people via skin to skin contact. Must be extremely cautious around small children and pregnant people.

Initial dosing:

Lower dose – 1 pump (1%/12.5mg) once a day
Standard dose - 1 pump (1%/12.5 or 1.62%/20.25mg) once a day
Higher dose – 2 pumps once a day
Dose titration – Increase by 1 pump once a day every 3-6 months. Max adult dose 81 mg (4 pumps) of 1.62% gel or 62.5 mg (5 pumps) of 1% gel.

Prescription tips:

- Some insurances may prefer to cover 1% vs 1.62%, or pump vs packet. There may be high out of pocket costs even with insurance coverage. WA state medicaid may cover 1% gel fully.
- Instructions to apply need to match the mechanism of delivery (i.e. pump vs. packets)
- This is a handy reference for gel dosing and application: Dosing Information for AndroGel (testosterone gel) 1.62% CIII (https://www.androgel.com/hcp/dosing-titration)
- When prescribing anything OTHER than testosterone cypionate, you must document clearly in your clinic note why you are prescribing something else, besides patient preference (i.e. needle phobia, site reaction, etc) for insurance coverage

Transdermal Patch

Androderm patch

- Only 2 mg and 4 mg patches available
- CANNOT cut patch (reservoir patches dose dump if cut)

Formulation specific side effects:

- High rates of skin irritation
- Variable absorption and testosterone levels achieved

Initial dosing:
Lower dose – 2 mg every other day
Standard dose - 2 mg once a day
Higher dose – 2 mg once a day
Dose titration – Increase by 2 mg every 3-6 months. Max adult dose 8 mg (need to apply 2 patches). *Because there is less control over titration of dose, this form is less ideal for younger patients.*

Prescription tips:
- 2 mg patches only come in box of 60 → must write for #60
- 4 mg patches come in box of 30 → can write for #30 or #60
- For patients on both 4 mg and 2 mg patches → need to write both for #60
- When prescribing anything OTHER than testosterone cypionate, must document clearly in your clinic note why you are prescribing something else, besides patient preference (i.e. needle phobia, site reaction, etc) for insurance coverage
- There may be high out of pocket costs even with insurance coverage ($200-300).

Considerations for dosing (age/puberty stage/weight/effects/etc)
- ***Patient goals*** for desired effects and rate of changes
- ***Age of patient.*** For younger patients, testosterone's changes and testosterone levels should increase over the course of 1-2 years to mimic puberty. Older patients can increase more quickly if desired. We typically recommend injections for patients under age 15 to start lower doses and titrate more slowly.
- ***Testosterone levels.*** Typical adult total testosterone levels are 400-700 ng/dL but vary widely based on the lab facility. Use your lab's reference ranges. Trough levels should not exceed 700 ng/dL. Total testosterone level can be falsely low in patients with higher BMI due to low SHBG. Patients with goals for fewer physical changes may not desire testosterone levels in the adult range.
- ***Menses.*** Amenorrhea typically occurs after 3-6 months even on low dose testosterone. If patient is continuing to have menses, increasing testosterone dose may be needed to help them achieve amenorrhea.

Considerations if changing formulations
- There is no clear dosing equivalent between forms of testosterone. If a patient is on a lower dose of one form, we generally switch to a lower dose of a different form if they choose to change formulations.

Changes associated with testosterone:
- Voice deepening*
- Facial hair and body hair*
- Clitoromegaly*
- Body fat redistribution
- Increased muscularity
  *indicates permanent changes

Side effects:

- Acne
- Mood swings/emotional changes: often described as emotions feeling more simple or less complex, less sensitive, less tearful. Some patients report more irritability or impatience.
- Increased libido
- Androgenic hair loss: very dependent on genetics, a later change and less likely to occur during testosterone puberty

Risks:

- Erythrocytosis (hematocrit >50%)
    - If HCT 50-52%, hydrate and repeat labs in 1-3 months.
    - If HCT 52-54%, hydrate and repeat labs in 1-3 months. Consider therapeutic phlebotomy and decreasing testosterone dose or route switch (we see erythrocytosis more frequently with injectable testosterone than transdermal)
    - If HCT >54%, start therapeutic phlebotomy and either decrease testosterone dose or switch routes
    - Always consider other potential causes for elevated HCT including sleep apnea and cigarette smoking. Management of these may improve HCT such that testosterone does not need to be adjusted
- Dyslipidemia: increase LDL, decrease HDL
- May affect fertility.
    - The degree to which testosterone impacts fertility is not fully known.
    - Pregnancy can occur in patients taking testosterone EVEN IN THE ABSENCE OF MENSES, thus all patients should be counseled accordingly and should use contraception if they are engaging in any sexual activity that could result in pregnancy.
    - Consider fertility preservation prior to starting testosterone if the patient is interested.
    - Additional information about fertility preservation for patients can be found here: https://www.seattlechildrens.org/globalassets/documents/for-patients-and-families/pfe/pe3359.pdf
- *Previously, liver dysfunction, coronary artery disease, and hypertension were thought to be risks, but recent studies do not show a clinically significant risk. Breast and uterine cancer has also been listed as a theoretical risk previously, but there have only been few case reports showing this and no evidence of a true increased risk.*

Lab monitoring:

Baseline

- Total testosterone by LC/MS, estradiol, hematocrit

Follow up

- Total testosterone by LC/MS, hematocrit
- Check every 3 months until on maintenance dosing, then check every 6 months. Labs are typically done annually for adults on stable testosterone dosing

PRN

- Urine hcg if at risk for pregnancy based on sexual history
- AST/ALT, lipid panel, A1c (if patient has risk factors or family history of liver dysfunction, obesity, hyperlipidemia, diabetes)

Lab timing:

- Injections: labs should be checked the day prior to injection if given weekly (trough), or midway point between injections if given every 2 week
- Gel or patch: get labs at least 5 hrs after application

*if labs return very high levels of testosterone on average doses, the draw site may have been contaminated by the testosterone product. Verify dose and have draw repeated.

Formulation	*Starting dose-low dose*	*Starting dose-standard*	*Starting dose-higher dose*	*Max adult dose*	*Notes*
Testosterone cypionate	20 mg once a week	30 mg once a week	40 mg once a week	100 mg once a week	SQ or IM
Testosterone patch	2 mg every other day	2 mg daily	2 mg daily	8 mg daily	
Testosterone gel	1 pump daily	2 pumps daily	3 pumps daily	4-5 pumps daily	1% or 1.62%

References:

Guidelines

- Hembree WC et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Nov 1;102(11):3869-3903.
- UCSF Guidelines: https://transcare.ucsf.edu/guidelines/masculinizing-therapy

Formulations

- McFarland J et al. Serum Testosterone Concentrations Remain Stable Between Injections in Patients Receiving Subcutaneous Testosterone. J Endocr Soc. 2017 Jul 21;1(8):1095-1103.
- Laurenzano S et al. Subcutaneous Testosterone Is Effective and Safe as Gender-Affirming Hormone Therapy in Transmasculine and Gender-Diverse Adolescents and Young Adults: A Single Center's 8-Year Experience. Transgend Health. Epub ahead of print Feb 2021.

Risks

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- Jarin J et al. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics. 2017;139(5):e20163173.
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Lab monitoring

- Allen AN et al. Dynamic Impact of Hormone Therapy on Laboratory Values in Transgender Patients over Time. J Appl Lab Med. 2021 Jan 12;6(1):27-40.

Menstrual Suppression

- For patients who are menstruating, please consider discussing and starting menstrual suppression if menses are causing distress.
- Menstrual suppression can be used alone or in combination with testosterone.
- Menstrual suppression can be achieved with the same medications typically used for contraception.
- For patients who do not need contraception, Aygestin (norethindrone acetate pills) is the most common form of menstrual suppression we use. Patients often prefer this because of the ease of taking pills, and many patients do not want to take pills containing estrogen if this does not align with their gender identity. Aygestin is started at 5 mg (1 tab) once a day, and can be increased to 10 mg (2 tabs) once a day if the patient continues to experience bleeding or spotting.

Treatment	Additional Benefits	Potential Risks
Oral combined contraceptive pills	- Provides contraception	- Contains estrogen - Abnormal uterine bleeding if missed doses
Norethindrone acetate (oral pill, brand name Aygestin 5 mg)	- Does not contain estrogen	- Not approved for contraception - Abnormal uterine bleeding if missed doses
Norethindrone (oral pill, brand name Micronor 0.35 mg)	- Does not contain estrogen	- Less effective contraception - Abnormal uterine bleeding if missed doses
Depo medroxy progesterone acetate (IM, Depo Provera)	- Does not contain estrogen - Provides contraception - 3 month interval	- Possible weight gain - Possible mood changes
Subdermal etonorgestral implant (Nexplanon)	- Provides excellent contraception - Long-term (lasts 3-5 years)	- Requires insertion and removal - Higher rates of abnormal uterine bleeding
Levonorgestrel intrauterine device	- Provides excellent contraception - Long-term (lasts 5-7 years) - 50-80% experience amenorrhea	- Requires gynecological exam and intrauterine insertion

- Carswell JM, Roberts SA. Induction and Maintenance of Amenorrhea in Transmasculine and Nonbinary Adolescents. Transgend Health. 2017;2(1):195-201. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5684657/

Estradiol

Formulations and dosing:

Transdermal Patch

Estradiol patch

- Multiple brands available in a wide range of doses (25 mcg-100 mcg).
- Some patches are changed twice weekly and some are changed weekly, depending on the brand. Either can be used depending on patient preference and insurance coverage.
- Dosing of patch is listed as mcg/24hr. Dosing is the same for weekly and twice weekly patches.
- Commonly used brands are Climara (weekly) and Vivelle Dot (twice weekly)
- Can cut patch for lower dosing. Can apply multiple patches for higher dosing.

Initial dosing:
Lower dose – 6.25-12.5 mcg (1/4 - 1/2 of 25 mcg patch)
Standard dose - 25 mcg patch
Higher dose – 37.5 mcg patch
Dose titration – Increase by 12.5-25 mcg every 3-6 months. Typical adult dose is 100-200 mcg. Max adult dose 400 mcg.

Oral/Sublingual

Estradiol pills (17 beta- estradiol)

- Only available in 0.5 mg, 1 mg or 2 mg tablets
- Often recommended to use sublingual administration to bypass 1st pass metabolism
- Typically taken once a day. Consider BID dosing if >2 mg/day.

Initial dosing:
Lower dose – 0.5 mg daily
Standard dose - 1 mg daily
Higher dose – 2 mg daily
Dose titration – Increase by 0.5-1mg every 3-6 months. Typical adult dose is 4-6 mg. Max adult dose 8 mg.

Subcutaneous

Estradiol valerate 10 mg/mL, 20 mg/mL, or 40 mg/mL

- 5 mL vials
- Sesame oil or castor oil
- Can be administered IM or subQ at the same dosing. We recommend subQ due to easier administration. Limited data is available on subQ dosing.
- Estradiol valerate seems to be used more in gender care (compared to estradiol cypionate) and may give more consistent estradiol levels.
- Avoid in younger adolescents due to risk of higher levels.

Initial dosing:
Lower dose – 1-2 mg every week
Standard dose – 2-3 mg every week
Higher dose – 4 mg every week
Dose titration – Increase by 1-2 mg every 3-6 months. Max adult dose 6-8 mg weekly.

- We usually recommend weekly (instead of every 2 weeks) dosing for more steady hormone levels.

Estradiol cypionate 5 mg/mL

- 5 mL vials
- Cottonseed oil
- Can be administered IM or subQ at the same dosing. We recommend subQ due to easier administration. Limited data is available on subQ dosing.

Initial dosing:
Lower dose – 1 mg every week
Standard dose - 2 mg every week
Higher dose – 2 mg every week
Dose titration – Increase by 1 mg every 3-6 months. Max adult dose 5 mg every week.

- We usually recommend weekly dosing for more steady hormone levels. However, limited dosing data is available and the only protocols found listed every 2 week dosing for estradiol cypionate.

Considerations for dosing (age/puberty stage/weight/effects/etc)

- ***Patient goals*** for desired effects and rate of changes
- ***Age of patient.*** For younger patients, physical and emotional changes and estradiol levels should increase over the course of 1-2 years to mimic puberty. Older patients can increase more quickly if desired.
- ***Estradiol levels.*** Typical adult ranges are 100-200 pg/mL, but physiologic estradiol levels can increase to 300 pg/mL during some phases of the cycle. Patients who want fewer changes in response to estrogen may not desire estradiol levels in the physiologic range.
- ***Testosterone levels***. Estradiol can decrease testosterone levels at higher doses. If GnRH agonists are used, this will suppress testosterone and lower estradiol levels can be used. If estradiol is used in combination with spironolactone, we often aim for total testosterone <50 ng/dl to decrease further changes from testosterone. Generally, testosterone is more significantly suppressed by increasing the estradiol dose than the spironolactone dose.
- ***Side effects.*** If a patient is at high risk of blood clots, aim for the lowest dose of estradiol possible (often used with puberty blockers to suppress testosterone). Transdermal estradiol has the lowest risk of blood clots compared to other formulations and should be used if possible.

Considerations if changing formulations

- There is no clear dosing equivalent between forms of estradiol. If a patient is on a lower dose of one form, we generally switch to a lower dose of a different form if they choose to change formulations.

Changes in response to estradiol:

- Breast development*
- Skin softening
- Body fat redistribution

*indicates permanent changes

Side effects:

- Headaches/migraines
- Mood swings/emotional changes
- Nausea

Risks:

- Thromboembolic disease
    - Most of the data showing increased risk of thromboembolic disease is based on contraception use with ethinyl estrogen-containing OCPs. Research on oral/sublingual 17 beta estradiol shows lower risk of thromboembolic disease, and even lower risk (if any) with transdermal estradiol.
    - While this is not specific to estradiol use in gender-affirming care, the CDC MMWR can be a helpful resource to consider risks of estradiol use in patients with specific underlying diseases (https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6503.pdf, page 57 appendix D).
    - If a patient has a high risk of blood clots (personal history of blood clot, known thrombogenic mutation), we typically recommend consultation with hematology prior to starting estradiol
    - History of migraine with aura has been associated with an increased risk of ischemic stroke in patients taking ethinyl estradiol, but this has not been studied with 17 beta estradiol use.
    - Tobacco use and uncontrolled hypertension can also increase risk of thromboembolic disease
- Macroprolactinoma
    - Estrogen can increase growth of pituitary lactotroph cells.
    - Reports of prolactinomas with long-term high-dose estrogen. Only a few case studies reported prolactinomas, not in large cohorts.
    - Prolactin levels usually return to normal range with reduction or discontinuation of estrogen.
    - Risk is likely very low and prolactin screening is only recommended for patients with symptoms of prolactinoma.
- Breast cancer (if there is a genetic family risk such BRCA mutation)
- Cholelithiasis

- May affect fertility.
    - The degree to which estradiol impacts sperm quality and quantity is not completely known. Patients who are sexually active in ways that may result in a pregnancy should be counseled to use contraception if they desire pregnancy prevention.
    - If a patient is interested in completing fertility preservation, this should be completed prior to starting estradiol or Spironolactone.
    - Additional information about fertility preservation for patients can be found here: https://www.seattlechildrens.org/globalassets/documents/for-patients-and-families/pfe/pe3359.pdf

Lab monitoring:

Baseline

- Estradiol, total testosterone by LC/MS
- LH (if considering GnRH agonist as anti-androgen)
- Potassium, BUN, creatinine (if considering spironolactone as anti-androgen)

Follow up

- Estradiol, Total testosterone by LC/MS
- If using spironolactone: potassium, BUN, creatinine
- Check every 3 months until on maintenance dosing, then check every 6 months.

PRN

- Lipid panel, A1c (if patient has risk factors or family history of obesity, hyperlipidemia, diabetes)

Lab timing:

- Injections: labs should be checked the day prior to injection if given weekly (trough), or midway point between injections if given every 2 weeks
- Patch: get labs at least 24 hrs after application
- Oral/SL: get labs at least 4 hours after dose administration

Formulation	*Starting dose-low dose*	*Starting dose-standard*	*Starting dose-higher dose*	*Max adult dose*	*Notes*
Oral estradiol	0.5 mg/day	1 mg/day	2 mg/day	8 mg/day	PO vs SL Consider BID if >2mg/day
Estradiol patch	6.25-12.5 mcg/ 24hr (1/4 - 1/2 of 25mcg patch)	25 mcg/ 24hr	37.5 mcg/ 24hr	400 mcg/ 24hr	Once or twice a week (based on patch type)
Estradiol valerate	1-2 mg/week	2-3 mg/week	4 mg/week	6-8 mg/week	SQ or IM
Estradiol cypionate	1 mg/week	2 mg/week	2 mg/week	5mg/week	SQ or IM

References:

Guidelines

- UCSF Guidelines: https://transcare.ucsf.edu/guidelines/feminizing-hormone-therapy
- Hembree WC et al.. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Nov 1;102(11):3869-3903.

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- Oriowo MA et al. A comparison of the pharmacokinetic properties of three estradiol esters. Contraception. 1980 Apr;21(4):415-24.
- Cirrincione LR et al. Sublingual Estradiol Is Associated with Higher Estrone Concentrations than Transdermal or Injectable Preparations in Transgender Women and Gender Nonbinary Adults. LGBT Health. 2021 Feb-Mar;8(2):125-132.

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- Olson-Kennedy J et al. Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. J Adolesc Health. 2018 Apr;62(4):397-401.

Lab monitoring

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Spironolactone

Available in 25mg, 50mg, and 100mg tablets.

Timing of initiation

- Typically started in late or post-pubertal patients with testicles prior to starting estradiol or at the time of starting estradiol (as an alternative to puberty blockers)

Potential benefits

- Androgen antagonist. Decreases facial/body hair growth.
- Spironolactone alone does not typically cause a significant decrease in testosterone levels though decreases in testosterone levels can occur when used in conjunction with estradiol.
- Gynecomastia (considered a benefit if patient desires breast development)

Potential risks

- Hyperkalemia (biggest risk in patients with underlying kidney disease)
- Increased urination
- Low blood pressure, pre-syncope
- Gynecomastia (considered a risk if patient does not desire breast development)
- Decreased sperm motility can occur with Spironolactone use. Patients interested in completing fertility preservation should do so prior to starting Spironolactone.

Dosing

- Initial: 25 mg PO BID
- Increase by 25 mg BID every 3-6 months
- Max: 100 mg PO BID

Monitoring

- Check potassium, BUN, creatinine levels at baseline and q3 months while titrating dose.
- Increase based on clinical effects.

References:

- Angus LM et al. A systematic review of antiandrogens and feminization in transgender women. Clin Endocrinol (Oxf). 2021 May;94(5):743-752.

Progesterone

Bio-identical micronized progesterone (prometrium) is preferred.

Limited data is available on the use of progesterone in gender-affirming care. There are some potential reported benefits, and few risks. We often consider a trial of progesterone if patients are interested after they have been on estradiol for 2-3 years.

Timing of initiation

- We often consider a trial of progesterone if patients are interested after they have been on estradiol for at least 2 years (some providers and patients choose to start as early as 6 months)

Potential benefits

- Breast development
- Central androgen blocker
- Positive emotional effects

Potential risks

- Mood swings/emotional changes (rarely worsening of depression)
- Acne
- Some reports of tubular breast shape or decreased breast development if started too early (limited data available)
- Caution: capsule has peanut seed oil, do not use if patient has a **peanut allergy**

Dosing (Prometrium)

- Initial: 100 mg PO qHS
- Max: 200 mg PO qHS

Monitoring

- No lab monitoring or follow up needed.
- Increase based on clinical effects.
- Discontinue if there are no benefits.

References:

- Jain J et al. Medroxyprogesterone Acetate in Gender-Affirming Therapy for Transwomen: Results From a Retrospective Study. J Clin Endocrinol Metab. 2019 Nov 1;104(11):5148-5156.
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- Wierckx K et al. Clinical review: Breast development in trans women receiving cross-sex hormones. J Sex Med. 2014 May;11(5):1240-7.

Summary of Baseline Labs for Primary Care Providers

These are things that may be helpful to discuss with your patient prior to their initial visit at the Seattle Children's Gender Clinic (SCGC).

Baseline labs:
Labs need to be done prior to starting puberty blockers or gender-affirming hormone therapy. Ordering labs for your patient prior to their first visit at SCGC will help get these started more quickly. Labs should be drawn at least 2 weeks prior to the SCGC appointment.
Please fax lab results to 206-985-3499.

A patient must be in puberty (at least Tanner 2) to start puberty blockers. The earliest we typically start estradiol or testosterone is age 13.5-14.

For patients interested in **puberty blockers**:
**Labs are best done in the morning (before 9am) especially in early puberty when there can be diurnal secretion of LH and estradiol/testosterone.

- Ultrasensitive LH (sometimes called "pediatric assay")
- FSH
- Endogenous sex steroid (estradiol or total testosterone by LC/MS)
- Vitamin D 25OH

For patients interested in starting **testosterone**:

- Total testosterone by LC/MS
- Estradiol (may be low if patient is on medications for menstrual suppression or contraception)
- CBC (no diff)
- Consider AST/ALT, lipid panel, A1c (if patient has risk factors or family history of liver dysfunction, obesity, hyperlipidemia, diabetes).
- Hcg if at risk for pregnancy based on sexual history

For patients interested in starting **estradiol**:

- Estradiol
- Total testosterone by LC/MS
- LH (if considering GnRH agonist as anti-androgen)
- Potassium, BUN, creatinine (if considering spironolactone as anti-androgen)
- Consider lipid panel, A1c (if patient has risk factors or family history of obesity, hyperlipidemia, diabetes)