GENDER-AFFIRMING CARE

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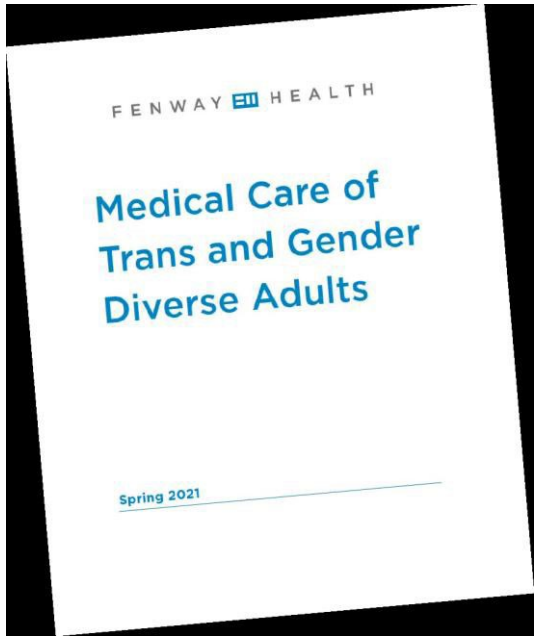
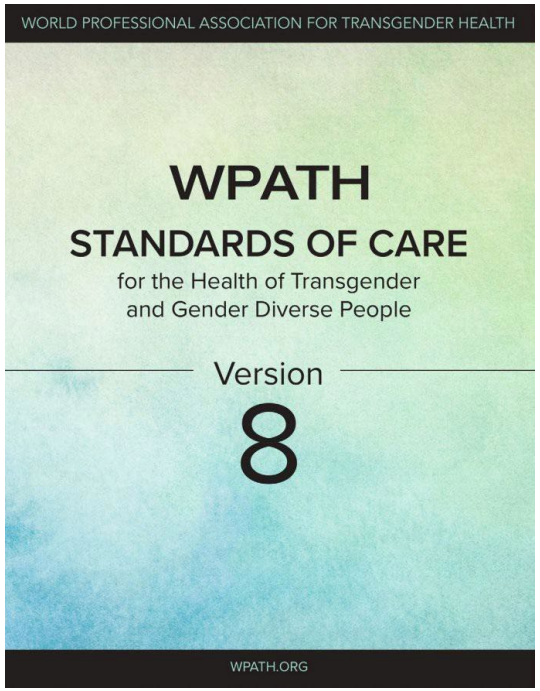
GUIDELINES AND STANDARDS OF CARE





PubMed®

UCSF Transgender Care

Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People

DISCLOSURES

- I have no disclosures

GOALS AND OBJECTIVES

1. Understand the importance of gender-affirmation
2. Discuss affirming services
3. Review the process for initiating hormone therapy
4. Provide an overview of options for GAHT (gender affirming hormone therapy)
5. Review expectations, benefits, and risks of GAHT
6. Discuss recommendations for monitoring

Why is gender affirming care important?

SIGNIFICANT HEALTH INEQUITIES EXIST

- Higher rates of reported psychological stress and suicidal ideation
- Greater incidence of HIV and other STIs
- Lower rates of cervical cancer screening
- Lower rates of mammography among transwomen
- Greater prevalence of osteopenia in transwomen

GENDER-AFFIRMING
CARE IS SAFE,
EVIDENCE-BASED,
AND LIFE-SAVING.

MULTIFACTORIAL CAUSES OF HEALTH INEQUITIES

Individual Factors

- Smoking, alcohol, other substances
- “High-risk” sexual behavior
- Low physical activity
- Nutrient-poor diet
- Obesity
- Experiences of bullying & violence
- Limited social connection
- Nulliparity

Systemic Issues

- Mistrust in healthcare system
- Stigma – both experienced & anticipated
- Lack of clinician training/competence
- Lack of data to guide decision making
- Discriminatory policies & legislation
- Economic disadvantage

GENDER AFFIRMING CARE IS PRIMARY CARE

Wellness promotion	• Inclusive preventive screening
Psychosocial Context	• Address mental health and social needs
Chronic Health Management	• Align gender affirming medications with any concurrent health conditions
Inter-professional Teamwork	• Collaborate with pharmacists, social work, registration
Engagement with Specialists	• Coordinate scope and timing of referrals

Cancer Screening

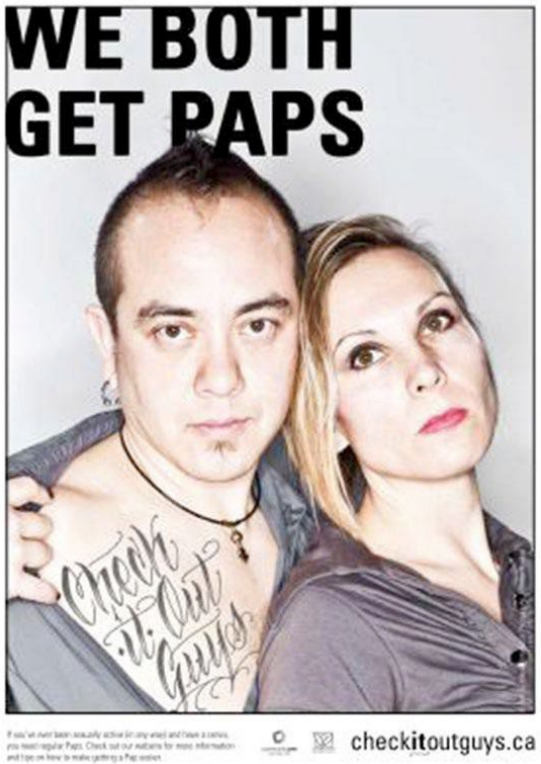
Behavioral Health

Cardiovascular Risk Assessment and Mitigation

Bone Health

Sexual Health and Family Planning

Vaccines



Older LGBTQ+ Adults

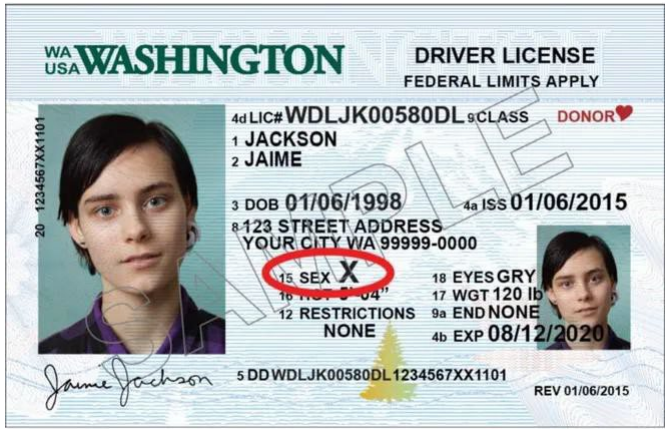
- Social Isolation:
  - 2x more likely to live alone
  - 4x less likely to have children
  - More socially connected LGBTQ+ people are healthier
- Long Term Care Concerns
  - 89% of nursing home residents fear discrimination
  - Trans/gender diverse older adults may be outed
  - Denial of visits from family of choice
- Less likely to have advanced directives

How can we affirm our patients?

SOCIAL/LEGAL GENDER AFFIRMATION

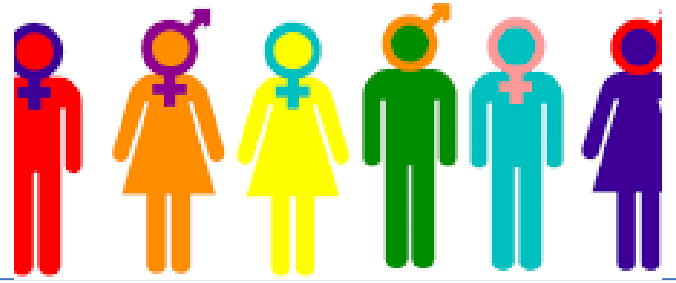
- Ask & Offer chosen names and pronouns
- Update medical record with chosen name and pronouns

- Information on legal name and sex marker change:
  https://transequality.org/documents
  People can ask for financial lenience for court costs



- Support groups
- Individual therapy
- Community events

MEDICAL GENDER AFFIRMING SERVICES



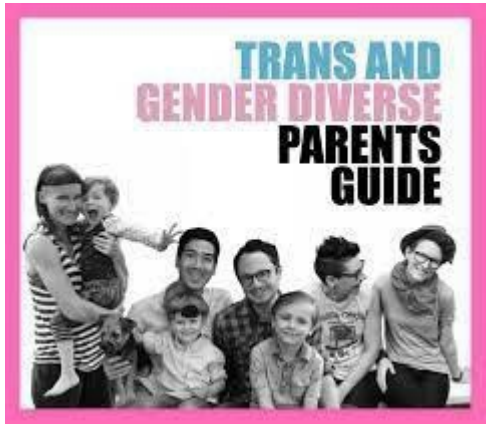
- Voice therapy
- Permanent hair removal (Laser/Electrolysis)
- Gamete storage/Cryopreservation
- Pelvic physical therapy
- Menstrual suppression
- Contraception and/or Pregnancy management
- STI testing and PREP medication
- Prosthetics

Further GENDER AFFIRMING SERVICES

- **Prosthetic devices:**
- Chest binders
- Packers
- STP devices
- Wigs
- Gaffs
- Vaginal dilators
- Breast forms

Further GENDER AFFIRMING SERVICES

- Gender affirming surgery options:
  - Masculinizing chest surgery
  - Facial feminization surgery
  - Tracheal shave
  - Vaginoplasty
  - Metoidioplasty/Phalloplasty
  - Breast augmentation
  - Hysterectomy
- Surgery referral letters, pre-op evaluation and post-op care



FERTILITY EFFECTS

~50-70% of TGD individuals desire biological children

- The effects of estrogen therapy on fertility are unknown.

- The ability to get someone pregnant may decrease significantly or stop (infertility). The time this takes and whether this becomes permanent varies greatly.

- Estrogen is NOT a reliable birth control. Other birth control methods will be necessary to prevent pregnancy if you are having genital sex with a partner who has a uterus.

FERTILITY EFFECTS

- The effects of testosterone therapy on fertility are unknown.

- The ability to have a pregnancy may decrease significantly or stop (infertility). The time this takes and whether this becomes permanent varies greatly.

- Testosterone is a TERATOGEN so if you have having genital sex with someone with sperm, it is important to use another form of contraception to prevent pregnancy

- Testosterone is NOT a reliable birth control. Other birth control methods will be necessary to prevent pregnancy if you are having genital sex with a partner who has sperm.

How to initiate GAHT therapy

Which hormone formulations can we provide

What are the expectations, benefits, and risks of GAHT

How to monitor GAHT

INFORMED CONSENT MODEL/ TREATMENT AGREEMENT

Informed Consent Model:

- Refers to communication of the risks, benefits and realistic expectations for the full range of treatment options.
- There is NO one method or right way

Goals of care:

- What are the priorities and goals?

Treatment Agreement for Estrogen Therapy

Legal Name: _____ Date of Birth: _____ Name Used: _____
Name as listed in chart Name if different from chart

The goal of this form is to provide the most up to date information about the expected effects of estrogen hormone therapy, including both desired effects and possible unwanted side effects. Hormone therapy is not the only way you can affirm yourself in your gender. Please ask questions and discuss any concerns you have with your treatment team at any time.

Estrogen (most commonly estradiol) is used to cause certain changes to the body that some people find affirming. Some people also use an androgen blocker, a medication that reduces or blocks the effects of testosterone, to further enhance the effects of estrogen. Each person's body responds to hormones differently; it is hard to predict some aspects of how your body might change. Your medical provider will review the forms of estrogen (pills, gels injections, patches) and/or androgen blockers that are best for you, based on your personal goals and any medical conditions you might have. Your medical provider will talk with you throughout treatment to best support your goals of care as safely as possible.

Our approach to gender affirming care is based on scientific evidence, national and international guidelines on hormone therapy, and the feedback and experience we get from working with gender diverse Veterans. Continuing research provides us with information on the safety and effectiveness of hormone therapy to achieve your goals. Despite available research, the long-term effects are not yet fully understood. This document outlines what we currently know about these medications.

Expected Effects of Estrogen Therapy

For someone on cis-female levels of estrogen, the associated physical changes can take several months to become noticeable and 3-5 years to fully progress. Some changes are permanent (they will not go away even if you decide to stop taking estrogen) and others are not permanent (they will likely go away if you stop taking estrogen).

Taking estrogen at doses above the cis-female range increases health risks, without making physical changes happen faster or better.

Expected Effects	Onset (months)	Maximum (years)
Breast growth (size A-B cup)*	3–12	2-3
Testicular shrinkage	3-6	2-3
Fat redistribution	3-6	2–3
Decrease in muscle mass/strength	3–6	1–2
Softening of skin	3–6	
Decreased libido	1-3	½
Decreased erections	1-3	½
Decreased sperm production	variable	>3
Slowed growth facial/body hair	6-12	>3

Treatment Agreement for Testosterone Therapy

Legal Name: _____ Date of Birth: _____ Name Used: _____
Name as listed in chart Name if different from chart

The goal of this form is to provide the most up to date information about the expected effects of testosterone hormone therapy, including both desired effects and possible unwanted side effects. Hormone therapy is not the only way you can affirm yourself in your gender. Please ask questions and discuss any concerns you have with your treatment team at any time.

Testosterone is used to cause certain changes to the body that some people find affirming. Each person's body responds to testosterone differently; it is hard to predict some aspects of how your body may change. Hormone therapy will not change some body features like bone structure or height. Your medical provider will review the forms of testosterone (injections, gels, pellets) that is best for you based on your personal goals and any medical conditions you may have. Your medical provider will talk with you throughout treatment to best support your goals of care as safely as possible.

Our approach to gender affirming care is based on scientific evidence, national and international guidelines on hormone therapy, and the feedback and experience we get from working with gender diverse Veterans. Continuing research on hormone therapy provides us with information on the safety and effectiveness of hormone therapy to achieve your goals. Despite the available research, the long-term effects are not yet fully understood. This document outlines what we currently know about these medications.

Expected Effects of Testosterone Therapy

For someone on cis-male levels of testosterone, the associated physical changes can take several months to become noticeable and 3-5 years to fully progress. Some changes are permanent (they will not go away even if you decide to stop taking testosterone) and others are not permanent (they will likely go away if you stop taking testosterone).

Taking testosterone at levels above the cis-male range increases health risks without making physical changes happen faster or better. Additionally, extra testosterone can convert into estrogen in a process called aromatization, which may slow or stop the physical effects of testosterone.

Expected Effects	Onset (months)	Maximum (years)
Facial/body hair growth*	6–12	4–5
Scalp hair loss * (if genetic)	6–12	
Deepening of voice*	3–12	1–2
Clitoral enlargement*	3–6	1–2
Increased muscle mass	6–12	2–5
Fat redistribution	1–6	2–5
Cessation of menses	2–6	
Vaginal atrophy	3–6	1–2
Skin oiliness/acne	1–6	1–2

WPATH CRITERIA FOR HORMONE THERAPY

- Persistent, well-documented gender dysphoria
  - of at least 6months
- Capacity to make a fully informed decision and consent to treatment
- Age of majority in a given country (not a minor)
- If significant medical or mental health concerns are present, they should be reasonably well controlled

Why should these medications be treated any different??

GENDER AFFIRMING HORMONE THERAPY (GAHT)

- ALL people have varying amounts of hormone in their body.
- What is affirming for some, is not for others

- Heredity and age limit the tissue response to hormones

- More is not always better

ESTROGEN/ANDROGEN BLOCKERS

- Formulations
- Effects/Timeline
- Risks/Side effects
- Monitoring

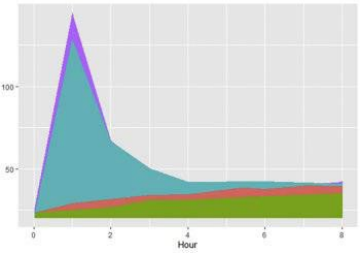
ESTROGEN OPTIONS

- **Oral Estrogens**
  - Estradiol (estrace) 2-8 mg PO or SL daily (can be divided into BID dosing)
  - Premarin (conjugated estrogens) and ethinyl estradiol

Original Article

Pharmacokinetics of Sublingual Versus Oral Estradiol in Transgender Women

Elizabeth Doll BS [1], Ian Gunsolus PhD [2], Abigail Thorgerson MPH [3], Vin Tangpricha MD, PhD [4], Nathan Lamberton PharmD, BCPS [5], Jenna L. Sarvaideo DO [6]

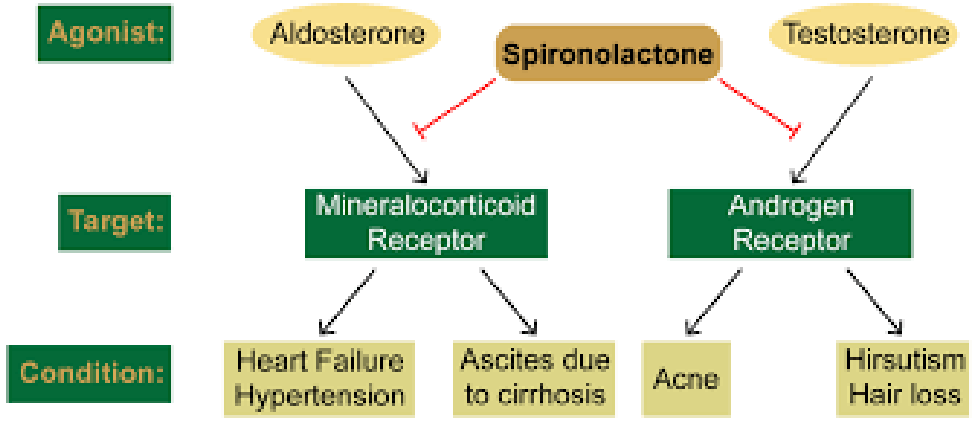


- **Injectable Estrogens**
  - Estradiol valerate 5-20mg IM q1-2 weeks
  - Estradiol cypionate 1-10mg IM q1-2weekly

- **Transdermal Estrogens**
  - Estradiol patch 0.1-0.4mg twice weekly, may start lower in patients at risk of side effects. Maximum single dose patch available is 0.1 mg
  - Estradiol gel: 1.25mg daily via packet or pump (Divigel, EstroGel)

ANTIANDROGENS

- **Spironolactone** (aldactone) 50-400mg PO BID



- Finasteride (Proscar) 2.5-5mg PO daily - Inhibits conversion of testosterone to DHT; does NOT affect systemic testosterone levels

- Progesterone, micronized 100-200mg PO qhs – Suppresses the hypothalamic-pituitary-gonadal axis

- Lupron injection IN CLINIC q3months - GnRH agonist aka LH

WHAT ABOUT PROGESTERONE?

WPATH8: “Although there are anecdotal reports of progesterone use for breast development and mood management, there is currently insufficient evidence the potential benefits of progesterone administration outweighs the potential risks.”

Potential Risks

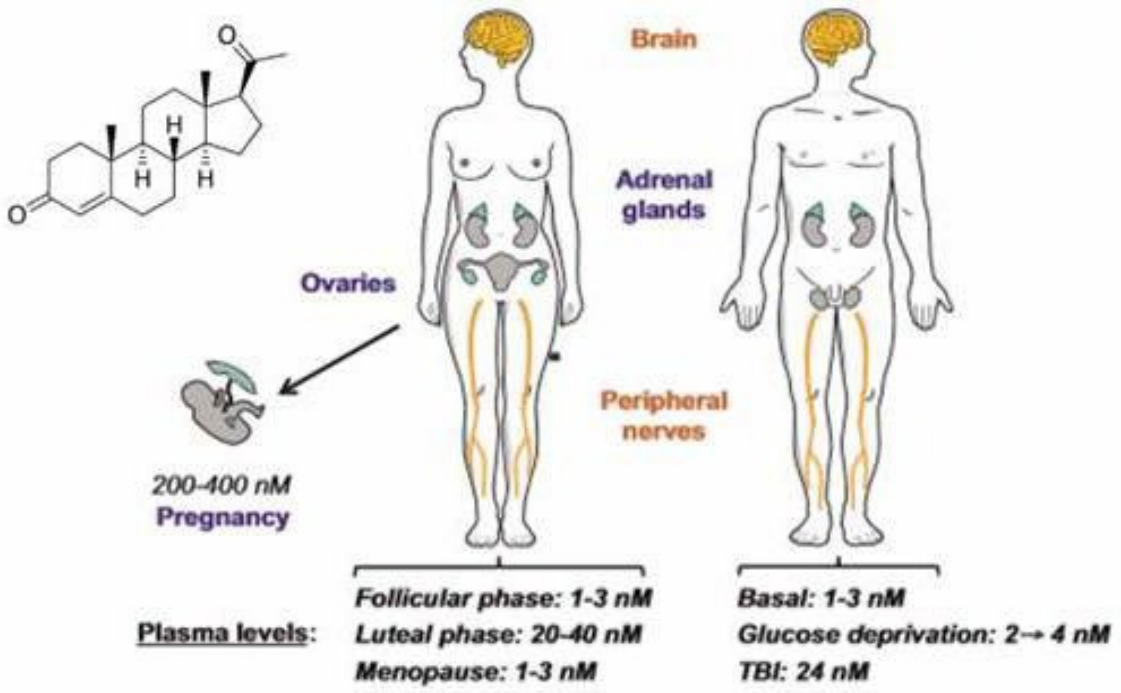
- Increased risk of cardiovascular events and breast cancer in WHI *(with Medroxyprogesterone) - but how does this translate to trans women?*
- Weight gain, fatigue, depression

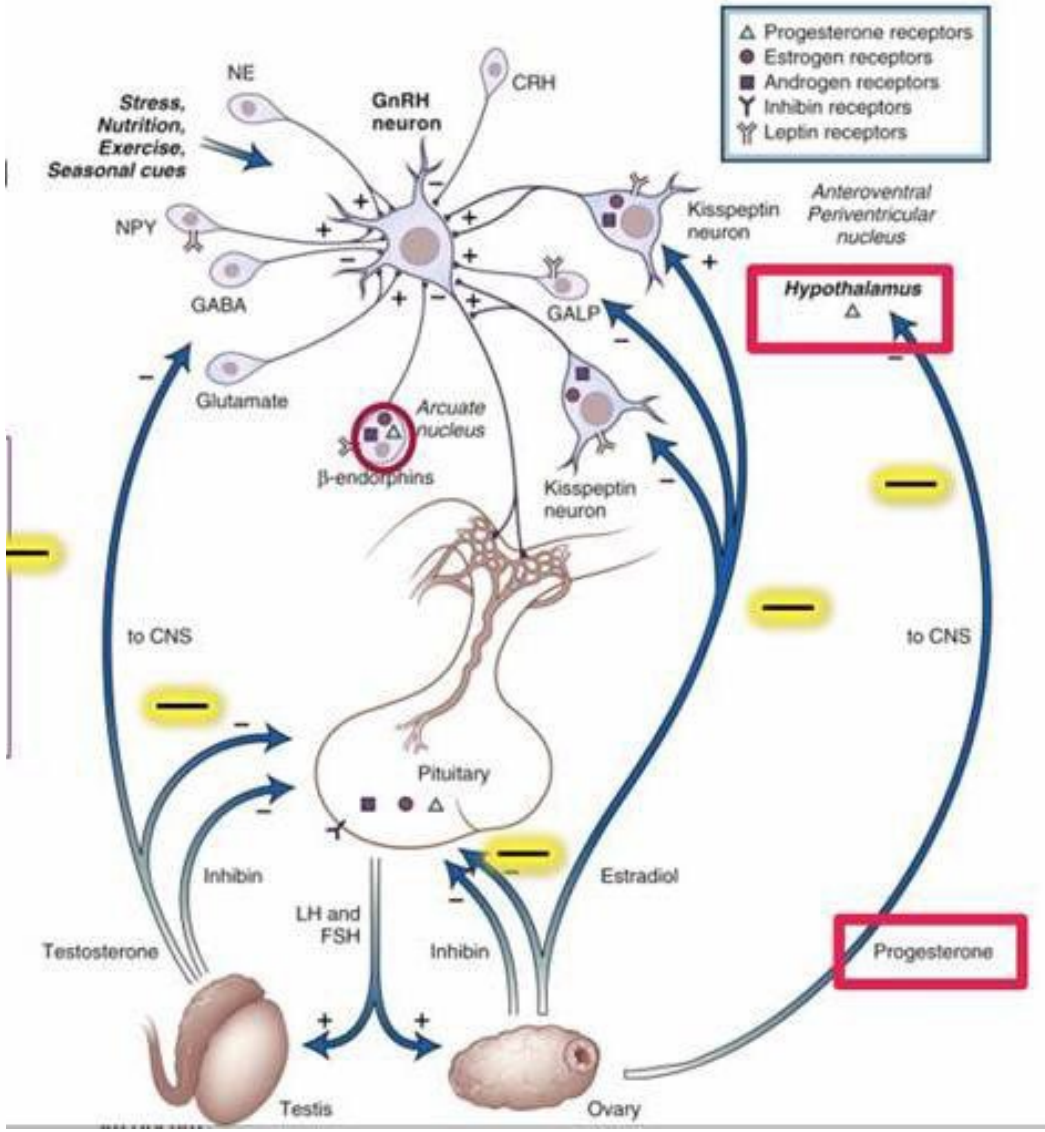
Potential Benefits

- Weight gain, moodiness/cycling
- Improved mood
- Improved libido, energy
- Anti-androgen effect
- Higher HDL, lower LDL
- Potential neuroregenerative effects

Progesterone MOA

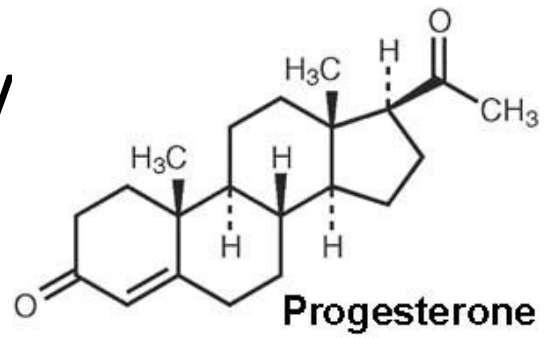
Estrogen, progesterone & testosterone create negative feedback loops that affect LH & FSH production so that innate gonads will not be stimulated to produce sex steroids





PROGESTERONE

- **Prometrium 100 mg – 200 mg po daily***
- Medroxyprogesterone 2.5 to 10 mg PO daily
- Depo-Provera 150 mg IM q 3 months



Progesterone

No quality evidence supporting benefit; potential harm of some progestins in multi-year exposure. Consider collaborative decision regarding a trial of progesterone therapy with re-evaluation within a year.

Consider daily dosing vs cyclic (10nights/month) to lower total exposure and/or to more closely mimic cis-female physiology

When selecting a medication, we advise using those which have been studied in multiple transgender populations (i.e., estrogen, spironolactone, GnRH agonists) rather than medications with little to no peer-reviewed scientific studies (i.e., bicalutamide, rectal progesterone, etc.) — WPATH8

EFFECTS OF ESTROGENS & ANTIANDROGENS

Effect	Onset (months)	Maximum (years)
Decreased Libido	1-3	
Decreased Spontaneous Erections		
Breast Growth (size A-B)*	3-6	2-3
Decreased Testicular Volume*	3-6	2-3
Decreased Sperm Production*	Unknown	Unknown
Redistribution of Body Fat	3-6	2-3
Decrease in Muscle Mass	3-6	1-2
Softening of Skin	3-6	Unknown
Decreased Terminal Hair Growth	6-12	>3

NOTE: Possible slowing or cessation of scalp hair loss, but no regrowth
No change in voice

CONSIDERATIONS ON ESTROGEN THERAPY

- Increased incidence of VTE
- ?Increased incidence of stroke.
- Rates of MI are aligned with rates seen in cisgender men

Risk Ratios of MI, VTE, and Stroke in E-treated TGW vs cis-men in three recent large cohort studies

Study		MI	VTE	Stroke
Getahun et al "Kaiser study" CA and GA, USA	N=853	1.0 (0.3-3.2)	3.2 (1.5-6.5)	2.3 (1.2-4.3)
Nota et al Netherlands	N=2517	0.79 (0.54-1.11)	4.55 (3.59-5.69)	1.80 (1.23-2.56)
Asscheman et al US and Europe	N=1248	0.75 (0.33-1.49)	3.0 (1.86-4.59)	1.05 (0.45-2.07)
Conclusion		No change	2-4x Increase	Unclear

Nota, 2019. Circulation
Asscheman, 2011. Eur J Endocrinol
Getahun, 2018. Ann Intern Med

CONSIDERATION OF ESTROGEN FORMULATIONS

ESTHER Study
Canonico, 2007

	Matched OR			
	Cases	Controls	Crude	Adjusted*
Nonuse	145	384	1	1
Oral Estrogen	45	39	3.6 (1.5-8.8)	4.2 (1.5-11.6)
Transdermal Estrogen	67	180	0.8 (0.4-1.6)	0.9 (0.4-2.1)

THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH & REVIEWS

TRANSGENDER HEALTH

Risk for Venous Thromboembolism in Transgender Patients Undergoing Cross-Sex Hormone Treatment: A Systematic Review

Check for updates

Vasanth S. Kotamarti, MD,[1] Nicolas Greige, BS,[2] Adee J. Heiman, MD,[1] Ashit Patel, MBChB,[1] and Joseph A. Ricci, MD[2]

Ethinyl estradiol	Conjucated equine estrogens	Estradiol valerate	Oral estradiol	Transdermal estradiol
3 studies	1 study	4 studies	7 studies	3 studies
293.1	49.0	31.5	34.0	11.2

Incidence of VTE per 10,000 person years

RISKS OF ESTROGEN THERAPY

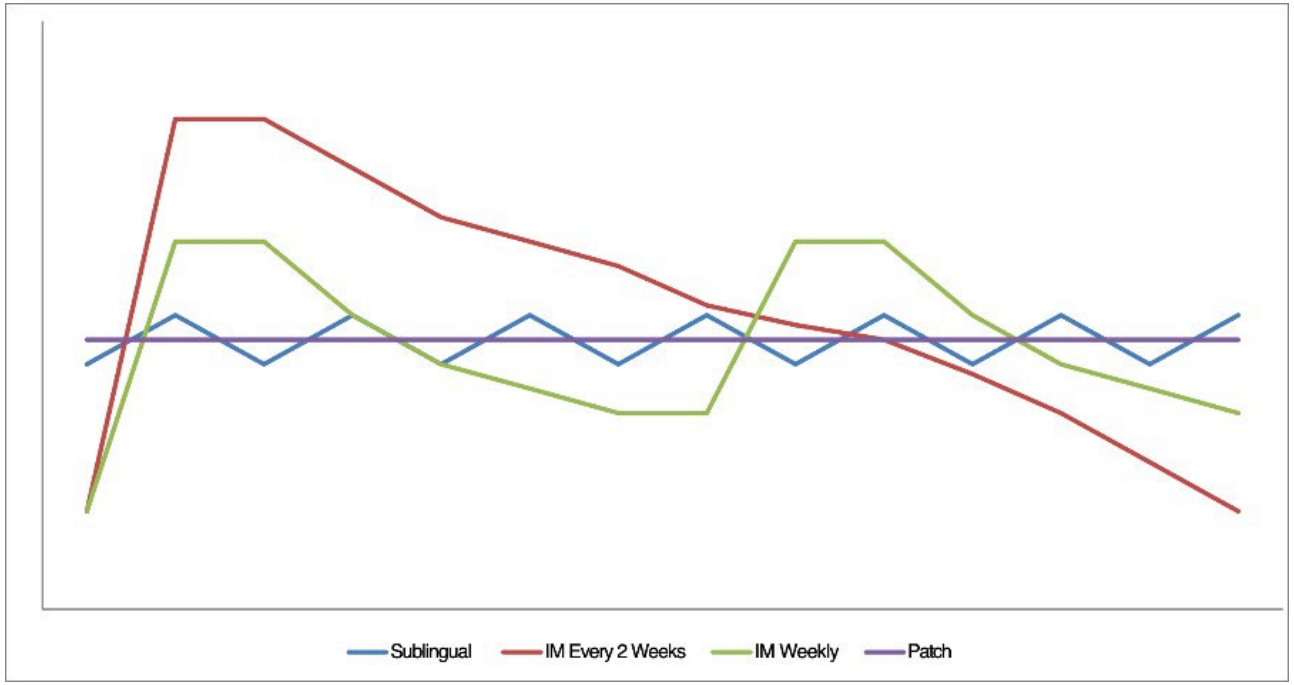
- **Venous thrombosis/ thromboembolism**
- Nausea/Vomiting
- Worsening headaches/migraines
- Liver inflammation
- Gallbladder disease
- Benign pituitary prolactinoma
- ?Mental health effects
- ?Infertility
- Breast cancer risk

LAB MONITORING

- Baseline:
  - BMP
  - Lipids, glucose, LFTs only as clinically indicated
- If on Spironolactone —
  - BMP 1 to 6 weeks after start/dosage change
  - then yearly
- Prolactin (only with +ROS)
- *Hgb/Hct will often drop into the normal female range in women on GAHT

LAB MONITORING Continued

- Serum Estradiol Levels (at 6-8weeks, 6, and 12 months then prn)
  - Ideal level = mean daily level for premenopausal ciswomen (100-200 pg/ml)*
- Serum total Testosterone level
  - Expected to be less than 50-75 ng/dl
- Timing of blood draw:
  - Injection – mid-dose
  - PO – 2hrs after
  - SL – 4-6hrs after



TESTOSTERONE

- Formulations
- Effects/Timeline
- Risks/Side effects
- Monitoring

TESTOSTERONE FORMULATIONS

CONTROLLED SUBSTANCE

Injectable Testosterone

- **Testosterone Enanthate or Cypionate** IM or SQ q1 or 2 weeks
  - Standard Weekly Dose: 50 – 100 mg / week
  - Standard Biweekly Dose: 150-200 mg / 2 weeks.
- **Xyosted Testosterone auto-injector**

Topical gels in packets and pumps

- Apply 50 – 100 mg / day
- **Androgel pump**: 1.62% gives 20.25 mg per pump
- **Androgel or Testim packets**: provide 25 mg (2.5 gm) or 50 mg (5 gm)
  - Standard dose: ~50mg
  - Marked to apply to Arm > Abdomen > Inner thigh

OPTIONS

- **Testosterone Pellet (Testopel)**
  - 8-12 self-dissolving pellets q 3 to 4 months

- **Testosterone undecanoate (AVEED) inj**
  - Long-acting. 750mg/3mL inj q 10wks
  - administered in office
  - rare cases of pulmonary oil microembolism and anaphylaxis

- **Oral Formulation: testosterone undecanoate (Jatenzo, Tlando, Kyzatraz)**
  - dosed BID with food
  - Black Box warning regarding BP increase

ADDITIONAL MEDICATIONS

- **Estrogen vaginal cream** for frontal canal atrophy
  - Also can be used for inadequate pap tests
- **Minoxadil or Finasteride** for androgenic hair loss
- **Progesterone – LARC (IUD, Nexplanon), Depo**, **PO** to aid in cessation of menses and for contraception

TIMELINE OF TESTOSTERONE EFFECTS

Effect	Onset (months)	Maximum (years)
Skin oiliness/acne	1-6	1-2
Clitoral enlargement*	3-6	1-2
Increased Sex Drive		
Cessation of Menses	2-6	
Fat redistribution	1-6	2-5
Deepening of Voice*	3-12	1-2
Facial/Body Hair Growth*	6-12	4-5
Scalp Hair Loss*	6-12	
Increased Muscle Mass and Strength	6-12	2-5
Vaginal atrophy	3-6	1-2
Emotional changes		

CONSIDERATIONS ON TESTOSTERONE THERAPY: CVD

Cardiovascular Risk:

- May increase in risk factors
- No increase in CVD morbidity or mortality

Circulation
Volume 144, Issue 6, 10 August 2021; Pages e136-e148
https://doi.org/10.1161/CIR.0000000000001003

AHA SCIENTIFIC STATEMENT

Assessing and Addressing Cardiovascular Health in People Who Are Transgender and Gender Diverse: A Scientific Statement From the American Heart Association

Reference	n	Follow-up	Treatment regimen	Outcome
Asscherman, 1989	122	Median duration of HRT of 4.4 yrs	Testosterone 250mg IM q2wks or undecanoate 120-160mg/d	No increased cardiovascular morbidity
VanKesteren, 1997	293	Mean duration HRT of 8.2yrs	Testosterone 250mg IM q2wks or undecanoate 160mg/d	No increased cardiovascular morbidity
Asscherman, 2011	365	Median duration HRT 18.5yrs	Testosterone 250mg IM q2wks or undecanoate 160mg/d	No increased cardiovascular mortality rate
Dhejne, 2011	133	Median times since SRS was 9.1yrs	Not specified	Higher mortality due to CVD compared with controls
Bazarro-Castro, 2012	37	Mean duration HRT 4.9yrs	Difference T preparations	No difference in CV morbidity compared with control men and women
Weirckx, 2013	138	Median duration HRT of 6yrs	Difference T preparations	No difference in CV morbidity compared with control men and women

RISKS OF TESTOSTERONE THERAPY

- Polycythemia
- ?Lowers HDL & Elevates TG
- ?Increases blood pressure
- ?Weight gain
- ?Increases risk of OSA
- Possible risk of liver inflammation

- **?Infertility**
- Chronic pelvic pain
- Limited long-term data: breast, endometrial tissue, ovarian tissue

RISKS OF TESTOSTERONE: Polycythemia

- Erythrocytosis occurs in 11-20% in AFAB people rx Testosterone
- May be associated with increased VTE, though evidence is weak.
- Cohort studies of 923 transmale/nonbinary individuals prescribed testosterone:
    - 104/519 patients **(20%) developed hematocrit > 50%**.
    - Thromboembolic events occurred in 5/519 patients (0.9%) with 4 (80%) meeting criteria for erythrocytosis at any time during their care.

OPTIONS TO ADDRESS POLYCYTHEMIA

- To address polycythemia (Hct > 54%):
  - Switch to weekly Testosterone injections then recheck CBC
  - Switch to Testosterone gel and recheck CBC
  - Continue current injections and regular blood donations
  - Stop Testosterone therapy *if within patient goals

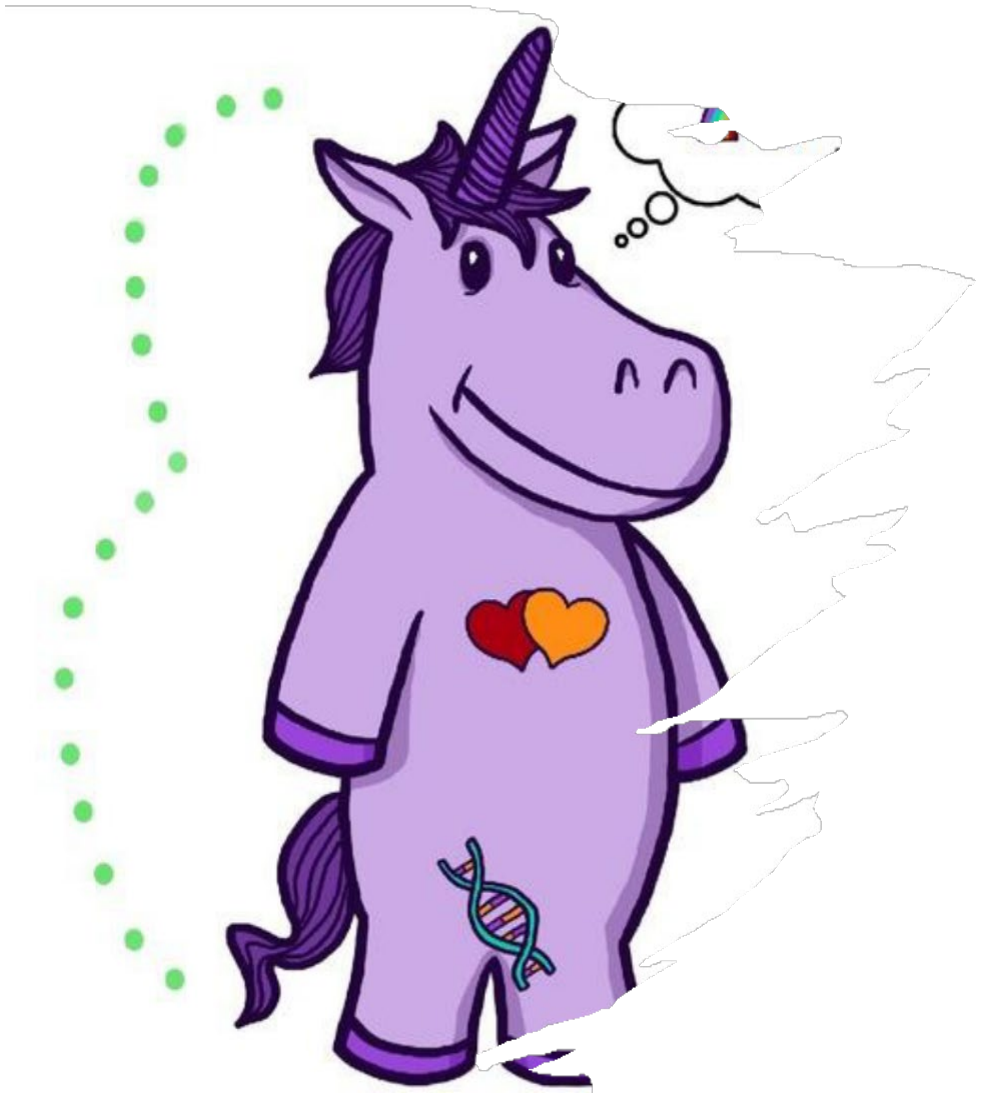
LABORATORY MONITORING

- **Baseline:**
  - Hgb/Hct
  - *Lipid Profile, only as clinically indicated
  - *Liver Enzymes, only if evidence of underlying liver disease
  - *Fasting Glucose, only if clinically indicated
  - ? Screen for PCOS with +ROS

LAB MONITORING CONTINUED

- **Serum testosterone levels + Hct/Hgb**
  - At 3, 6 & 12 months, then as clinically indicated
  - Recheck 2-3months after dosage change
  - Goal Range Total Testosterone: 400-700ng/dl
- **Estradiol levels?**
  - Goal Range: <50pg/ml
  - Do not need to check if T in therapeutic range.

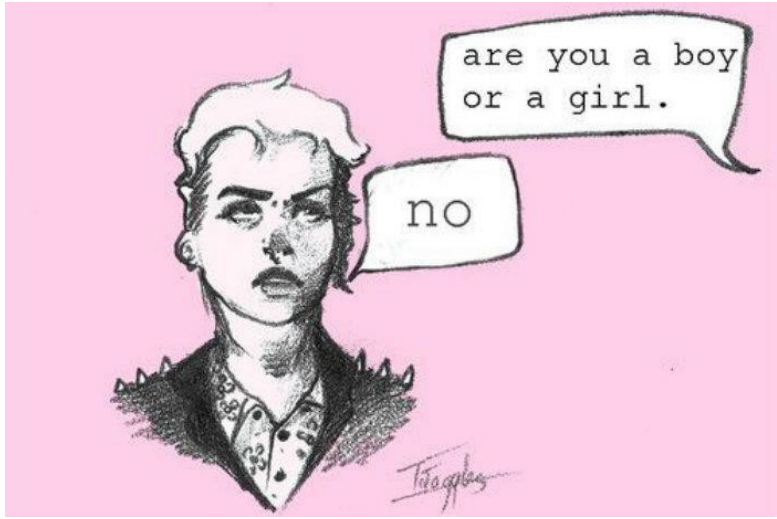
FOLLOW UP CARE



- Assess if patient is feeling affirmed
- Review medication use
- Discuss social supports and safety in the community
- Monitor mental health
- Review sexual history
- Review surgical desire and options
- Plans for legal document changes
- Review CAD risk factors, liver disease, and other underlying health considerations

NON-BINARY INDIVIDUALS

- Prosthetics: breast forms, binders, gaffs, packers
- Hair removal
- Voice therapy
- Surgical affirmation without hormones
- Adjust doses of estradiol and/or testosterone to maintain levels in a range between cis-male and cis-female levels
- Use of anti-androgens/blockers alone
- Limited courses of hormone therapy



“Microdosing”

Using low dose or limited courses of hormone therapy to affirm gender

- Important to discuss goals and realistic expectations
- Start low and monitor closely
- Remind patient they can stop whenever medication is no longer affirming or desired

- A flexible approach to dosing should be presented during the informed consent process for ALL

- QUESTIONS?