UC San Diego Health

Common Questions with GAHT

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Disclosures

- I have no financial relationships to disclose.

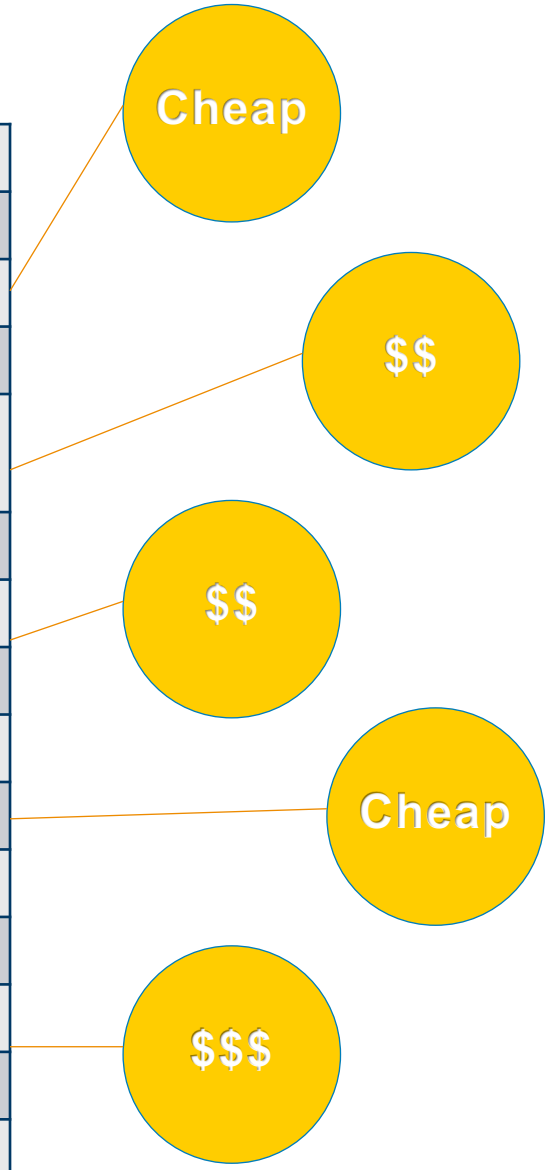
Objectives

- Review commonly asked clinical questions pertaining to gender affirming hormone therapy
- Understand evidence-based answers to these questions and gender affirming hormone therapy

Management of GAHT

Feminizing Therapy

	Route	Dose
Estradiol (17-beta-estradiol)	**Oral**	
	Estradiol	2.0 – 6.0 mg/day PO
	Transdermal	
	Estradiol patch	0.025 – 0.2 mg once or twice weekly
	Parenteral	
	Estradiol cypionate	5 – 30 mg IM or SC Q1 weeks
	Estradiol valerate	2 – 10 mg IM or SC Q1 weeks
Anti-Androgen	**Oral**	
	Spironolactone	50 – 200 mg/day
	Cyproterone acetate	25 – 50 mg/day
GnRH Agonist	**Parenteral**	
	GnRH Injection	3.75 – 7.5 mg monthly
		11.25 mg Q 3 months
	GnRH Subcutaneous Implant	Q 1 – 2 years



Effects of Feminizing Therapy

Psychological and CNS
↓Gender dysphoria
↓Anxiety
↓Depression
↓Perceived stress
↑Quality of life

Breast
↑Breast tissue

Skin
↑Softness
↓Sebum and acne

Reproductive system
↓Penile erections
↓Prostate size
↓Sperm count and quality

Body composition
↓Lean mass
↑Fat mass
↑Visceral fat

Sexual health
↓Sexual desire

Hair
↓Facial and body hair
↓Male pattern baldness

Voice
No change

Blood pressure
↓Systolic blood pressure

Blood
↓Hemoglobin and hematocrit

Lipids and metabolism
↑LDL cholesterol
↑Triglycerides
↑Sex hormone-binding globulin

Hormone concentrations
↓Testosterone
↓Luteinising hormone
↓Follicle-stimulating hormone
↑Prolactin

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

(T'Sjoen et al. Endocrine Reviews. 2019.)
(Hembree et al. JCEM. 2017.)

Anti-Androgen Therapy

- Spironolactone is the mainstay of anti-androgen therapy in the U.S.
  - Partial androgen receptor blocker and inhibitor of testosterone synthesis
  - May not be necessary in patients on injectable estradiol

- Is there a role for biclutamide?
  - Androgen receptor blocker - cannot measure androgen levels
  - Risk of liver toxicity

- Finasteride is a weak anti-androgen and not recommended

Monitoring on Feminizing Therapy

- Obtain baseline CMP, CBC, lipid panel, and prolactin
- Monitor patient for physical changes every 3 months in the first year
- Visits should include measurement of serum testosterone and estradiol every 3 months
  - Goal testosterone is <50 ng/dL
  - Estradiol should not exceed 200 pg/mL

- Serum electrolytes and potassium should be monitored in those on spironolactone

Ultimately, our goal is treat based on clinical outcomes while keeping patients safe within biochemical parameters.

Measuring Estrone vs Estradiol

- The body produces 3 types of estrogens: E1 (estrone), E2 (estradiol), and E3
- E1 and E2 can be interconverted with E2 having stronger binding to the estrogen receptor and estrogenic effects
- E1 (estrone) lab assays are generally not good or reliable
- No sufficient data exists on a reliable ratio/measurement translating to improved estrogenic effects

https://www.med.umich.edu/1libr/ComprehensiveGenderServicesProgram

Potential Risks of Feminizing Therapy

Bone Density

- BMD is preserved in patients on estradiol and antiandrogen therapy
- Increased BMD at lumbar spine

(Ruetsche AG, et al. Osteoporosis International. 2005.)
(T'Sjoen et al. Endocrine Reviews. 2019.)

Cardiovascular

- May be associated with increased risk of VTE, specifically with first-pass effect
- Studies are contradictory and remain to be determined. May be associated with higher rates of CV events compared to cis females +/- cis males.

(Getahun D, et al. Annals of Internal Medicine. 2018.)
(T'Sjoen et al. Endocrine Reviews. 2019.)

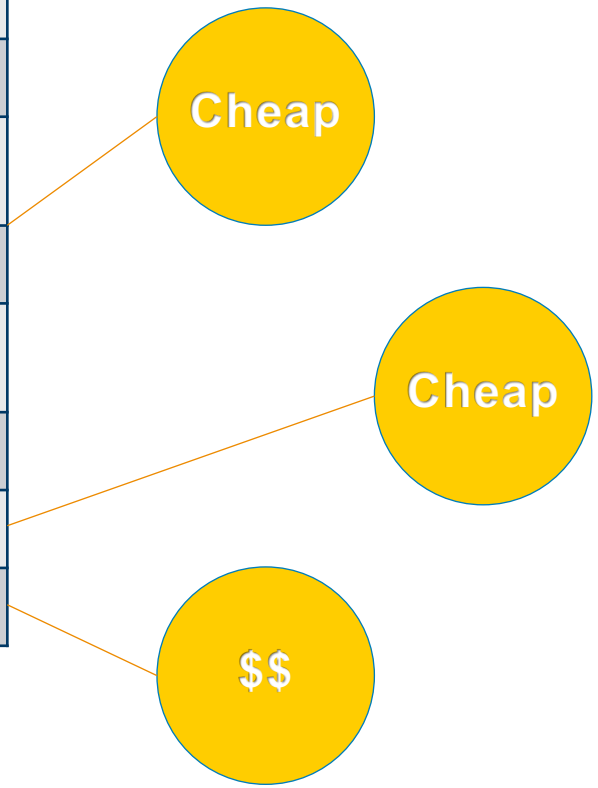
Cancer

- No increased risk of breast cancer compared to cisgender women (without family history in first degree relative), but may be increased compared to cisgender men.

(Hembree WC, et al. JCEM. 2017.)

Masculinizing Therapy

	Route	Dose
Testosterone	**Intramuscular**	
	Testosterone enanthate or cypionate	40 – 150 mg Q1 week 100– 200 mg Q2 weeks
	Subcutaneous	
	Testosterone enanthate or cypionate	40 – 150 mg Q1 week
	Transdermal	
	Testosterone gel 1% or 1.62%	20 – 100 mg/day
	Testosterone patch	2.5 – 7.5 mg/day



Effects of Masculinizing Therapy

Psychological and CNS
↓Gender dysphoria
↓Anxiety
↓Depression
↓Perceived stress
↑Total grey matter volume
↑Cortical thickness in several areas

Hair
↑Facial and body hair
↑Hair density, diameter, and growth rate
Alopecia

Breast
↓Breast cancer
↓Glandular tissue
↑Fibrous connective tissue

Reproductive system
Cessation of menstruation and infertility
↑Clitoral size
↓Vaginal epithelium thickness
Atrophic endometrium (according to data from some studies)
Ovarian hyperplasia and polycystic ovaries

Body composition
↑Sexual desire

Skin
Acne

Voice
↓Pitch

Muscle
↑Lean mass
↑Cross-sectional area
↑Bodyweight
↑Grip strength

Blood pressure
↑Systolic blood pressure

Blood
↑Hemoglobin and hematocrit

Lipids and metabolism
↓HDL cholesterol
↑Triglycerides
↓Sex hormone-binding globulin

Hormone concentrations
↓Estradiol
↓Luteinising hormone
↓Follicle-stimulating hormone
↓Prolactin

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

(T'Sjoen et al. Endocrine Reviews. 2019.)
(Hembree et al. JCEM. 2017.)

Monitoring on Masculinizing Therapy

- Obtain baseline CMP, CBC, and lipid panel
- Monitor patient for physical changes every 3 months in the first year
  - Visits should include measurement of serum testosterone
  - Goal testosterone in 400 – 700 ng/dL range
  - For those on injections, measurement should occur between injections

- Measure hematocrit every 3 months in the first year
  - Should not exceed 55%

Ultimately, our goal is treat based on clinical outcomes while keeping patients safe within biochemical parameters.

Potential Risks of Masculinizing Therapy

Bone Density

- Neutral effect on bone density, possible increased BMD at femoral neck

(Turner A, et al. Clinical Endocrinology. 2004.)

(T'Sjoen et al. Endocrine Reviews. 2019.)

Cardiovascular

- Data is suggestive of low to no risk regarding cardiovascular events in these patients
- Increase in LDL – clinically significant?

(Nora et al, Circulation, 2019)

(Getahun D, et al. Annals of Internal Medicine. 2018.)

(T'Sjoen et al. Endocrine Reviews. 2019.)

Cancer

- No known increase in breast/cervical/uterine cancer

(Hembree WC, et al. JCEM. 2017.)

Uterine Findings

Current belief is that testosterone will result in atrophy of the endometrial lining.

- More numbers are needed to determine uterine morphology.
  - 11 studies looking at uterine findings in trans men dating 1986 – 2019
  - Adding all known cases/pathology results in near 50/50 split of atrophic versus proliferative uterine lining

Why does this matter?

- Endometrial cancer is fourth leading cause of cancer in cisgender women.

(Moravek, MB. *Endocrinology*. 2020)

What is my cardiovascular risk?

Clinical Case

54 year old trans woman (she/they) presents to start on gender affirming hormone therapy.

PMH: Hypertension (controlled), Hyperlipidemia

PSH: Appendectomy (age 23)

Allergies: NKDA

Current Medications: Losartan 50 mg daily, Atorvastatin 20 mg daily, D3 2000 units

Family History: Father with CAD (s/p PCI age 76), Mother with pre-diabetes

Social History: Never smoker, drinks 3-5 glasses of wine weekly, no cannabis use or other substances

Physical Exam:

- Vitals: BP 128/78, HR 74, BMI 28.8 kg/m2
- Rest of exam unremarkable

Pertinent Labs:

- CMP: Normal, eGFR >60
- CBC: Normal
- Lipid panel: LDL 94, HDL 52, TG 163
- Hemoglobin A1C: 5.4%

Cardiovascular Risk

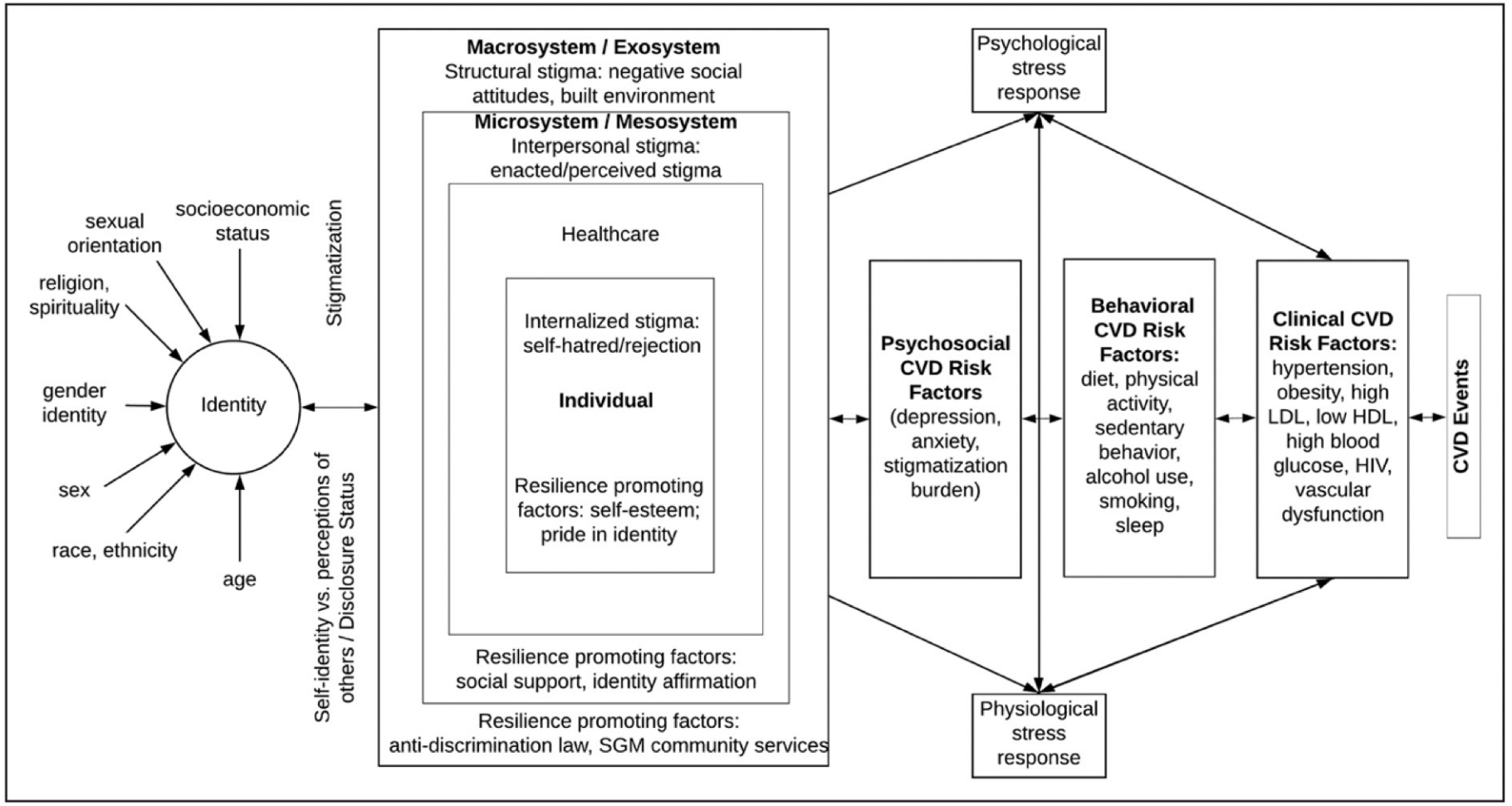


Figure 2. The intersectional transgender multilevel minority stress model.
CVD indicates cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SGM, sexual and gender minority.

(Streed, C. et al. Circulation. AHA. 2021)

VTE Risk

Annals of Internal Medicine

ORIGINAL RESEARCH

Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons

A Cohort Study

Darios Getahun, MD, PhD, MPH; Rebecca Nash, MPH; W. Dana Flanders, MD, MPH, DSc; Tisha C. Baird, MD; Tracy A. Becerra-Culqui, PhD; Lee Cromwell, MS; Enid Hunkeler, MA; Timothy L. Lash, PhD; Andrea Millman, MA; Virginia P. Quinn, PhD; Brandi Robinson, MPH; Douglas Roblin, PhD; Michael J. Silverberg, PhD; Joshua Safer, MD; Jennifer Slovis, MD; Vin Tangpricha, MD, PhD; and Michael Goodman, MD, MPH

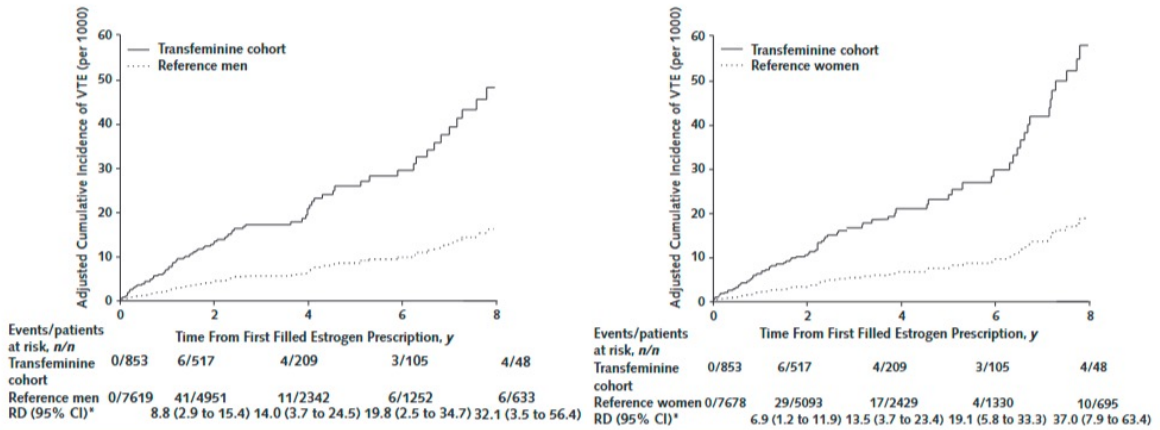
- 2018 Retrospective Cohort Study of 2842 transfeminine and 2118 transmasculine individuals (with 10:1 cis:trans match) across KP systems in Georgia and northern and southern California
- Identifying through diagnostic codes events including VTE, ischemic stroke, and myocardial infarction from 2006-2016

Table 2. Incidence Rates and Adjusted HRs for ACVEs Among Transfeminine Cohort Members Compared With Matched Reference Cohorts From KPNC, KPSC, and KPGA, 2006–2016

Cohort and Event of Interest	Transfeminine Cohort		Adjusted HR (95% CI)*	
	ACVEs, *n*	Incidence Rate (95% CI)†	Versus Reference Men	Versus Reference Women
Transfeminine overall cohort (*n* = 2842)				
VTE	61	5.5 (4.3–7.0)	1.9 (1.4–2.7)	2.0 (1.4–2.8)
Ischemic stroke	54	4.8 (3.7–6.3)	1.2 (0.9–1.7)	1.9 (1.3–2.6)
Myocardial infarction	33	2.9 (2.1–4.1)	0.9 (0.6–1.5)	1.8 (1.1–2.9)
Transfeminine estrogen initiation cohort (*n* = 853)				
VTE‡	17	6.6 (4.1–10.6)	3.2 (1.5–6.5)	2.5 (1.2–5.0)
At 0–2 y of follow-up	6	4.3 (1.9–9.6)	1.5 (0.5–5.1)	1.7 (0.5–5.5)
At >2 y of follow-up	11	9.3 (5.2–16.8)	5.1 (2.1–12.6)	3.2 (1.3–7.6)
Ischemic stroke‡	17	6.6 (4.1–10.6)	2.3 (1.2–4.3)	2.9 (1.5–5.5)
At 0–6 y of follow-up	9	3.8 (2.0–7.3)	1.3 (0.6–2.9)	2.3 (1.0–5.4)
At >6 y of follow-up	8	36.2 (18.1–72.4)	9.9 (3.0–33.1)	4.1 (1.5–11.4)
Myocardial infarction in the cohort overall	4	1.5 (0.6–4.1)	1.0 (0.3–3.2)	2.4 (0.6–9.4)

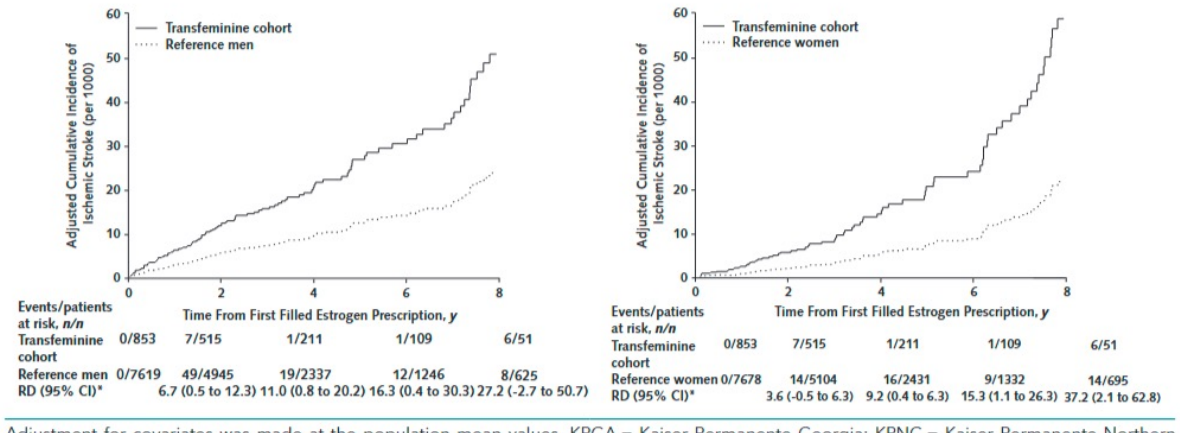
ACVE = acute cardiovascular event; HR = hazard ratio; KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; VTE = venous thromboembolism.
* Stratified by cluster identification number and history of any ACVE; body mass index (normal, overweight, or obese), smoking status (current vs. not current), blood pressure (elevated, borderline, or normal), and total blood cholesterol level (normal, not done [for persons <40 y], borderline, or high) are included in the model as covariates (see the **Supplement** [available at Annals.org] for details of variable characterization).
† Calculated as number of cases per 1000 person-years.
‡ Models were extended because of violation of proportional hazards assumptions.

Figure 1. Adjusted cumulative incidence curves comparing rates of VTE among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006–2016.



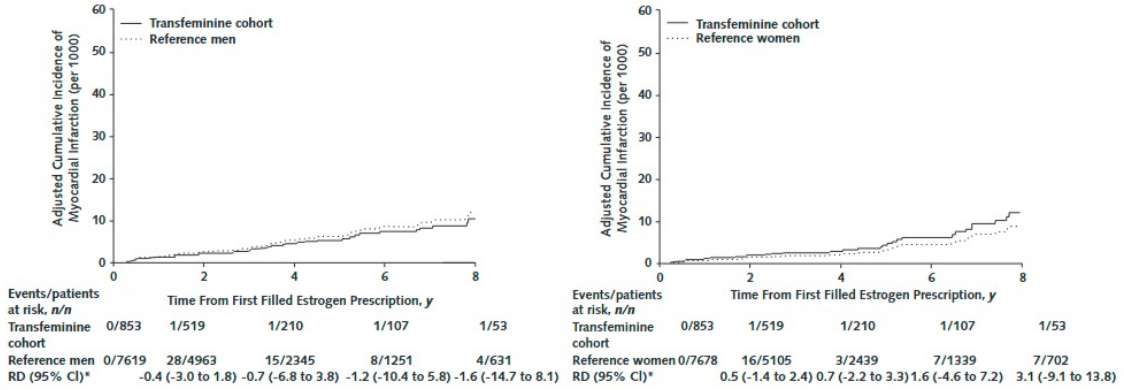
Adjustment for covariates was made at the population mean values. KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; RD = risk difference; VTE = venous thromboembolism.
* Per 1000 persons.

Figure 2. Adjusted cumulative incidence curves comparing rates of ischemic stroke among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006–2016.



Adjustment for covariates was made at the population mean values. KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; RD = risk difference.
* Per 1000 persons.

Figure 3. Adjusted cumulative incidence curves comparing rates of myocardial infarction among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006–2016.



Adjustment for covariates was made at the population mean values. KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; RD = risk difference.
* Per 1000 persons.

Table 3. Incidence Rates and Adjusted HRs for ACVEs Among Transmasculine Cohort Members Compared With Matched Reference Cohorts From KPNC, KPSC, and KPGA, 2006–2016

Cohort and Event of Interest	Transmasculine Cohort		Adjusted HR (95% CI)*	
	ACVEs, *n*	Incidence Rate (95% CI)†	Versus Reference Men	Versus Reference Women
Transmasculine overall cohort (*n* = 2118)				
VTE	23	3.1 (2.0–4.6)	1.6 (0.9–2.9)	1.1 (0.6–2.1)
Ischemic stroke	16	2.1 (1.3–3.5)	1.1 (0.6–2.0)	1.3 (0.7–2.5)
Myocardial infarction	9	1.2 (0.6–2.3)	0.7 (0.3–1.8)	1.3 (0.5–3.9)
Transmasculine testosterone initiation cohort (*n* = 585)				
VTE	4	3.3 (1.3–8.9)	2.7 (0.6–12.1)	1.5 (0.4–5.6)
Ischemic stroke	2	1.7 (0.4–6.7)	NC‡	NC‡
Myocardial infarction	0	–	–	–

ACVE = acute cardiovascular event; HR = hazard ratio; KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; NC = not calculated; VTE = venous thromboembolism.
* Stratified by cluster identification number and history of any ACVE; body mass index (normal, overweight, or obese), smoking status (current vs. not current), blood pressure (elevated, borderline, or normal), and total blood cholesterol level (normal, not done [for persons <40 y], borderline, or high) are included in the model as covariates (see the **Supplement** [available at Annals.org] for details of variable characterization).
† Calculated as number of cases per 1000 person-years.
‡ Because of small numbers.

Circulation
Volume 139, Issue 11, 12 March 2019; Pages 1461-1462
https://doi.org/10.1161/CIRCULATIONAHA.118.038584

RESEARCH LETTER

Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy

Results From a Large Cohort Study

Nienke M. Nota, MD, Chantal M. Wiepjes, MD, Christel J.M. de Blok, MD, Louis J.G. Gooren, MD, PhD, Baudewijntje P.C. Kreukels, PhD, and Martin den Heijer, MD, PhD

- Retrospective cohort study of 2517 trans women and 1358 trans men in an Amsterdam gender health clinic from 1972 – 2015 identifying incidences of VTE, stroke, and MI.
- Similar findings to Getahun, et al.

Table. Standardized Incidence Ratios for Acute Cardiovascular Events in Transwomen and Transmen Receiving Hormone Therapy (Table view)

Acute Cardiovascular Events	OCs (IR)*	Using Women as Reference		Using Men as Reference	
		ECs	SIR (95% CI)	ECs	SIR (95% CI)
Transwomen					
Stroke	29 (127)	12.01	2.42 (1.65–3.42)†	16.08	1.80 (1.23–2.56)†
Myocardial infarction	30 (131)	11.38	2.64 (1.81–3.72)†	38.03	0.79 (0.54–1.11)
Venous thromboembolism	73 (320)	13.22	5.52 (4.36–6.90)†	16.04	4.55 (3.59–5.69)†
Transmen					
Stroke	6 (55)	3.49	1.72 (0.70–3.58)	4.10	1.46 (0.59–3.04)
Myocardial infarction	11 (100)	2.98	3.69 (1.94–6.42)†	10.99	1.00 (0.53–1.74)
Venous thromboembolism	2 (18)	4.84	0.41 (0.07–1.37)	5.56	0.36 (0.06–1.19)

ECs indicates expected cases; IR, incidence rate; OCs, observed cases; and SIR, standardized incidence ratio.
* Per 100 000 person-years.
† Significant finding.

Recommendations

- Assess and address cardiovascular risk factors for all individuals
  - Dietary and lifestyle interventions
  - Medically optimizing hypertension and hyperlipidemia
  - Screening for diabetes mellitus
  - Affirming weight loss strategies for BMI >25 kg/m2
  - Smoking and alcohol use

- Tailor GAHT based on cardiovascular risk

- WPATH recommendations: Start with topical estradiol for all patients >45 years old if initiating GAHT

What is my risk for osteoporosis?

Clinical Case

45 year old trans man (he/him) presents for routine visit monitoring on gender affirming hormone therapy. Started on testosterone 10 years ago.

PMH: Hyperlipidemia

PSH: Chest surgery (age 40)

Allergies: NKDA

Current Medications: Testosterone cypionate 75 mg once weekly SC injection, Rosuvastatin 5 mg

Family History: Adopted

Social History: Former smoker (10 pack years), no alcohol use or other substances.

Physical Exam:

- Vitals: BP 118/74, HR 78, BMI 23.6 kg/m2
- Rest of exam unremarkable

Pertinent Labs:

- CMP: Normal, eGFR >60
- CBC: Normal
- Lipid panel: LDL 82, HDL 59, TG 120
- Hemoglobin A1C: 5.6%

Risk for Low Bone Mineral Density (BMD)

- What we know:
  - Low bone mineral density may exist for trans and nonbinary individuals even prior to starting GAHT
    - Cross-sectional study of 25 trans women matched to cis men identified decreased muscle mass, strength, and 16% high prevalence of lower BMD at the lumbar spine and hips *(Van Caenegem E, et al. Bone. 2013.)*
      - 25-OH vitamin D lower in this cohort compared to cis men
    - Cross-sectional study of 63 trans youth across 4 pediatric centers with lower BMD compared to cis matches *(Lee, J., et al. JES. 2020.)*
      - Suboptimal calcium intake in all youth
      - Decreased physical activity in trans youth

- Highest risk for loss of BMD is seen in patients after gonadectomy with decreased adherence to GAHT

BMD Does Not Decrease with GAHT

- Systematic review of 13 studies with 392 transfeminine and 247 transmasculine individuals
- No difference in BMD in transmasculine individuals in the lumbar spine, femoral neck, or total hip at 12 and 24 months
- Increase in BMD in transfeminine individuals in the lumbar spine at 12 and 24 months
- No increased rate of fractures within 12 months

Effect of Sex Steroids on the Bone Health of Transgender Individuals: A Systematic Review and Meta-Analysis FREE

Naykky Singh-Ospina, Spyridoula Maraka, Rene Rodriguez-Gutierrez, Caroline Davidge-Pitts, Todd B Nippoldt, Larry J Prokop, Mohammad Hassan Murad ✉ Author Notes

The Journal of Clinical Endocrinology & Metabolism, Volume 102, Issue 11, 1 November 2017, Pages 3904–3913, https://doi.org/10.1210/jc.2017-01642

- Prospective, observational multicenter study in Europe monitoring BMD 12 months after initiation of GAHT
- 231 tran women and 199 trans men included
- 3.67% increase in BMD in lumbar spine and 1.86% in femoral neck found in trans women
- 1.04% increase in BMD in total hip found in trans men, femoral neck increase not significant
  - 4.32% increase in BMD in lumbar spine for age >50

ORIGINAL ARTICLE

JBMR®

Bone Mineral Density Increases in Trans Persons After 1 Year of Hormonal Treatment: A Multicenter Prospective Observational Study

Chantal M Wiepjes,[1] Mariska C Vlot,[1,2] Maartje Klaver,[1] Nienke M Nota,[1] Christel JM de Blok,[1] Renate T de Jongh,[1] Paul Lips,[1] Annemieke C Heijboer,[2] Alessandra D Fisher,[3] Thomas Schreiner,[4] Guy T'Sjoen,[5] and Martin den Heijer[1]

Recommendations

- International Society for Clinical Densitometry and Endocrine Society: Consider baseline BMD screening before starting GAHT
- Screening is indicated for patients with gonadectomy
- Screening is indicated for patients with chronic biochemical hypogonadism
- All other screening follows standard USPSTF guidelines
  - Screen everyone over age 65
  - Screen over age 50 with one or more risk factor for osteoporosis

What about progesterone?

Clinical Case

29 year old trans woman (she/her) presents for routine follow-up with gender affirming hormone therapy. Started oral estradiol and spironolactone 2 years ago and feels she has not appreciated significant breast growth.

PMH: None

PSH: None

Allergies: NKDA

Current Medications: Estradiol 6 mg PO daily, Spironolactone 100 mg PO BID

Family History: None reported

Social History: Former smoker, drinks socially 3-5 cocktails on weekends, occasional marijuana use.

Physical Exam:

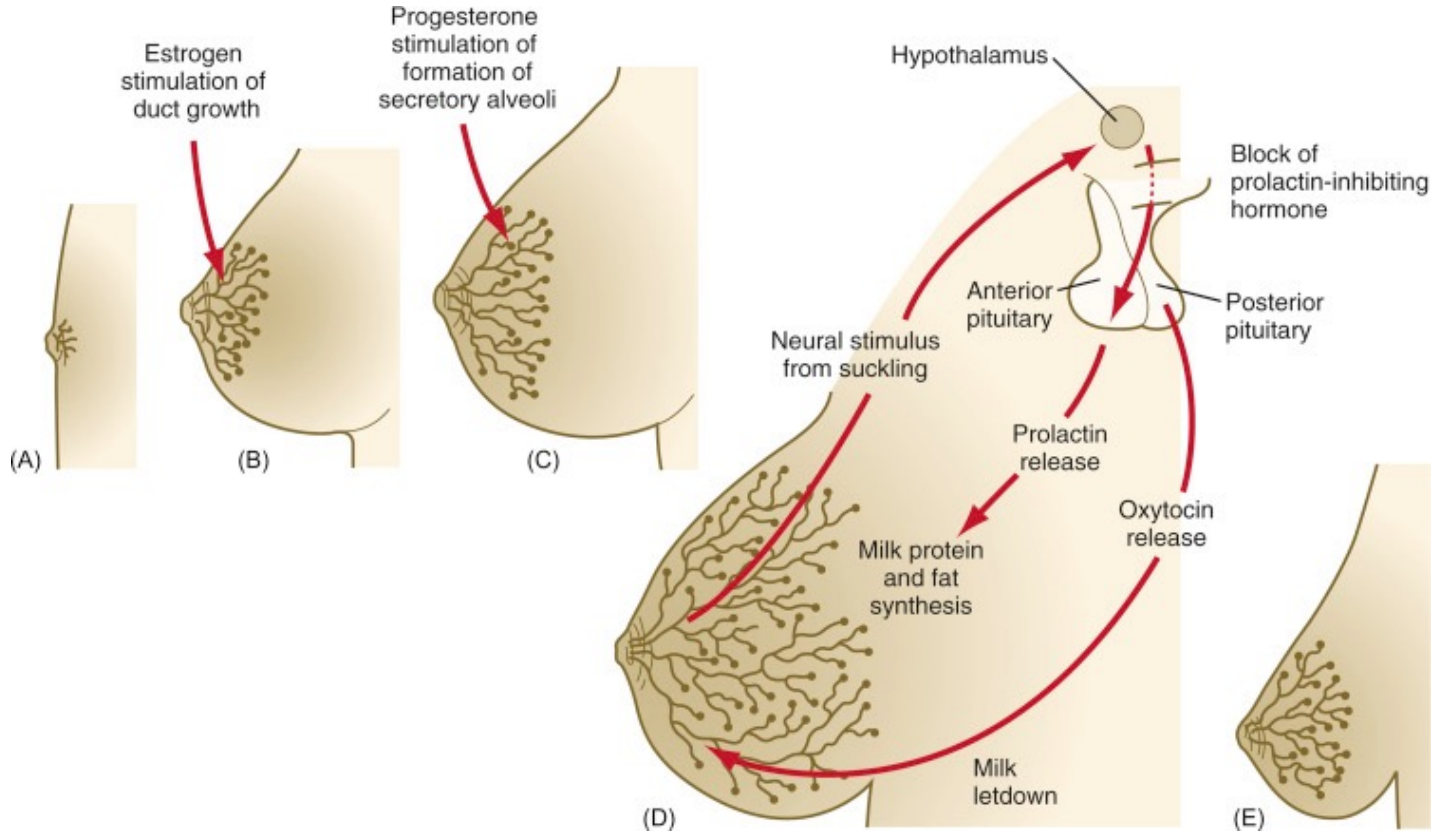
- Vitals: BP 116/70, HR 68, BMI 22.1 kg/m2
- Tanner stage 3 chest development

Pertinent Labs:

- CMP: Normal, eGFR >60
- CBC: Normal
- Lipid panel: LDL 72, HDL 54, TG 95
- Estradiol: 215 pg/mL
- Total testosterone: 15 ng/dL

Common Impressions of Progesterone

- Common impressions with use of progesterone:
  - Increases breast size – particularly curvature and areolar development
  - Improves mood
  - Improves libido



(Campbell C, et al. Handbook of Child and Adolescent Sexuality. 2013.)

Limited Data on Progesterone

- No established evidence to suggest use of progesterone improves these items – also no evidence that it does not
  - Formulations of medroxyprogesterone acetate can increase cardiovascular and breast cancer risk in post-menopausal cis women when combined with conjugated estrogens
- Limited data on use of micronized progesterone which is used more widely
- Domperidone?

Recommendations

- Tailor therapy for patient after discussed known evidence

- Patients without known risk factors can start oral micronized progesterone 100 mg QHS
  - Can increase to 200 mg QHS after 3 months
  - Consider total trial of 6-12 months and discontinuation afterwards
  - Advise against rectal administration

Are injections more potent and will I see faster results?

Clinical Case

20 year old nonbinary individual (they/them) presents to discuss starting masculinizing hormone therapy with testosterone.

PMH: Asthma

PSH: None

Allergies: NKDA

Current Medications: Lexapro 25 mg daily

Family History: None reported

Social History: No smoking history, social alcohol use. Junior in college studying biomechanics.

Physical Exam:

- Vitals: BP 108/72, HR 64, BMI 24.3 kg/m2
- Rest of exam unremarkable

Pertinent Labs:

- CMP: Normal, eGFR >60
- CBC: Normal
- Lipid panel: LDL 81, HDL 49, TG 101

Testosterone

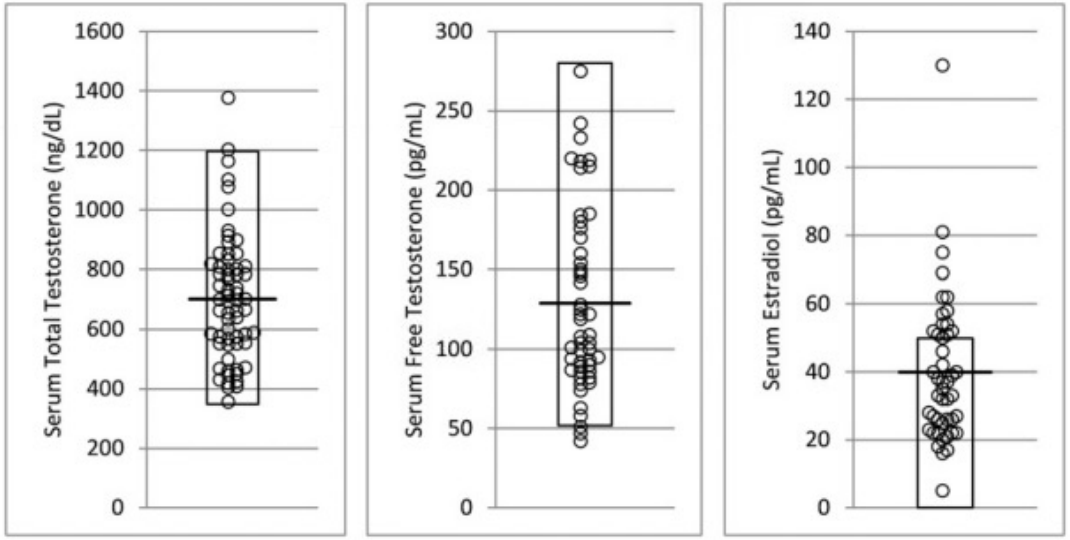


Figure 1. Serum hormone levels in FTM patients receiving SC T injections. Serum total T data were available for all 63 patients; free T data were available for 50 patients; and serum E2 concentrations measured by LabCorp were available for 47 of 53 premenopausal patients. Rectangles indicate normal ranges. Bars designate mean values. Note that the patient with an E2 level of 130 pg/mL had a previous serum E2 measurement of 37 pg/mL on the same dose (see text).

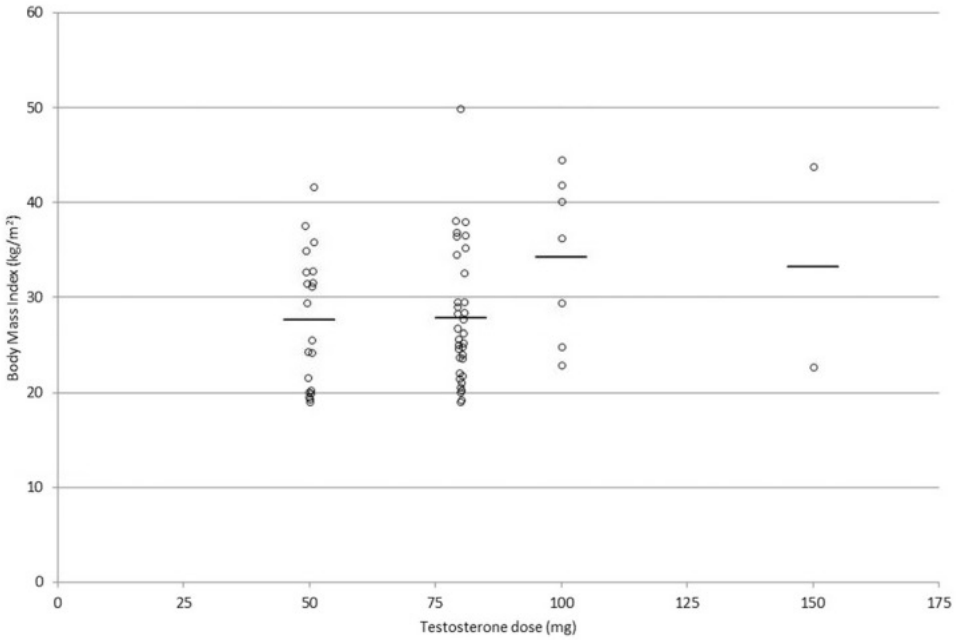
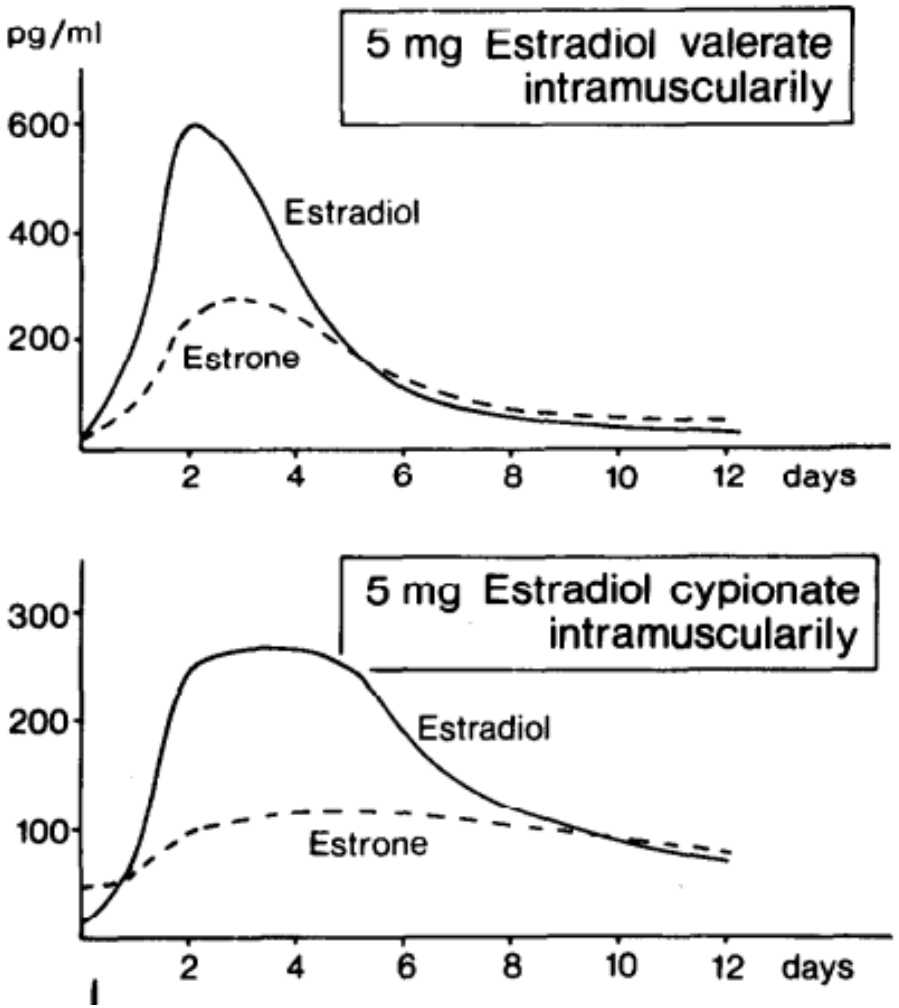


Figure 3. Optimized doses of SC T in patients according to BMI. SC T injections were effective across the broad range of BMI values encountered in our patients. No effect of BMI on dosing requirements was observed. The bars indicate mean values. Note that patients administered a dose of 75 mg were combined with patients administered a dose of 80 mg for this graph.

Estradiol

- Two main injectable formulations available: estradiol valerate and estradiol cypionate
- Valerate associated with quicker, steeper peak and decline
  - May be easier to dose every 7 days
  - No evidence available to suggest adverse risk associated with quicker peak
- Cypionate associated with slower peak and longer decline
  - Harder to dose every 7 days and may ”stack”



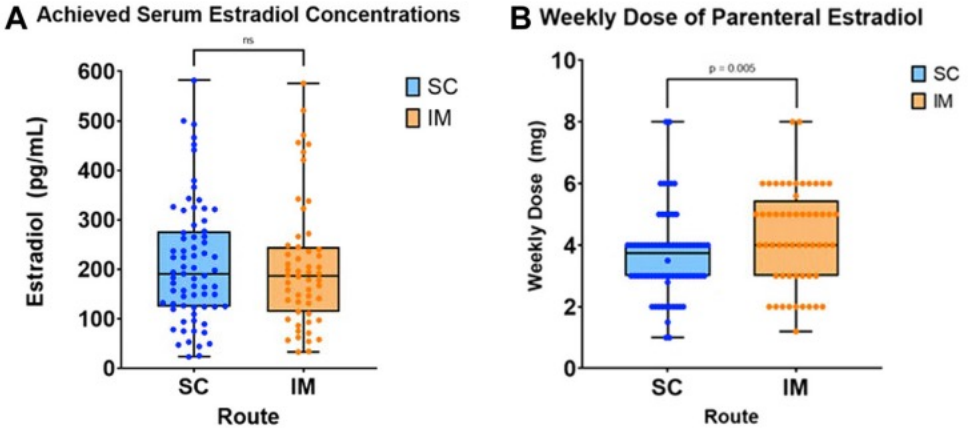
(Kuhl H.. Maturitas. 1990.)

Intramuscular vs Subcutaneous Estradiol

Table 2
Weekly Estradiol Doses by Route and Stratified by Therapeutic Effect, Gonadectomy Status, and Antiandrogen Use

Variable	Intramuscular E2 n = 56	Subcutaneous E2 n = 74	*P* value
Median doses (mg/wk) (IQR)	4 (3-5.15)	3.75 (3-4)	**.005**
Serum E2 level of >100 pg/mL (mg/wk) (IQR)			
Yes	4 (3-5)	3 (3-4)	**.028**
No	4.5 (3.75-6)	4 (3-4)	.12
Serum T level of <50 ng/dL (mg/wk) (IQR), patients not having undergone gonadectomy[a]	5 (4-6)	3 (3-4)	**<.001**
History of gonadectomy (mg/wk) (IQR)			
Yes	4 (3-5)	4 (2.5-4)	.26
No	5 (4-6)	3.5 (3-4)	**.002**
Antiandrogen use (mg/wk) (IQR)			
Yes	4 (4-5.25)	3 (3-4)	**.001**
No	4.5 (2.75-5.15)	4 (3-5)	.45

Abbreviations: E2 = estradiol; IQR = interquartile range; T = testosterone.
[a] Three patients in the subcutaneous estradiol group did not have available testosterone levels.



(Herndon JS, et al. Endocrine Practice. 2023.)

Recommendations

- Potency with testosterone is not necessarily based on formulation but on dose
- Injectable estradiol may seem more potent due to rise and fall of levels over the course of the week
  - PO and topical formulations have more steady delivery and stability of levels
- Ultimately, GAHT is not intended to cause rapid changes and slow progression is desired

How can I grow more facial hair?

Clinical Case

32 year old trans man (he/him) presents for routine follow up after starting testosterone therapy 1 year ago. Frustrated over lack of facial hair growth.

PMH: PCOS

PSH: None

Allergies: NKDA

Current Medications: Metformin 500 mg BID, testosterone cypionate 80 mg subcutaneous weekly injection

Family History: None reported

Social History: No smoking history, no alcohol use or other substances.

Physical Exam:

- Vitals: BP 121/82, HR 76, BMI 31.2 kg/m2
- Coarse, dark hair over forearms and legs. Scant and patchy facial hair around mandible.

Pertinent Labs:

- CMP: Normal, eGFR >60
- CBC: Normal
- Lipid panel: LDL 101, HDL 42, TG 143
- Total testosterone: 648 ng/dL

Is There a Role for Minoxidil?

- Minoxidil is typically thought of in context of addressing androgenic alopecia
  - Still limited knowledge on exact mechanism of action – increases cutaneous blood flow, activates potassium channels, prolongs anagen and shortens telogen phases of hair growth
  - Side effects of hypertrichosis outside of the scalp

- Case reports for increased facial hair growth with topical minoxidil
  - Can increase skin dryness and irritation
  - Messy!

- Oral minoxidil increasingly used in low doses to promote body and facial hair growth
  - Main side effects include hypotension and lower extremity edema

Table II. Summary of adverse effects with varying oral minoxidil doses

Minoxidil dosage, mg/d	Men, n	Women, n	Hypertrichosis, n (%)	Lower limb edema, n (%)	Hypotension, n (%)	ECG changes, n (%)
0.25	25	106	9 (6.8)	1 (0.7)	3 (2.3)	0
0.45*	33	31	8 (12)	2 (3.1)	5 (7.8)	0
0.5	0	15	4 (27)	0	0	0
1†	0	220	46 (21)	3 (1.4)	1 (1.4)	2 (0.9)
1.25	33	17	8 (16)	1 (2)	1 (5.5)	0
2.5	10	15	13 (52)	1 (4)	0	0
5	66	0	36 (55)	5 (7.6)	0	3 (4.5)
Total	167	404	117 (20.5)	13 (2.2)	10 (1.8)	5 (0.9)

ECG, Electrocardiography.
*Sublingual administration.
†Includes data from Rodrigues-Barata et al.[20] Patients took a range of doses; however, the mean dose was 1 mg, and multivariate analysis showed no significant statistical differences among dosages.

- Systematic review of 17 studies with 634 cisgender patients utilizing oral minoxidil for hair loss
- Found oral minoxidil to be a safe and effective alternative to topical treatments in healthy patients

(Randolph M, Tosti A. J Am Acad Dermatol. 2021.)

Recommendations

- Discussion on topical versus oral Minoxidil after 1-2 years of testosterone therapy
- Low threshold of starting oral Minoxidil 1.25 mg in healthy patients

Thank You!

References

- Coleman E, Radix AE, Bouman WP, Brown GR, De Vries AL, Deutsch MB, Ettner R, Fraser L, Goodman M, Green J, Hancock AB. Standards of care for the health of transgender and gender diverse people, version 8. International Journal of Transgender Health. 2022 Aug 19;23(sup1):S1-259.
- Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, Hunkeler E, Lash TL, Millman A, Quinn VP, Robinson B. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. Annals of internal medicine. 2018 Aug 21;169(4):205-13.
- Hembree W, Cohen-Kettenis P, Gooren L, Hannema S, Meyer W, Murad M, Rosenthal S, Safer J, Tangpricha V, T'Sjoen G. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. JCEM. 2017. 102(11):3869-3903.
- Herndon JS, Maheshwari AK, Nippoldt TB, Carlson SJ, Davidge-Pitts CJ, Chang AY. Comparison of the Subcutaneous and Intramuscular Estradiol Regimens as Part of Gender-Affirming Hormone Therapy. Endocrine Practice. 2023 May 1;29(5):356-61.
- Lee JY, Finlayson C, Olson-Kennedy J, Garofalo R, Chan YM, Glidden DV, Rosenthal SM. Low bone mineral density in early pubertal transgender/gender diverse youth: findings from the trans youth care study. Journal of the Endocrine Society. 2020 Sep;4(9):bvaa065.
- McFarland J, Craig W, Clarke N, Spratt D. Serum Testosterone Concentrations Remain Stable Between Injections in Patients Receiving Subcutaneous Testosterone. Journal of the Endocrine Society. 2017. 1(8):1095-1103.
- Motosko CC, Tosti A. Dermatologic care of hair in transgender patients: a systematic review of literature. Dermatology and therapy. 2021 Oct;11:1457-68.
- Nota NM, Wiepjes CM, de Blok CJ, Gooren LJ, Kreukels BP, den Heijer M. Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy: results from a large cohort study. Circulation. 2019 Mar 12;139(11):1461-2.
- Randolph M, Tosti A. Oral minoxidil treatment for hair loss: A review of efficacy and safety. Journal of the American Academy of Dermatology. 2021 Mar 1;84(3):737-46.
- Safer JD. Research gaps in medical treatment of transgender/nonbinary people. The Journal of Clinical Investigation. 2021 Feb 15;131(4).
- Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, Davidge-Pitts C, Nippoldt TB, Prokop LJ, Murad MH. Effect of sex steroids on the bone health of transgender individuals: a systematic review and meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2017 Nov 1;102(11):3904-13.
- Spratt D, Stewart I, Savage C, Craig W, Spack N, Chandler D, Spratt L, Eimicke T, Olshan J. Subcutaneous Injection of Testosterone Is an Effective and Preferred Alternative to Intramuscular Injection: Demonstration in Female-to-Male Transgender Patients. JCEM. 2017. 102:2349-2355.
- Wiepjes CM, Vlot MC, Klaver M, Nota NM, de Blok CJ, de Jongh RT, Lips P, Heijboer AC, Fisher AD, Schreiner T, T'Sjoen G. Bone mineral density increases in trans persons after 1 year of hormonal treatment: a multicenter prospective observational study. Journal of Bone and Mineral Research. 2017 Jun;32(6):1252-60.
- Van Caenegem E, Taes Y, Wierckx K, Vandewalle SA, Toye K, Kaufman JM, Schreiner T, Haraldsen I, T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. Bone. 2013 May 1;54(1):92-7.
- Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle SA, Toye K, Lapauw B, Kaufman JM, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case–controlled study (ENIGI). European journal of endocrinology. 2015 Feb;172(2):163-71.