AT THE FOREFRONT
UChicago Medicine

Routine Issues to Consider When Providing Hormone Therapy to Transgender Patients

Isabel Casimiro, MD PhD

September 2019

Disclosure Information

Endocrine Research Seminar Series

Isabel Casimiro

I have the following financial relationships to disclose:

- Consultant for: _____
- Speaker's Bureau for: _____
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- or -

_X_ I have no financial relationships to disclose.

- and -

_ I will not discuss off label use or investigational use in my presentation.

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_X_ I will discuss the following off label use and/or investigational use in my presentation:

Progesterone use for feminizing HT

Objectives

- To discuss outpatient management of hormone therapy in a transgender woman
- Update on transgender man on dual hormone therapy for gender affirmation and hot flashes
- To discuss issues that Endocrinologists may encounter when providing transgender care that fall outside Society Guidelines

Table 1. Estimated Population of Adults Who Identify as Transgender by State of Residence

STATE	POPULATION	PERCENT	RANK
United States of America	1,397,150	0.58%	-
Alabama	22,500	0.61%	15
Alaska	2,700	0.49%	33
Arizona	30,550	0.62%	12
Arkansas	13,400	0.60%	18
California	218,400	0.76%	2
Colorado	20,850	0.53%	27
Connecticut	12,400	0.44%	37
Delaware	4,550	0.64%	9
District of Columbia[7]	14,550	2.77%	-
Florida	100,300	0.66%	6
Georgia	55,650	0.75%	4
Hawaii	8,450	0.78%	1
Idaho	4,750	0.41%	43
Illinois	49,750	0.51%	30
Indiana	27,600	0.56%	23

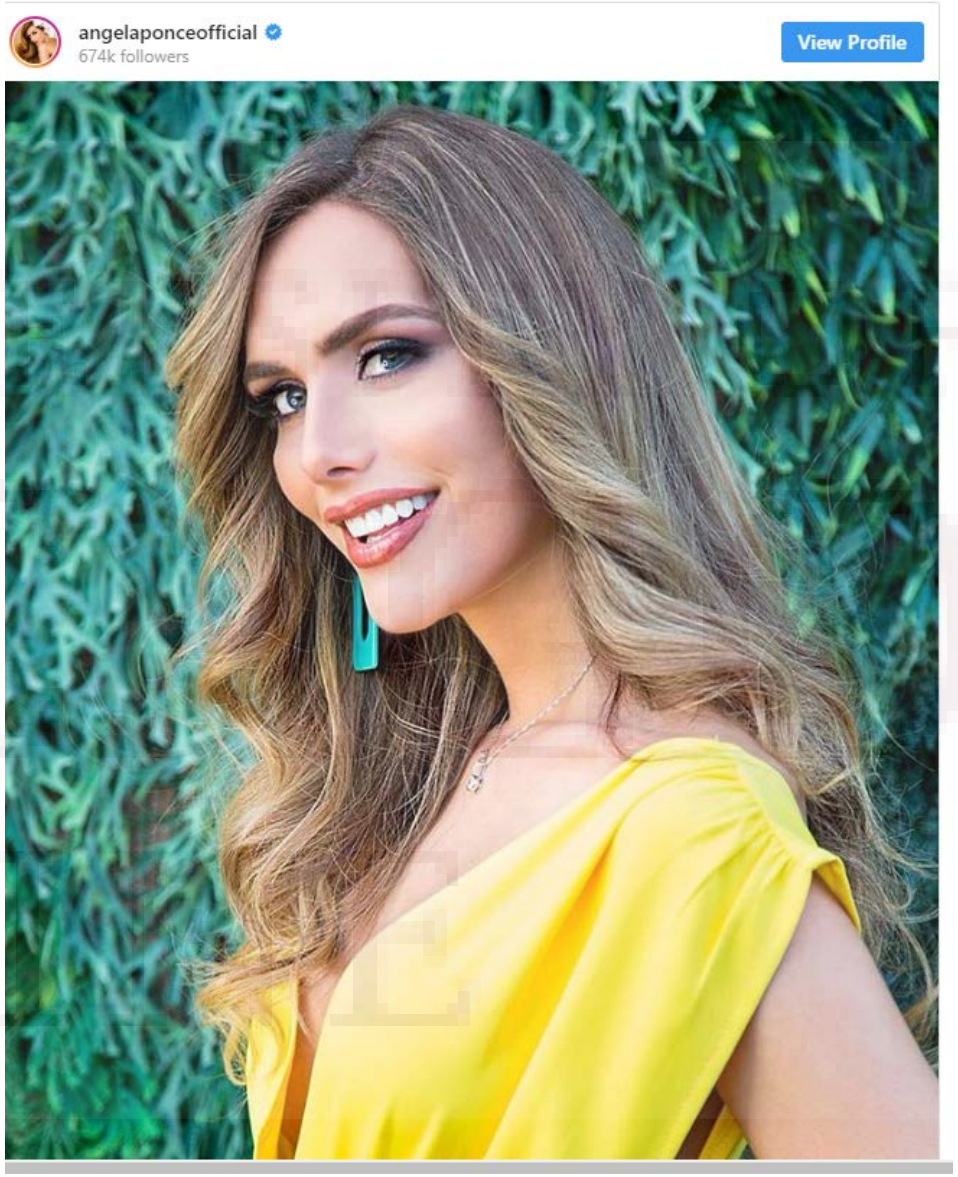
CDC's Behavioral Risk Factor Surveillance System 2016

Epidemiology

- Estimated population of adults who identify as transgender in Illinois:
  - 0.51% of state population (25,372 people in Illinois) (CDC BRFSS 2016)

- Prevalence of acromegaly
  - 25,000 cases in the US (Endocr Pract. 2016 Nov;22(11):1327-1335)

- A number of longitudinal studies have shown that hormonal treatment in transgender people wanting gender-affirmation treatment results in improved QOL, mental health & social functioning



Angela Ponce, 1st transgender woman Crowned as Miss Universe Spain, 2018

Case

- 28yo patient born male presents to Endocrinology clinic to request hormone therapy (HT) for female transition
- Pt is referred to me for care
- Pt states feeling they are “in the wrong gender” since they can remember
- Things worsened during puberty
- Feels that “inadequacy” has been root of their depression and anxiety most of their life
- Following with a Psychiatrist & Psychologist regularly
- Never been on HT before, denies taking street hormones

PMH

- Depression
- Obesity

Meds

- Escitalopram 20mg
- Trazodone 50mg
- Vitamin D 50K/mo

SH

- Lives alone
- Smokes 6-8 cigarettes a day
- No IVDU
- Works as a computer programmer
- Working on weight loss
- Not sexually active

FH

- No Hx of DVT
- Mother: benign skin cancer
- No Hx of other cancer or prolactinomas, thyroid issues

Physical Exam

- Vitals: BP 124/77 | Pulse 76 | Ht 175.3 cm (5' 9") | Wt 99.8 kg (220 lb) | BMI 32.49 kg/m2
- General: No apparent distress. Appears stated age, overweight.
- HEENT: No pharyngeal erythema. PERRL, EOMI.
- Neck: No neck tenderness. No thyromegaly or thyroid nodules appreciated.
- Cardiovascular: regular rate and rhythm. No peripheral edema.
- Pulmonary/Chest: clear to auscultation bilaterally.
- Gastrointestinal: soft, non-tender, non-distended. No rebound or guarding.
- Musculoskeletal: normal range of motion of joints.
- Neurological: Alert & oriented, no focal deficits
- Lymph: No cervical, supraclavicular, lymphadenopathy.
- Skin: No apparent bald spots. No acanthosis nigricans or skin tags
- Psychiatric: normal mood, thought content, appropriate.

OSH Labs

- Na: 143, K: 4.4, Cl: 108, CO2: 28, BUN: 9, Cr: 1.09, Calcium: 9.5, ALT: 32, AST: 24, Alk Phos: 66, Bili: 2.4 (0.3-1.2), Tot protein: 6.8, Alb: 4
- Prolactin 7.9
- TSH: 1.47
- Total Testosterone: 355
- Vit D: 29.6 ng/mL
- Hg: 15.9, HCT: 46.8, WBC: 9.2, PLT: 297

Next Steps?

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

Wylie C. Hembree,[1] Peggy T. Cohen-Kettenis,[2] Louis Gooren,[3] Sabine E. Hannema,[4] Walter J. Meyer,[5] M. Hassan Murad,[6] Stephen M. Rosenthal,[7] Joshua D. Safer,[8] Vin Tangpricha,[9] and Guy G. T'Sjoen[10]

[1]New York Presbyterian Hospital, Columbia University Medical Center, New York, New York 10032 (Retired); [2]VU University Medical Center, 1007 MB Amsterdam, Netherlands (Retired); [3]VU University Medical Center, 1007 MB Amsterdam, Netherlands (Retired); [4]Leiden University Medical Center, 2300 RC Leiden, Netherlands; [5]University of Texas Medical Branch, Galveston, Texas 77555; [6]Mayo Clinic Evidence-Based Practice Center, Rochester, Minnesota 55905; [7]University of California San Francisco, Benioff Children's Hospital, San Francisco, California 94143; [8]Boston University School of Medicine, Boston, Massachusetts 02118; [9]Emory University School of Medicine and the Atlanta VA Medical Center, Atlanta, Georgia 30322; and [10]Ghent University Hospital, 9000 Ghent, Belgium

*Cosponsoring Associations: American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society–appointed task force of nine experts, a

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Letter from Psychiatrist?

"Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence."

(1) competence in using the DSM and/or the ICD for diagnostic purposes,

(2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder)

(3) training in diagnosing psychiatric conditions

(4) the ability to undertake or refer for appropriate treatment

(5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings.

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Letter from Psychiatrist?

- Letter from mental health provider (MHP) not mentioned in current Guidelines
  - MHP involvement for adult treatment is recommended if the provider cannot make a diagnosis
- MHP should confirm gender dysphoria in adolescents & should be involved in the multi-disciplinary team in the treatment of adolescents

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Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
   - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
   - gender dysphoria worsened with the onset of puberty,
   - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
   - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
   - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
   - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
   - agrees with the indication for GnRH agonist treatment,
   - has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2),
   - has confirmed that there are no medical contraindications to GnRH agonist treatment.

Back to Our Patient

Healthy Driven
Edward-Elmhurst HEALTH

LINDEN OAKS MEDICA
8 Salt Creek Lane,
Hinsdale IL 60
331-

3/27/2017

Dr. Meyer:

[redacted] has been spent under my care since 2-9-2017 for treatment of Gender Dysphoria, Major Depression, Recurrent, severe, Dysthymia, and Social Phobia.

The purpose of this letter is to communicate patient's confirmed diagnosis with his primary care physician or other specialist (endocrinologist) to assist patient in his process.

Sincerely,

Christine Dahl, PMHNP

Christine Dahl, PMHNP
Linden Oaks Medical Group
331-221-2505

What Medical Concerns Should We Consider When Prescribing HT in This Patient?

PMH

- Depression
- Obesity

SH

- Lives alone
- Smokes 6-8 cigarettes a day
- No IVDU
- Works as a computer programmer
- Working on weight loss
- Not sexually active

FH

- No Hx of DVT
- Mother: benign skin cancer
- No Hx of other cancer or prolactinomas, thyroid issues

Risk Assessment for HT

- Estrogen use increases the risk of VTE in particular in patients who are over 40, smokers, highly sedentary, obese or who have underlying thrombophylic disorders
- "Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications."
- Different types of estrogen may be associated with different risk profiles
  - Ethinyl estradiol (most common estrogen in OCPs) has the highest risk of VTE
  - This risk is decreased with use of the transdermal route of estradiol administration, which is recommended for patients at higher risk of VTE

ESCPG 2017 & WPATH SOC 7th version

Journal of Blood Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Managing the risk of venous thromboembolism in transgender adults undergoing hormone therapy

This article was published in the following Dove Press journal:
Journal of Blood Medicine

Zil Goldstein[1]
Musaub Khan[2]
Tamar Reisman[1]
Joshua D Safer[1]

[1]Center for Transgender Medicine and Surgery at Mount Sinai, Mount Sinai Health System and Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [2]New York Medical College, Valhalla, NY USA

Introduction: Venous thromboembolism (VTE) is a potential risk of estrogen therapy. However, data show an improvement in the quality of life for transgender people who use feminizing hormone therapy. With few transgender-specific data, guidance may be drawn from cisgender (nontransgender) data, with a focus on hormonal birth control and postmenopausal hormone replacement therapy (HRT). The aim of this review is to examine the degree to which routes of administration, patient comorbidities, and type of hormone utilized affect the safety of estrogen therapy.

Methods: We identified 6,349 studies by searching PubMed with the terms "transgender", "estrogen", "VTE", and "HRT". Of these, there were only 13 studies between 1989 and 2018 that investigated the effects of hormone therapy, including types of estrogens used, in transgender women and men.

Results: The data suggest that the route of hormone administration, patient demographics, and patient comorbidities all affect estrogen's link with VTE. For example, avoiding ethinyl

Table 1 VTE rates reported in studies of transgender women on estrogen therapy

Study	Sample size	VTE (%)	Hormone dose and route associated with VTE	Additional VTE risk factors	Age of sample (years)
Aschemann et al (1989)	303	6.3	0.05 mg ethinyl estradiol bid+50 mg bid cyproterone acetate	Age>40 years (VTE in 2.1% under age 40 vs 12% in over age 40) Smoking Hypercholesterolemia	32 (median)
Wierckx et al (2012)[34]	50	2	0.625 mg conjugated estrogens (n=1)	Smoking Hypercholesterolemia Hypertension	52 (age of patient with VTE)
Wierckx et al (2013)[5]	214	5.1	17β-estradiol gel, 1.5 mg/24u (n=76; VTE* n=3) 2 mg estradiol valerate (n=91; VTE* n=4) 50 μg ethinyl estradiol (n=2; VTE* n=1) 0.625 conjugated equine estrogen (VTE* n=1) Cyproterone acetate (VTE* n=1) Unknown (VTE* n=1)	Smoking Hypercholesterolemia Hypertension Surgery/immobilization Clotting disorder	48 (mean)
van Kesteren et al (1997)[8]	816	5.5	100 μg ethinyl estradiol+100 mg cyproterone acetate daily (VTE* n=40) Transdermal 17β-estradiol (VTE* n=1)	Suicide AIDS COPD Malignancies	41 (mean)
Prior (1989)	61	0	Premarin 2.5 mg/day	–	–
Dittrich (2005)	60	1.7	Estradiol 2–4 mg/day+GnRH analog 1×/month (VTE* n=1)		
Wilson et al (2009)[37]	30	0	Premarin 2.5 mg/day (n=23) Transdermal estradiol+cyproterone acetate or finasteride (n=7)		36 (oral estrogen group) 47 (transdermal estradiol group)
Schlatterer (1998)	46	0	Estrogen esters IM 100 mg/2 weeks Cyproterone acetate 100 mg/day 2 patients were on unknown estrogen	Clotting history Nicotine Cardiovascular disorders	30 (mean)
Ott et al (2010)[36]	162	0	Transdermal estrogen 0.1 mg 2×/week Cyproterone acetate 50 mg/day Finasteride 5 mg every other day	BMI Clotting history Smoking Hypertension Hypercholesterolemia	36.6
Cuypere (2011)	32	0	2 mg estradiol+50 mg cyproterone acetate/day	Hypertension (n=1) Depression (n=8) Diabetes (n=2)	37.8

Table 1 (Continued).

Study	Sample size	VTE (%)	Hormone dose and route associated with VTE	Additional VTE risk factors	Age of sample (years)
Arnold et al (2016)[40]	676	0.15	Estradiol (PO) + spironolactone or finasteride or progesterone	HIV (n=149)	• 33.2
Getahun et al (2018)[7]	2,842	2	4.1 mg estradiol, oral (n=11) Unknown (n=2,440) 4.2 mg estradiol, oral (n=391; VTE* n=6)	CVD history Smoking Hypercholesterolemia	

Abbreviations: bid, twice daily; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; IM, intramuscularly; PO, per os; VTE, venous thromboembolism.

Conclusions from this study

- Patient demographics and comorbidities affect their venous thromboembolic risk profile, including age, smoking habits, hypertension, thrombophilic conditions, history of thromboses, and mental illness, among others

- Clinicians should avoid the use of ethinyl estradiol

- Transdermal estrogens dosed up to 0.1mg/day or below appear to have lower risk of VTE than other forms of estrogen

Continued Pt Course:

- Provided informed consent & went through “Feminizing Treatment Informed Consent Form” with Pt & scanned to the chart
- Informed consent ensures:
  - The person has the correct information about HT (how HT can change the body, expectations, fertility aspects, potential side effects, screening for mental health concerns, expectation for continued monitoring)
  - The person can understand the information about HT
  - The person can use the information to make a decision

Continued Pt Course:

- Provided smoking cessation counseling & recommended Pt meet with Behavioral Extern that day to “check in”

- Prescribed:
  - Estradiol patch 0.1mg 2x/week & spironolactone 50mg Qd
  - Scheduled for next labs in 3 mos

- Monitoring?

Continued Pt Course:

- Provided smoking cessation counseling & recommended Pt meet with Behavioral Extern that day to “check in”

- Prescribed:
  - Estradiol patch 0.1mg 2x/week & spironolactone 50mg Qd
  - Scheduled for next labs in 3 mos

- Monitoring:
  - Every 3 mos in the first year; and then 1-2x /yr thereafter (estradiol, T, K)
  - Monitor for signs of feminization or for development of adverse reactions
  - Routine cancer screening for tissues present
  - Can do BMD at baseline; screen for osteoporosis risk at age 60 (or if off HT)

Hormone Therapy Options

Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate[b]	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate[c]	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

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Transdermal testosterone	
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Testosterone transdermal patch	2.5–7.5 mg/d

0.1mg 2x/wk=
0.029mg daily

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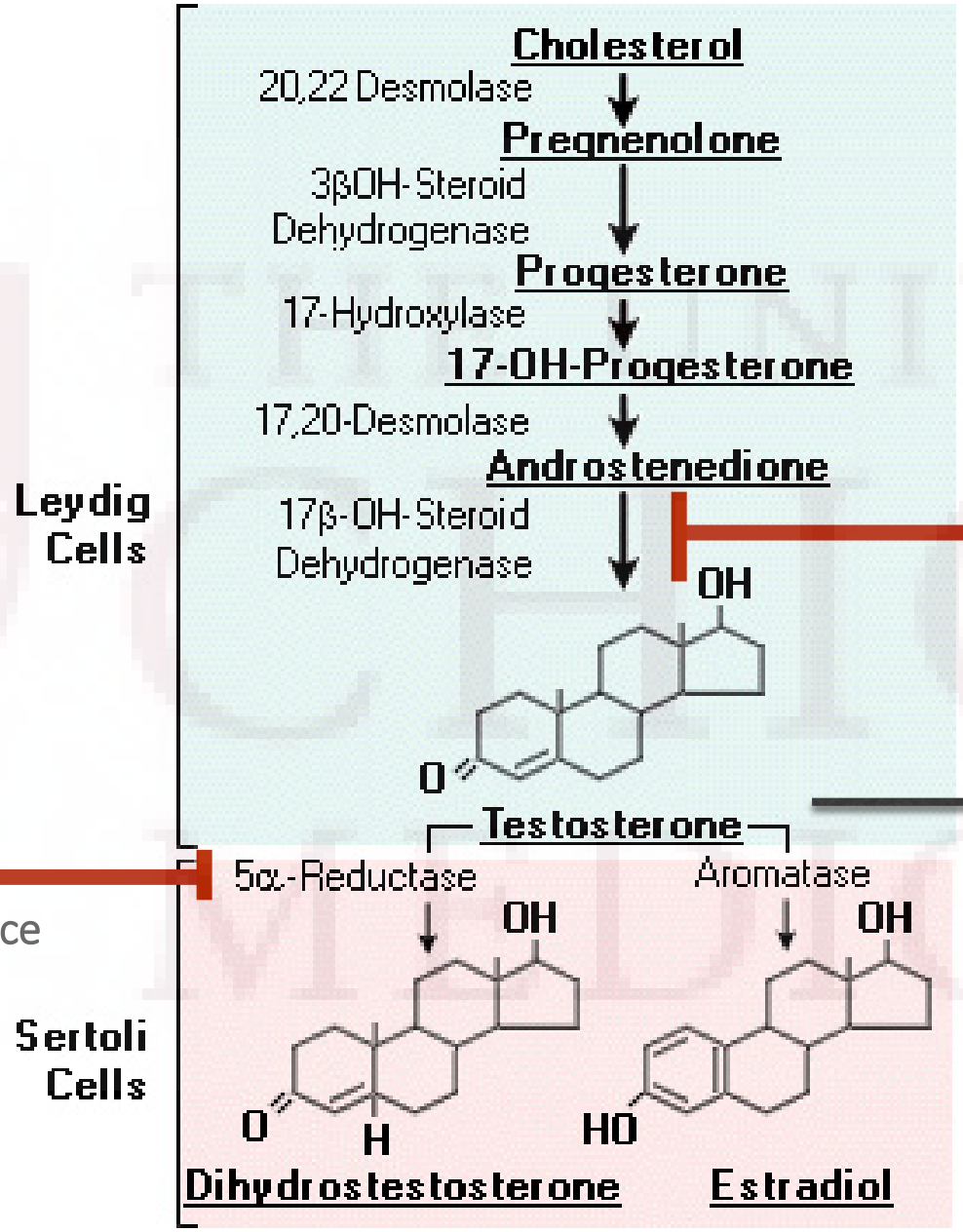
Anti Androgens Blockers

Anti Androgens Blockers



Spironolactone

Androgen receptor

Finasteride (does not reduce testosterone)

Flutamide

5α-Reductase inhibitors

- A few case series in transgender women with androgenetic alopecia have demonstrated finasteride therapy to be effective to improve hair loss without significant side effects
- The routine use of 5α-reductase inhibitors has been limited over previous concerns of long-term sexual dysfunction and depression reported to be found in cisgender men
- In general, lowering serum testosterone levels into the cisgender female range is often adequate to arrest hair loss in most transgender women; If not, it is ok to try 5-a-reductase inhibitor
- In trans men with androgenetic alopecia, treatment with oral finasteride at 1 mg daily for 12 months induced improvement (improvement seen at 5 months) *Clin Exp Dermatol*. 2017;42(7):743–748.

Labs in 3 months

Testosterone: **149** (175 – 781 ng/dl, male ref range; female range <60)
-[3 mos prior: 355ng/mL]

Estradiol: **80** (20 – 47 pg/mL, male ref range; female range: 30-400)

Chol: 168, TG: 108, LDL: 105, HDL: 41

Na: 136, K: 3.8, Cl2: 103, CO2: 24, BUN: 11, Cr: 0.98, Calcium: 9.4

Goal HT levels in someone undergoing feminizing treatment?

- Based on ESCPG, goals are to:

(1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and

(2) maintain sex hormone levels within the normal range for the person's affirmed gender

- Trans women: testosterone <50ng/dL & estradiol 100-200 pg/mL (>400 pg/mL is not recommended)

- Trans men: testosterone range, normal male range (400-700 ng/dL, measure mid injections)

Continued Course

6/2017

	Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd
Testosterone	355
Estradiol	
Effects/Comments	

Continued Course

	6/2017	9/2017
	Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd	**Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd**
Testosterone	355	149
Estradiol		80
Effects/Comments		Pt quit smoking

Continued Course

	6/2017	9/2017	11/2017
	Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd	**Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd**	**estradiol 3mg PO Qd & spiro 50mg Qd**
Testosterone	355	149	322
Estradiol		80	73
Effects/Comments		Pt quit smoking	-Reported skin was softer & that she had some change in body fat distribution -Reduced morning erections & reduced libido

Continued Course

	6/2017	9/2017	11/2017	2/2018
	Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd	**Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd**	**estradiol 3mg PO Qd & spiro 50mg Qd**	**Estradiol 2mg BID & spiro 100mg Qd**
Testosterone	355	149	322	125
Estradiol		80	73	73
Effects/Comments		Pt quit smoking	-Reported skin was softer & that she had some change in body fat distribution -Reduced morning erections & reduced libido	-Some breast fullness

Continued Course

	6/2017	9/2017	11/2017	2/2018	11/2018
	Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd	**Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd**	**estradiol 3mg PO Qd & spiro 50mg Qd**	**Estradiol 2mg BID & spiro 100mg Qd**	**Estradiol 6mg Qd & spiro 100mg Qd**
Testosterone	355	149	322	125	288
Estradiol		80	73	73	78
Effects/Comments		Pt quit smoking	-Reported skin was softer & that she had some change in body fat distribution -Reduced morning erections & reduced libido	-Some breast fullness	-No further changes noted

Table 11. Hormone Regimens in Transgender Persons

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Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
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What to do now?

- Estradiol lowers testosterone secretion from the testes by inhibiting the HPG axis & induces feminizing physical changes
  - There are no robust data comparing safety & efficacy of estrogen options
  - There are anecdotal reports of more rapid/increased feminization with injectable estrogen

Health

Shortages of Injectable Estrogen Are Screwing Over Trans Women

"If they're not compelled to serve us with this thing we need, what are we going to do?"

Like other trans women, Mel found that injecting estrogen, rather than taking it in its pill form, resulted in a more dramatic physical transformation in a shorter period of time. "I was starting to see a lot of changes in my body—my hips were finally appearing, and I had some significant breast growth," she says. "It felt like I was finally having a breakthrough."

https://www.vice.com/en_us/article/mbxe3x/shortages-of-injectable-estrogen-are-screwing-over-trans-women

Continued Course

- Discussed changing route of administration to IM injections

- Recommended:
  - Continue estradiol at 6mg daily x 1 week, then 2mg x 1 week then stop pills
  - Start estradiol valerate IM at 10mg Q 2 weeks, labs in 3 months

Three months later

Continued Course

	6/2017	9/2017	11/2017	2/2018	11/2018 -> 2/2019
	Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd	**Estradiol 0.1mg patch 2x /wk Spiro 50mg Qd**	**estradiol 3mg PO Qd & spiro 50mg Qd**	**Estradiol 2mg BID & spiro 100mg Qd**	**Estradiol 6mg Qd & spiro 100mg Qd- >10mgQ2wksIM & spiro 100mg**
Testosterone	355	149	322	125	288 **-> 13**
Estradiol		80	73	73	78 **-> 118**
Effects/Comments		Pt quit smoking	-Reported skin was softer & that she had some change in body fat distribution -Reduced morning erections & reduced libido	-Some breast fullness	-Noted fuller chest on exam -Pt reports feeling “softer” -New license & interested in surgery

Update on Transman on Dual HT

An Endocrine Society Thematic Issue: Transgender Health and Medicine

Volume 3, Issue 4
April 2019

Article Contents

Severe Vasomotor Symptoms Post-Oophorectomy Despite Testosterone Therapy in a Transgender Man: A Unique Case Study

Isabel Casimiro ✉, Ronald N Cohen

Journal of the Endocrine Society, Volume 3, Issue 4, April 2019, Pages 734–736, https://doi.org/10.1210/js.2018-00367

Published: 13 February 2019 **Article history** ▾

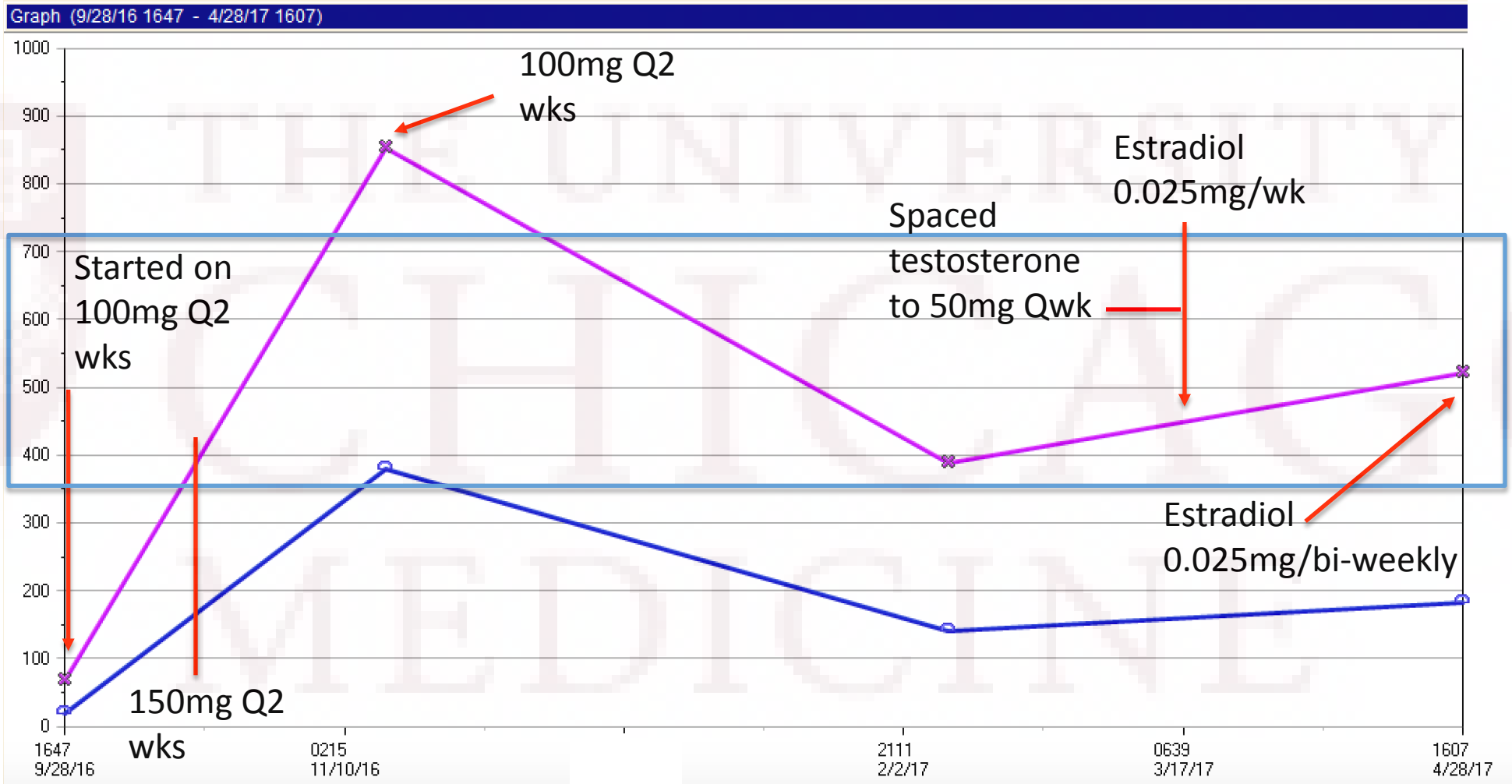
Abstract

Vasomotor symptoms (VMS), such as hot flashes and night sweats, are intense and rapid sensations of internal heat, peripheral vasodilation, and profuse sweating that can be debilitating. They occur as a result of central norepinephrine discharge and narrowing of the core body thermoneutral zone with dropping brain estrogen levels in women and men. Therapy options for the treatment of VMS in postmenopausal women have been widely studied. However, we address treatment strategies for VMS that occur in some transgender men who have undergone oophorectomy. A 35-year-old female-to-male transgender man presented with symptoms of severe and frequent VMS that began shortly after

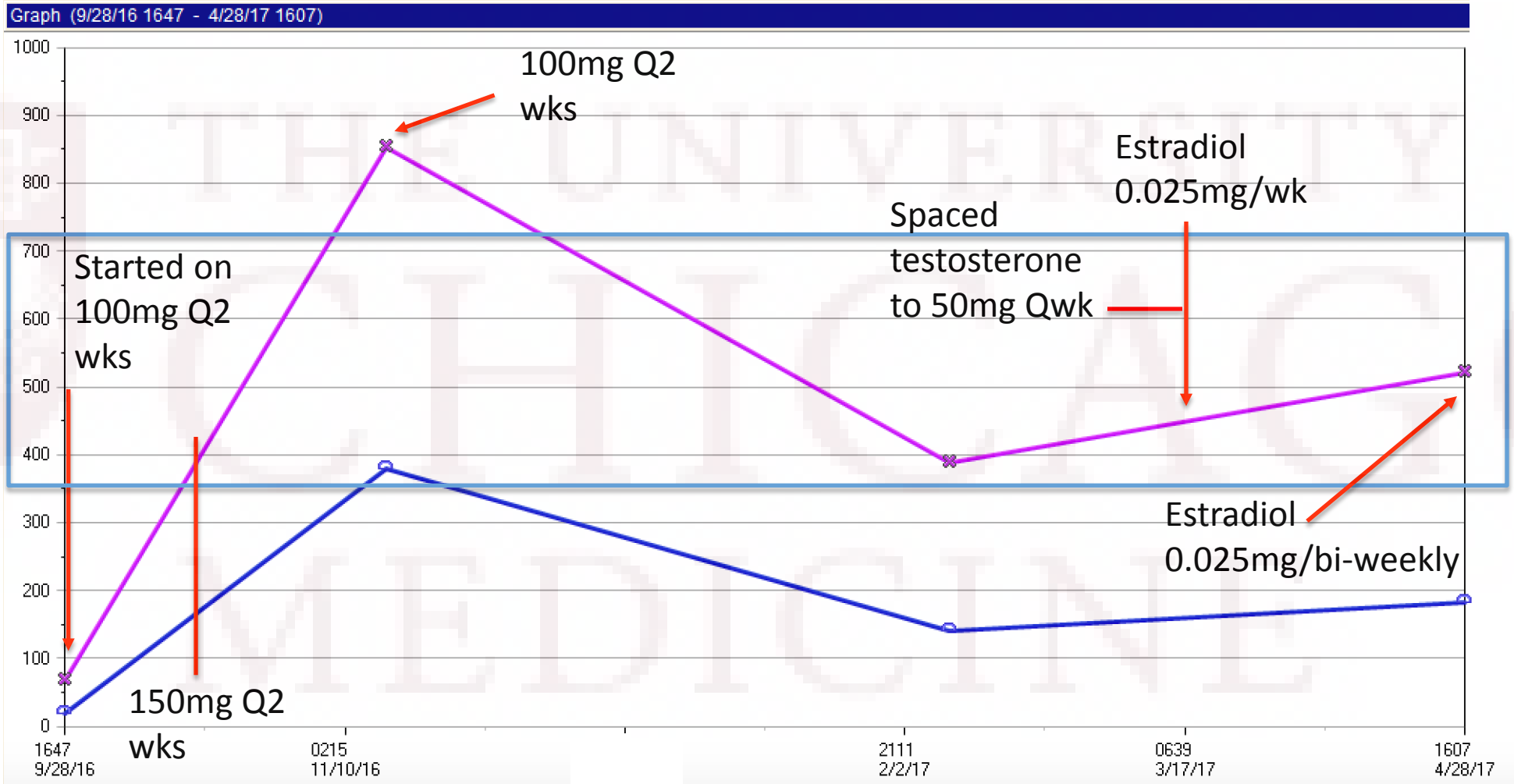
Patient HPI

- 35yo female to male transgender Pt presenting for continuation of testosterone
- Born genetically female but identifying as male since an early age & on T x 4 yrs
- Since removal of ovaries & uterus has been having significant “hot flashes” reports occurring “every hour”
- Reports symptoms are “very bothersome and embarrassing” significantly disrupting daily life

Estradiol Patch Increased from 1 to 2x Week; Asked to Increase Testosterone Dose



Estradiol Patch Increased from 1 to 2x Week; Asked to Increase Testosterone Dose



Pt continued T at 80mg Qwk; Symptoms of HFs improved on bi-weekly estrogen patches

Total Testosterone

Free Testosterone

	Estradiol 0.025mg 2x/wk & testosterone 80mg Qwk
Testosterone (ng/mL)	851
Estradiol (pg/mL)	43
Effects/Comments	Improved significantly but symptoms before patch is due

normal male reference ranges:

Testosterone: 400-700 ng/dL
Estrogen: 27 – 52 pg/mL

	Estradiol 0.025mg 2x/wk & testosterone 80mg Qwk	Off of estradiol patches and missed T dose
Testosterone (ng/mL)	851	233
Estradiol (pg/mL)	43	9
Effects/Comments	Improved significantly but symptoms before patch is due	Hot flashes returned just as before

normal male reference ranges:

Testosterone: 400-700 ng/dL
Estrogen: 27 – 52 pg/mL

	Estradiol 0.025mg 2x/wk & testosterone 80mg Qwk	Off of estradiol patches and missed T dose	Estradiol 0.037mg 3x/wk & testosterone 80mg Qwk
Testosterone (ng/mL)	851	233	414
Estradiol (pg/mL)	43	9	37
Effects/Comments	Improved significantly but symptoms before patch is due	Hot flashes returned just as before	Improved significantly, sometimes forget patch and will suffer

normal male referenc

Testosterone: 400-7(

Estrogen: 27 – 52 |

Progesterone?

- Progesterone therapies such as medroxyprogesterone (MPA) have been used as a second agent to lower testosterone concentrations in transgender women
- There are concerns regarding potential increased risk of thromboembolism and stroke found in cisgender women taking progesterone
  - Literature shows this has been MPA, not micronized progesterone (WHI)
- No clinical studies to support a positive effect of progesterone on breast development, only anecdotal

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Progesterone Is Important for Transgender Women's Therapy—Applying Evidence for the Benefits of Progesterone in Ciswomen FREE

Jerilynn C Prior ✉

The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 4, April 2019, Pages 1181–1186,
https://doi.org/10.1210/jc.2018-01777
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New Role for Progesterone in Feminizing HT Care?

- More rapid feminization: Progesterone competes for the 5-alpha reductase enzyme that converts T into DHT, the hormone that masculinizes skin and hair follicles. Thus, progesterone decreases the masculinizing effects of DHT on unwanted male-pattern hair

- Progesterone feeds back to the hypothalamus slowing the pulsatility of LH and lowering average LH levels, thus decreasing gonadal T production

- Progesterone and estradiol leads to optimal breast maturation and size; Progesterone is necessary for the ductal branching within the breast (and hence, for lactation) and eventual maturation leading to the enlargement of the normal ciswoman's areola diameter of ≥3 cm

- Progesterone adds to estradiol in increasing BMD

- Progesterone improves sleep and hot flushes/flashes (vasomotor symptoms)

What About Elevated Estradiol Levels in Transmen on Testosterone?

Elevated Estradiol in Transmen (FTM)

- Estrogen in the 100-200 range despite being on testosterone for years
  - Testosterone in the 600 range
  - No longer having menses
- In natal women we are concerned about unopposed estrogen in anovulatory cycles and concern for endometrial hyperplasia/increased risk for endometrial carcinoma
- Is there a risk for endometrial hyperplasia in transmen with unsuppressed estrogen levels?

Potential Risk of Endometrial Cancer

- Only two reported cases in the literature of endometrial cancer
- One was a trans male 54yo who started T at age 43 with cessation of menses at that time (Am J Obstet Gynecol. 2011 May;204(5)
- Presented for hysterectomy and found to have endometrial cancer
  - Reported spotting for the prior 4-5 years

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ARTICLE

Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population

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Analysis of genital tract from 112 FTM patients who underwent salpingoophorectomy

Conclusions From Study

- Ovarian architecture resembled those observed in women with PCOS
- Endometrial atrophy of the uterine mucosa was observed in ~50% of patients (50) after chronic androgen exposure
  - Cervical and myometrial histologies did not differ from those of natal women
- The other half showed proliferative or endometrial hyperplasia (54 vs 8)
  - One case of atypical endometrial hyperplasia with small focus of adenocarcinoma found
- Authors conclude there may be increased serum estrogen concentrations by aromatization

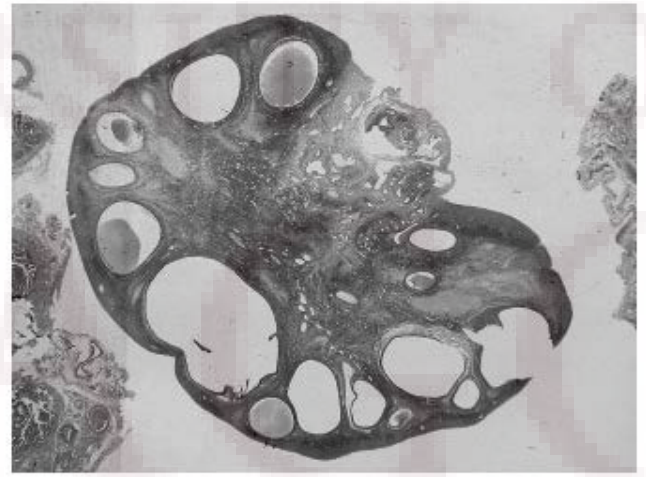

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Figure 1. Section through ovary of female-to-male transsexual showing multiple cystic atretic follicles (haematoxylin and eosin staining, 4× magnification).

Conclusions

- Gender-affirming treatment of transgender people requires a multidisciplinary approach in which endocrinologists play a crucial role
- Transgender patients seeking gender affirming care require a safe, effective hormone regimen that will 1) Suppress endogenous hormone secretion determined by biologic sex & 2) maintain sex hormone levels within the normal range for the person's desired gender
- Feminizing treatment with estrogens and antiandrogens has desired physical changes, such as enhanced breast growth, reduction of facial and body hair growth, and fat redistribution in a female pattern
    - Evaluate for conditions that can be exacerbated by HT (Hx of DVT, smoking, obesity, FH, hyper TG, and discuss RFs; consider transdermal treatment
- HT related cancers are rare, routine screening based on genital organs is highly recommended
- Prospective cohort studies focused on long term safety and efficacy are needed to optimize transgender care