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MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Providing Care for Transgender and Non-Binary Patients

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I have no disclosures

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Case

- Jason is a 24yo, assigned female at birth, who presents to your clinic requesting testosterone, and may want gender-affirming surgery in the future
- Jason sought you out because you are known to be LGBTQ friendly, and he has never felt comfortable with MDs
- As an OBGYN, you know a thing or two about hormones, but don't have a lot of experience in providing gender-affirming hormone therapy
- What now????

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Healthcare Considerations

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Health Care Needs

- Routine health care
  - Screening
    - Breast and cervix/uterus/ovaries in transmen
    - Breast and prostate in transwomen
    - STI in a traditionally high risk population
  - All other needs, with cultural competence
- Mental health care
  - High rate of need
  - Uncertain intersection of gender dysphoria and other mental health conditions

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Screening – GYN Cancer

- Transgender men with cervix require pap screening per ASCCP
  - Increased risk of insufficient sample on T therapy
    - Vaginal E2 can help
  - Need to tell pathology that sample will look like postmenopausal woman
- Transgender women do not require screening
- Screening for ovarian/endometrial cancer
  - Same recommendations as cisgender population

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Screening – Other Cancers

- Prostate Cancer
  - No PSA; instead, rectal or vaginal exam of prostate
- Breast Cancer
  - Same recommendations as cisgender population for anyone with breast tissue
  - Gender-affirming mastectomy does not always remove all breast tissue
- Colon Cancer
  - Same recommendations as cisgender population
  - Colonic neovaginas require vaginoscopy

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Health Care Needs

- Gender-affirming hormones
  - Transfeminine: estrogen, anti-androgen
  - Transmasculine: testosterone
- Surgery
  - Gender-affirming 'top' or 'bottom' surgery
  - Identity enhancing
    - Facial feminization/tracheochondroplasty/body contouring/implants
    - Vocal cord
    - Hair transplants

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Health Care Needs

- Reproductive care
  - Gamete cryopreservation/ART
  - Contraception/STI prevention
- Cosmetic options
  - Electrolysis/ laser for unwanted terminal hair
  - Counseling in make-up and hair care
- Behavior modification
  - Vocal coaching for pitch and speech patterns
  - Gender specific patterns of dress and action

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Hormone Therapy

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Guidelines for Care

- WPATH Standards of Care
  - Requires diagnosis of gender dysphoria, and any other mental health disorders controlled
  - Involves mental health professionals
- Informed consent model

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Beyond "WPATH" and "Informed Consent"

Universal Screening

Advantages	Disadvantages
Diagnosis of gender dysphoria	Creates barriers to care (financial, insurance, delay in care, lack of access)
Screening for severe mental illness	Decreases trust and honesty.
Practical reasons: assistance with bureaucracy, in preparation for surgery	Risk of exposing patients to non-affirming MHPs
	Increases stigma / pathologization

Referral of specific cases

Advantages	Disadvantages
Clarify identity or motivation	Concern over capability of many mental health providers
Support for patients with severe/uncontrolled mental illness	Futility
Clarify ability to give consent (mental/cognitive ability)	
Unrelated need for psychotherapy	

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Initiating Hormone Therapy

Extensive Discussion:

- Goals
- Expectations
- Risks and side effects
- Data limitations

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Two Primary Goals of Hormone Therapy

1) Induce the desired secondary sex characteristics ('Mini-puberty')

- Women: breast growth, body composition
- Men: voice deepening, terminal hair, body composition

2) Cause regression of already induced characteristics, through suppression of pituitary hormones (FSH/LH)

- Men: Amenorrhea, fat mass, some breast tissue
- Women: facial and body terminal hair, muscle mass, gonads, spontaneous erections
- Unnecessary after gonadectomy

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Adjunct goal of hormone therapy

- Do no harm
  - Short term:
    - Several studies of overall risk
  - Long term:
    - Few data on long term risks
- This is NOT evidence-based medicine
- Nonetheless, for most patients hormone therapy is not an elective option

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Peri-Pubertal Children

- There is no role for hormone therapy prior to puberty
- Gender dysphoria in adolescence likely to persist
- Gender dysphoria often worsens with onset of puberty
- No agreed upon age for starting hormone therapy

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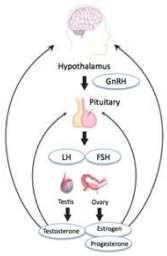
Peri-Pubertal Children

- GnRH analogues ideally initiated in tanner stage 2-3
  - Prevents development of unwanted secondary sex characteristics
- Progestins for menstrual suppression in postpubertal transfeminine youth not ready for hormone therapy



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Transfeminine Hormone Therapy

- Initial and principal therapy: Estrogens
  - Multiple formulations
  - Oral estradiol most common
  - Others may be safer
- If adequate suppression of testicular function is not achieved, consider adjunctive therapy, using:
  - Anti-androgens (usually used) – spironolactone, finasteride
  - GnRH agonists (rarely used)
- Progestins: Requests for breast growth
  - May actually inhibit breast growth early on
  - Contribution to breast cancer risk unclear

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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]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).
[a] Complete removal of male sexual hair requires electrolysis or laser treatment or both.
[b] Familial scalp hair loss may occur if estrogens are stopped.
[c] Treatment by speech pathologists for voice training is most effective.

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Risks of Estrogen Therapy

- VTE
- Macroprolactinoma
- Breast cancer
- CAD
- Cerebrovascular disease
- Cholelithiasis
- Hypertriglyceridemia

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Monitoring - Transfeminine

- Baseline, 2, 6, 12 months, then annually (varies)
  - Serum estradiol & testosterone
    - E2 100-200 pg/mL; T< 0.9 ng/mL.
  - Blood pressure
  - Electrolytes
- Per standard guidelines
  - Mammograms
  - Prostate

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Transmasculine Hormone Therapy

- Initial and principal therapy: Testosterone
- Routes
  - IM/SQ testosterone esters (cypionate or enanthate) - Standard
  - Transdermal gel
  - Transdermal patch (inconvenient & costly)
- If adequate suppression of ovarian function is not achieved, consider adjunctive therapy (rare):
  - Anti-estrogen (aromatase inhibitors, SERMs)
  - GnRH agonist

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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

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).
[a] Prevention and treatment as recommended for biological men.
[b] Menorrhagia requires diagnosis and treatment by a gynecologist.

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Risks of Testosterone Therapy

- Erythrocytosis (hct > 50%)
- Liver dysfunction
- Coronary artery disease
- Cerebrovascular disease
- HTN
- Breast or uterine cancer

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Monitoring - Transmasculine

- Baseline, 2, 6, 12 months, then annually
  - Serum testosterone & estradiol
    - T in the mid-normal male range; E2 <50 pg/mL.
  - Hemoglobin/hematocrit
  - Liver function tests
- Baseline, annually
  - Serum lipid profile
- Per standard guidelines
  - Gyn screening

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Assessment of Response

- *Short term:* Suppression of serum levels of the principal endogenous gonadal hormone
- *Long term:* Development of biological effects of the administered hormones, and suppression of the manifestations of the endogenous gonadal hormones

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Gender-Affirming Surgery

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Gender Affirming Surgery

- Irreversible and final
- Recommendation by an appropriate counselor
  - WPATH: **Two** letters for bottom surgery, one by an independent psychologist/psychiatrist
- Financial obstacles must be overcome
- Multidisciplinary surgeon teams
- May need several sessions of surgery

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Transfeminine Surgical Options

- Genital GAS
  - Orchiectomy
  - Penectomy with vaginoplasty/clitoroplasty/labiaplasty
- Cosmetic GAS
  - Augmentation mammoplasty (after achieving stable breast size)
  - Optional procedures to assist feminization:
    - Reduction chondroplasty
    - Suction lipoplasty/lipofilling
    - Rhinoplasty
    - Facial bone reduction, face-lift, blepharoplasty
    - Pectoral/gluteal implants
    - Vocal cord reconstruction

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Transmasculine Surgical Options

- Genital GAS
  - Hysterectomy +/- bilateral salpingo-oophorectomy
    - Usually laparoscopic
  - Vaginectomy
  - Phalloplasty or metoidioplasty
  - Scrotoplasty with testicular implants
- Cosmetic GAS
  - Reduction mammoplasty
  - Facial structure

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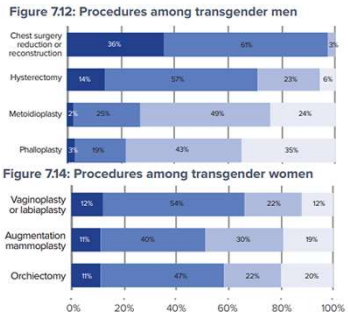

James *et al.*, National Center for Transgender Equality, 2016

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Reproduction in Transgender Individuals

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ASRM and Endocrine Society

ASRM:

- "Providers should **offer fertility preservation** options to individuals **before gender transition**"
- "…ensure that transgender patients who seek fertility services are informed about…the **lack of data** about long-term outcomes"

Endocrine Society:

- "All individuals seeking gender-affirming medical treatment should receive information and **counsel on options for fertility preservation prior to initiating** puberty suppression in adolescents and prior to treating with hormonal therapy in both adolescents and adults"

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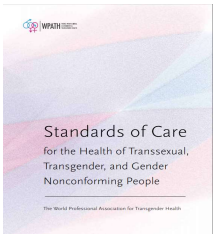
WPATH Guidelines

"Health care professionals… should **discuss reproductive options** with patients **prior to initiation** of these medical treatments for gender dysphoria."



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Effect of Gender-Affirming Tx on Fertility

- The effect of long-term gender affirming hormone therapy on future reproductive capacity is largely unknown
- Even less is known about fertility in transgender individuals who had puberty halted with GnRH agonists prior to starting hormone therapy
- Many gender affirming surgeries remove the gonads, and are therefore sterilizing

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Applicable Research

PUBMED (Sept 2020)

"cancer and fertility"
=15302

"transgender and fertility"
=169

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Psychosocial Data

- ~50% transgender people express a desire to have children
- ~40% transgender men would consider gamete cryopreservation
- Transgender men with children score better on mental health scales, and transgender women with children have a lower suicide risk
- There is no evidence that having a transgender parent results in adverse outcomes in long-term psychosocial functioning

De Roo C, et al. *Int Rev Psychiatry* 2015
Wierckx K et al. *Human Reprod* 2012
Hamada et al. *Andrologia* 2014

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Transgender Youth

- 24-36% transgender adolescents desire biologic parenthood
  - >25% "did not know"
- Qualitative study showed process is emotionally/physically demanding for transgender adolescents, even if:
  - Strongly desire fertility preservation
  - Had time to mentally prepare
  - Report satisfactory experience

Chen D, et al. *J Adolesc Health* 2018; Strang JF, et al. *J Adolesc Health* 2018; Chen & Simons. *Clin Pract Pediatr Psychol 2018*

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Options for Genetic Offspring

TRANSGENDER MEN	TRANSGENDER WOMEN
• Partner with sperm: – Willing/able to carry pregnancy—intercourse/IUI – Not willing/able to carry pregnancy—IVF with gestational carrier	• Partner with ovaries/uterus: – Partner willing to carry pregnancy – intercourse/IUI – Partner not willing/able to carry pregnancy – IVF with gestational carrier
• No partner with sperm: – Willing/able to carry pregnancy—donor insemination – Not willing/able to carry pregnancy – IVF to fertilize own eggs (donor sperm) and have partner or gestational carrier carry pregnancy	• No partner with ovaries/uterus: – Egg donation with gestational carrier
• Fertility preservation only: – Oocyte cryopreservation (postpubertal) – Ovarian tissue cryopreservation (pre- or postpubertal)	• Fertility preservation only: – Sperm banking (postpubertal) – Testicular tissue cryopreservation (prepubertal)

Moravek M, *Curr Opin Obstet Gyn*, 2019

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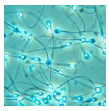

Fertility Considerations in Transgender Women

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Histologic Data

- Estradiol exposure leads to:
  - Smaller seminiferous tubules
  - Abnormal appearance of Sertoli and Leydig cells
  - Fatty degeneration of connective tissue
  - Impaired spermatogenesis (maturation arrest)
    - Regardless of anti-androgen use
    - Stage of maturation arrest and azoospermia incidence differed among studies

Levy M et al. *Sci Rep* 2017; Matoso A et al. *Hum Pathol* 2018; Kent MA et al. *Urology* 2018

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Effect of Estradiol on Semen Analysis

- Studies examining semen parameters both on E2 and after discontinuation
- Patients on estradiol – substantially worsened parameters, but sperm still present
- Extremely variable histology (even in women on E2)
- Level of gonadotropin suppression did not necessarily reflect degree of spermatogenesis
- Bottom line: FP is possible, although may not get same level of results

Schneider et al. *J Sex Med* 2015; Adeleye et al. *Fertil Steril* 2018.

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Transgender Women NOT on Estradiol

- Increased incidence abnormal semen parameters
  - Count
  - Motility
  - Morphology
- Pathophysiology unknown

Hamada A et al. *Andrologia* 2015; Li K et al. *Andrology* 2018

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Fertility Considerations in Transgender Men

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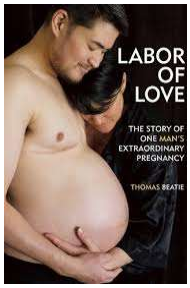
Popular Press



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Study on Pregnancy in Transgender Men

- Cross-sectional survey of 41 trans-men who had a live birth, mean age 28yo
- 84% of subjects on T before pregnancy used own eggs
- 32% conceived on T
- No difference in perinatal complications in those previously on T vs not

Table 2. Findings Among Those Who Used Testosterone Before Pregnancy of Report (n=25)

Characteristic	Value
Age (y) when testosterone was initiated	25 (17–35)
Length of testosterone use before pregnancy (y)	
Less than 1	10 (40)
1–2	6 (24)
3–10	4 (16)
More than 10	5 (20)
Stopped taking testosterone to become pregnant	17 (68)
Duration between stopping testosterone and resumption of menses (mo)	
No menses before pregnancy	5 (20)
Less than 1	2 (8)
1	6 (24)
2	7 (28)
3	4 (16)
4–6	1 (4)
Resumed or initiated testosterone after pregnancy*	20 (48)

Data are median (range) or n (%).
* Of total respondents in the study (N=41).

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Contents lists available at ScienceDirect
Contraception
journal homepage: www.elsevier.com/locate/con

Original research article

Family planning and contraception use in transgender men☆,☆☆

Alexis Light [a,*], Lin-Fan Wang [b], Alexander Zeymo [c], Veronica Gomez-Lobo [a,d]

- 197 transgender men
- 60 pregnancies among 32 respondents
  - 10 after stopping T, 1 while on T irregularly; most had never taken T
  - Those who had never taken T were nearly 3x more likely to have been pregnant than those who had taken T (36% vs 13.8%)
- 51% reported that their healthcare providers had not asked about their fertility desires

Light et al. 2018

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Case Series – Fertility Preservation

- **Maxwell et al**
  - Three transgender men who underwent oocyte cryopreservation prior to starting T
  - 2/3 have returned to use them with partner carrying pregnancy
- **Wallace et al**
  - Single case of transgender adolescent who underwent oocyte cryopreservation prior to starting T
- **Chen et al**
  - Five transmasculine youth who underwent oocyte cryopreservation prior to starting T
  - Higher than expected gonadotropin requirements
- **Rothenberg et al**
  - Case of oocyte cryopreservation in transgender adolescent who had been on GnRHa since Tanner Stage 2
  - Remained on GnRHa during stimulation

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Qualitative Experiences of Fertility Preservation

- Qualitative study of 15 transmen who had completed oocyte cryopreservation
  - 7 had started testosterone prior
- Majority found resumption of menses and increased estradiol levels to be psychologically distressing
- Regret not assessed
- Medical outcomes not assessed

Armuand G, et al. *Hum Reprod* 2017

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Study of ART Outcomes

	Cisgender Women (n=13)		Transgender Men				P-Value	
			All Transgender Men (n=13)		Transgender men with no testosterone (n=6)	Transgender men with testosterone history (n=7)	Cis vs. Trans[a]	T vs no T[b]
Peak Estradiol (pg/mL)	2753	[2268-4508]	2335	[1175-2800]	2713.5	[2335-3105]	1175	[559.5-2684]	**0.016**	**0.046**
Peak Estradiol per oocyte (pg/mL)	161.7	[141.3-185.3]	129.4	[99.4-145.9]	130.5	[100.0-145.9]	117.6	[97.9-178.9]	0.100	1.000
Oocytes retrieved	20	[18-27]	18	[12-27]	25.5	[18-28]	12	[4-26]	0.294	**0.038**
Number of M2s	16	[11-25]	13	[9-22]	14.5	[13-23]	9	[4-21]	0.396	0.148
Maturity rate(%)	83.3	[78.2-88.9]	84.4	[73.6-96.2]	77.2	[59.3-86.7]	91.2	[77.8-100]	0.823	0.147

Quality not known

Adeleye AJ, et al. *JARG* 2019

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Ovarian Tissue Cryopreservation?

- "Experimental," but promising results
- Could be performed at time of gender-affirming oophorectomy
- Provider/patient must be okay with relatively little data on both OTC and the effect of T on the ovaries

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Questions Remain

- There is likely a gap between the percentage of transgender individuals who desire children and those who have them
- Limited data on whether long-term gender affirming hormone treatment with testosterone or estradiol has an irreversible effect on gametes or offspring
- There are no data on effect of puberty blockers or testosterone administration in adolescents on future fertility

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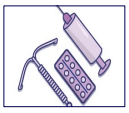

Contraception

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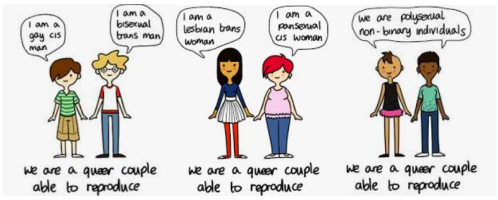
Assume not…



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≠ contraception

≠ contraception

Slide courtesy of H. Crissman, MD

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Contraception use among transmen - survey

- 62% had ever contracepted; 42% currently contracepting
- 40% not contracepting, with unclear pregnancy intentions
- 16% reported using T as contraceptive
- 5.5% reported their healthcare provider *told them* T was contraception

Light et al. 2018. Contraception

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Contraceptive options, transmen

- All of the same options as cisgender women
  - Progesterone-only options do not interfere with masculinization
- Potential discomfort with/need to avoid natal-female hormones
- Copper IUD side effect profile improved with T use

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Contraception use among transwomen

- No data regarding condom use by transwomen engaged in sex with pregnancy potential
- No data regarding contraceptive use by the partners of transwomen engaged in sex with pregnancy potential

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Inclusive Reproductive Care

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Common GYN Problems – Pelvic Pain

- Pelvic pain common complaint
  - Cramping- cyclical (with or without menses/bleeding), post orgasm cramping
  - Vs. with penetration
- Etiology: testosterone/hypo-estrogen effects vs standard differential
  - Endometriosis, fibroids, interstitial cystitis
- Consider progestin, vaginal estrogen, or DHEA
- Gender Affirming Pelvic Physical Therapy
- If imaging needed, consider abdominal US
  - Consider topical lidocaine or benzo for vaginal US
- Discuss hysterectomy if uterus significant cause of dysphoria
  - Not always effective in addressing pelvic pain

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Common GYN Problems – Irregular Bleeding

Differential:

- Irregular testosterone dosing- inconsistent access to hormones
- Insufficient testosterone dosing
- Aromatization to estrogen with higher doses of testosterone
- Thinned, destabilized endometrium
- Infection
- Neoplasm of cervix or endometrium (cancer rare)
- Pregnancy
- Often no etiology found

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Create an Inclusive Space

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CREOG Training Modules

Stroumsa *et al.*, CREOG, 2018

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CREOG Training Modules

Stroumsa *et al.*, CREOG, 2018

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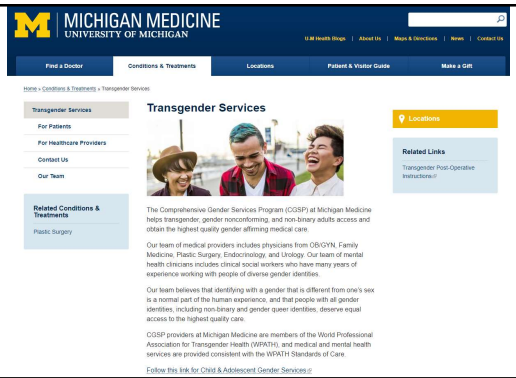

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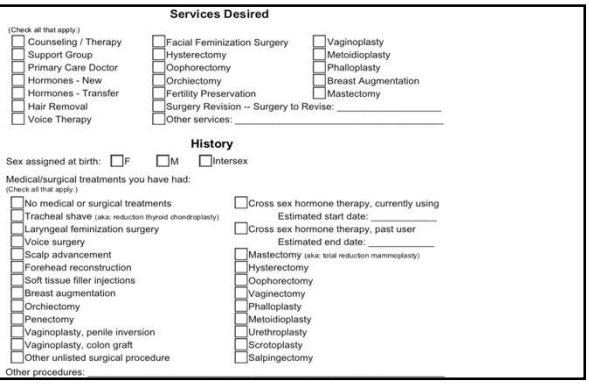

Services Desired

(Check all that apply.)

- Counseling / Therapy
- Support Group
- Primary Care Doctor
- Hormones - New
- Hormones - Transfer
- Hair Removal
- Voice Therapy
- Facial Feminization Surgery
- Hysterectomy
- Oophorectomy
- Orchiectomy
- Fertility Preservation
- Surgery Revision -- Surgery to Revise: _____
- Other services: _____
- Vaginoplasty
- Metoidioplasty
- Phalloplasty
- Breast Augmentation
- Mastectomy

History

Sex assigned at birth: ☐F ☐M ☐Intersex

Medical/surgical treatments you have had:
(Check all that apply.)

- No medical or surgical treatments
- Tracheal shave (aka: reduction thyroid chondroplasty)
- Laryngeal feminization surgery
- Voice surgery
- Scalp advancement
- Forehead reconstruction
- Soft tissue filler injections
- Breast augmentation
- Orchiectomy
- Penectomy
- Vaginoplasty, penile inversion
- Vaginoplasty, colon graft
- Other unlisted surgical procedure
- Cross sex hormone therapy, currently using
  Estimated start date: _____
- Cross sex hormone therapy, past user
  Estimated end date: _____
- Mastectomy (aka: total reduction mammoplasty)
- Hysterectomy
- Oophorectomy
- Vaginectomy
- Phalloplasty
- Metoidioplasty
- Urethroplasty
- Scrotoplasty
- Salpingectomy

Other procedures: _____

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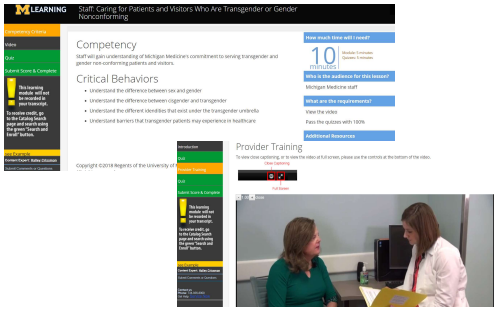
Staff Education



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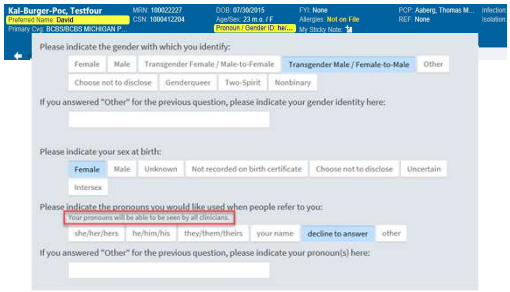
Changes in EMR



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Additional Information

- http://www.wpath.org/
- http://transhealth.ucsf.edu/
- https://transequality.org/issues/national-transgender-discrimination-survey
- http://fenwayhealth.org/care/medical/transgender-health/

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CLINICAL PRACTICE GUIDELINE

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]

https://academic.oup.com/jcem/article/102/11/3869/4157558

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Acknowledgments

- University of Michigan Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology
- Michigan Medicine Comprehensive Gender Services Program
- Funding: ASRM/SREI Research Grant; NICHD-NIH R01 HD098233-01

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MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Thank You!!

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CASES- GENDER AFFIRMING HORMONE MANAGEMENT

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CASE 1 – M.D. (CVD)

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M.D

- 55 yo affirmed woman
- AMAB, pronouns: she/her/hers
- 4/2018: requesting feminizing GAHT

76

PMH

- Type 2 insulin dependent DM. HbA1C 11% (8.7-15.3%)
- Metabolic syndrome with hyperlipidemia, HTN, BMI 38
- DVTs (2002, 2014), TIAs, CVA (2007)
- Thrombophilia, unspecified
- Chronic anticoagulation – Eliquis 5 mg BID
- CAD in mid-LAD per 2002 cath (incomplete); atrial septal aneurysm
- Bil. Carotid a. stenosis
- Erectile dysfunction (prior to anti-androgens)

77

Meds

- ASA 81 mg
- Fenofibrate
- High-dose Losartan
- Warfarin → Apixaban
- Buspirone

78

Social Hx

- Reports hx of DSD, low testosterone
- Married + 4 children (2 biological).
- Lives with her wife (hesitantly supportive)+ 2 adult children
- Fixed income (Arby's, maintenance work)
- Limited mobility
- Depression
- Limited engagement in primary care
- Non smoker, no substance use.

79

Shared decision making

- 1. Initiation of anti-androgen
- 2. Primary care and control of risk factors
- 3. Optimal secondary prevention: therapeutic anticoagulation, anti-platelet agent, high-dose statin
- 4. Minimize added risk: recommended transdermal estradiol at lowest satisfactory dose
  - Not covered, unable to afford cost; declined injections → sublingual
- 4. Full engagement in care and with risks

80

CASE 2 – K.L (THROMBOEMBOLIC DIS.)

81

K.L

- 56 yo affirmed woman
- AMAB, pronouns: She/her/hers
- Oct 2018: seeking hormone prescriber clearance for gender affirming vaginoplasty. Was told she is not a candidate for feminizing hormones.

82

PMH

- 2016 – Bil. LL segmental + subsegmental provoked PE, one month s/p initiation of GAHT
- Coumadin until 9/2018
- 40 pkyrs smoker.
- Currently 3-4 cigarettes/day (10 per day as documented in PCP notes). Declines pharmacotherapy

83

PMH

- Records review:
- History of alcoholism
- COPD
- Psoriatic arthritis, on MTX
- Osteoporosis, lumbar z score of -2.7
- Sick Sinus Syndrome, pacemaker in place (2008 →2017)
- GERD+ Barrett's esophagus

84

SH, FHx

- Recently lost her wife (sepsis) .Lives with her 27 yo stepson (supportive).
- Mother – metastatic cancer of uk primary; DM, HTN, COPD;
- Father – cancer (unsure)
- Sister – DM
- Negative for thrombosis

85

Plan

- Labs, followed by spironolactone
- Vascular medicine consult
- If appropriate, once recommendations received:
  transdermal estradiol 0.05 mg/24 h with subsequent increase to 0.1 mg/24h
- Initiated spiro 50 mg BID by PCP

86

Vascular medicine consult

- Prior to appointment: Cr 1.4. PCP d/ced spiro, started ketoconazole
- Quit smoking
- Rec: secondary VTE prophylaxis for combination of: Hx of provoked PE + estrogen
- 10 mg daily of rivaroxaban – low dose given ketoconazole (cyp3A4 inhibition)
- Follow lipids, if still elevated on E2 consider low- mod. Intensity statin.

87

- 3/2019 – initiated 10 mg/d of Rivaroxaban
- Transdermal estradiol 0.05 mg/24 → 0.1 mg/24h
- Rivaroxaban declined by insurance → Warfarin, goal INR 2-3
- Delay in initiation of E2 due to insurance authorization
- Transaminitis (70s), nausea, testicular pain attributed to ketoconazole → antiandrogen discontinued
- Started Pravachol; TC 260→ 199, LDL 166→ 100

88

Labs

	8/2019
Estradiol	106 pg/mL
Testosterone, total	24.5 ng/ mL
Cr	1.2
INR	2.8-3.2

89

- 10/22/2019:
- New diagnosis of monocolonal gammopathy
- Continued breast soreness & development
- Fat redistribution
- Some reversal of male pattern baldness (+ terminal crown hair)

90

Direct oral anti Xa inhibitors

- Apixaban (Eliquis) – twice daily dosing. 25% renal excretion
  - M.D. is on 5 mg BID dosing – dose for CVA ppx in A.fib
- Rivaroxaban (Xarelto) – once daily dosing. 35% renal excretion.
- Interact with CYP-3A4 and P-glycoprotein inhibitors – including Ketoconazole→ dose reduction
- Significant decrease in anticoagulation with missed doses

91

CVD risk reduction and feminizing estrogen

- 2,842 transfeminine people, matched cisgender men + women (~27,000 each)
- Mean f/u 4.0 years
- Data on age, smoking, BP, BMI, cholesterol
- Separate analysis for pts who initiated GAHT after enrollment

Getahun *et al.*, Annals of Internal Medicine, 2018

92

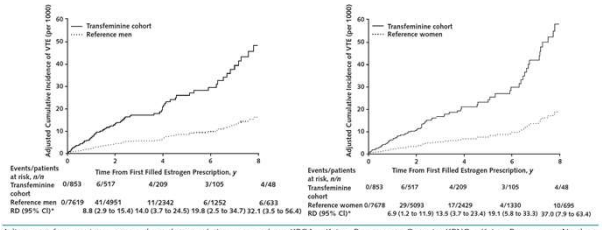
CVD risk reduction and feminizing estrogen

- Increased VTE risk at 2- and 8-years
- Risk differences of 4.1 (95% CI, 1.6 to 6.7) and 16.7 (CI, 6.4 to 27.5) / 1000 persons, relative to cisgender men
- and 3.4 (CI, 1.1 to 5.6) and 13.7 (CI, 4.1 to 22.7) relative to cisgender women.
- Ischemic stroke, MI - similar incidence across groups.
- More pronounced differences for VTE and ischemic stroke among participants who initiated hormone therapy during follow-up.

Getahun *et al.*, Annals of Internal Medicine, 2018

93

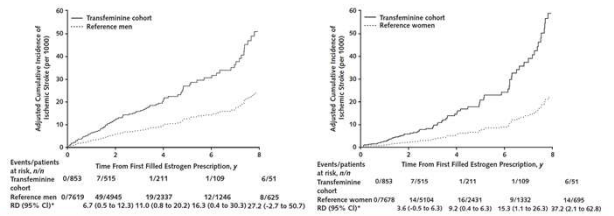
Figure 1. Adjusted cumulative incidence curves comparing rates of VTE among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006–2016.



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.

94

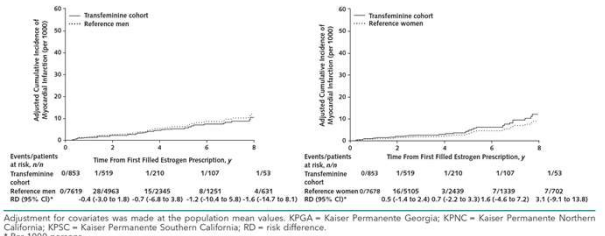
Figure 2. Adjusted cumulative incidence curves comparing rates of ischemic stroke among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006–2016



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.

95

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.

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Prothrombotic effects of estrogen

- Increased levels of factors II, VII, VIII, X, and fibrinogen,
- Decreased levels of antithrombin, protein S
- Activated protein C resistance

97

CASE 3 – E.E (UTERINE BLEEDING ON TESTOSTEREONE)

98

E.E.

- 30 yo affirmed man
- AFAB, pronouns: he/him/his
- Presents with abnormal bleeding on testosterone

99

PMH/ PSH

- Mild intermittent asthma
- Anxiety, well controlled (Lexapro)
- BMI 30
- Insomnia; OSA?
- D&C at age 21

FHx

- Negative for thromboembolic disease, bleeding, CVD, cancer

100

SH

- Lives with fiancée (cisgender male) and son (8 yo)
- Graphic designer/manager
- Rare EtOH, past smoker ~4pkyr, no drugs.
- History of rape as a child. Undergone therapy. Currently safe.

101

OB/Gyn Hx

- G2P1011
- NSVD X1; No postpartum hemorrhage
- Menarche at age 13
- Regular, lasting 3-6 days, heavy bleeding, moderate cramping
- Mirena IUD placed following delivery, no further bleeding until testosterone

102

Medical transition history

- 11/2016 – initiated testosterone
- Testosterone cypionate, 100 mg IM qw
- Cramping- responds to NSAIDs

103

IUD

- 1/2017: Mirena IUD replaced.
- Cramping
- 10/2018: cramping. IUD in cervical canal (per CT in ED); replaced.
- f/u US confirms appropriate positioning
- Cramping. No documentation of bleeding

104

- August 2018:
- Ongoing intermittent bleeding since IUD replacement. Non-cyclical. 3-4/month

105

Bleeding evaluation and treatment

- Testosterone levels 6.2-9.3 ng/mL
- Estradiol 44-58 pg/mL
- CBC: 15.5 / 47.3, 5.4, 181
- TSH 2.01 mIU/L
- PRL 5 (11/2016)
- uHCG negative (11/2016)

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Bleeding evaluation and treatment

- Pap ASCUS / HPV negative 5/2017
- Doxycycline 100 mg BID X 14 d
- Estradiol 2 mg oral daily X7d

107

Additional history

- + Bleeding from gums
- No epistaxis
- + vague FHx of heavy menses in mother, aunts

108

	Ref. Range	1/22/2019
Partial Thromboplastin Time	22.0 - 29.0 sec	25.2
Factor 8 Assay	50 - 150 %	102
Vonwillebrand's Factor Antigen	50 - 150 %	71
Ristocetin Cofactor Assay	50 - 150 %	61

Interpretation pending

109

Uterine Pathology in Transmasculine Persons on Testosterone: a retrospective case series

- Retrospective, multi-center case series
- N=94
- Mean age = 30, +/- 8.6y
- Interval from testosterone initiation 36.7 +/- 36.6 mo
- BMI 29.6 +/- 7.3 kg/m2

Grimstad *et al.,* AJOG. In press.

110

Bleeding and cramping

- 52 had complete gyn documentation. Of these:
- Persistent bleeding n=12(23.1%)
- Pelvic pain / cramping n=30 (57.7%)

Grimstad *et al.,* AJOG. In press.

111

Endometrial evaluation

- 23 had ultrasound evaluation
- Mean endometrial thickness 4.9mm +/- 2.1 (95% CI 4.0-5.9)
- Not associated with testosterone duration
- Active endometrium: (N=65; 69.1%)

Grimstad *et al.,* AJOG. In press.

112

Endometrial pathology

- N=94
- Atrophic endometrium n=23 (24.5%)
- Secretory endometrium n=4 (4.3%)
- Proliferative endometrium: n=61 (64.9%)
- No association with testosterone duration
- Similar distribution when excluding pts on E2/ progesterone
- No association with US EM thickness

Grimstad *et al.,* AJOG. In press.

113

Bleeding and cramping

- Amenorrhea not assoc/w estrogen or progesterone use
- Persistent bleeding was not assoc/w obesity or active endometrium
- No difference by testosterone levels

Grimstad *et al.,* AJOG. In press.

114

Other uterine pathology

- Polyps, fibroids, adenomyosis
- Hyperplasia w/o atypia
- Endometrial adenocarcinoma

- Suggested interventions for persistent bleeding: progresterone; aromatase inhibitors

Grimstad *et al.,* AJOG. In press.

115

Bleeding patterns with LNG 52 mg-IUD

- prospective multicenter trial; n = 1700 (cisgender women)
- Amenorrhea at 1 year – 19%
- Amenorrhea at 3 years – 37%
- Infrequent bleeding 14%→ 30% (1 year)

- Did not vary by parity or obesity

Schreiber *et al.*, Eur J Contracept Reprod Health Care. *2018*

116

Bleeding patterns with LNG 52 mg-IUD

- Contraceptive CHOICE study; n= 1802 (cisgender women)
- Participants with self-reported heavy bleeding at baseline were less likely to report amenorrhea at 12 months than those who reported moderate bleeding (aOR, 0.36; 95% CI, 0.16-0.69)

Mejia *et al.*, Contraception. *2016*

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