An Approach to the Transgender Patient

Aren Skolnick D.O.

Medicine and Surgery Grand Rounds

October 25, 2018

CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

- **COURSE NAME:**
- Medicine RSS eLearning Modules

- **CME eLEARNING ACTIVITY NAME:**
- An Approach to the Transgender Patient

PROGRAM DESCRIPTION, EDUCATIONAL GOAL AND RATIONALE:
Evidence based guidelines are constantly changing and being updated for several core areas of Internal Medicine throughout the year. It is important for physicians to practice the most up-to-date standard of care in all specialties to promote patient health and well-being. Our series of lectures at the medicine regularly scheduled series promotes continuing education for the practicing internist and highlights important updates in medical practice in these core areas. Physicians in general practice often and do not have the time to keep themselves up-to-date with medical advances as they are busy seeing patients in the clinical setting. The Medicine Regularly Scheduled Series gives these physicians the opportunity to learn these advances in an academic setting.

CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

- **TARGET AUDIENCE:**
- Physician Partners and Premium Network community-based providers

LEARNING OBJECTIVES:

Upon successful completion of this activity, participants should:

- Define gender dysphoria
- Identify treatment methods for gender dysphoria
- Identify risks & outcomes of treatment methods

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  Attending Physician
  Department of Medicine, Northwell Health

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  Site Director, Division of Hospital Medicine, Long Island Jewish Medical Center

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- **To receive credit the participants must:**
- Read/view the entire educational activity.
- Input name and credentials to gain CME credit.
- Answer at least 80% of the Post-Test questions correctly.
- Complete and return Post-Test.
- Complete and return Program Evaluation.

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CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

- **COURSE HOST:**
- Department of Medicine
- Northwell Health
-
- **ESTIMATED TIME TO COMPLETE ACTIVITY:**
- 90 minutes
-
- **ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT:**
- An announcement of program support will be made to all attendees at the beginning of each educational activity.

CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

- **DISCLOSURE POLICY:**
- Northwell Health adheres to the ACCME's Standards for Commercial Support. Any individuals in a position to control the content of a CME activity, including faculty, planners, reviewers or others are required to disclose all relevant financial relationships with commercial interests. All relevant conflicts of interest will be resolved prior to the commencement of the activity.
-
- **FACULTY DISCLOSURES:**
- Drs. Thomas McGinn, Dr. Aren Skolnick, George Boutis, John Raimo and Sean LaVine have nothing to disclose.

- **RELEASE DATE:** 1/18/19
- **REVIEW DATE:** 1/18/19
- **PROGRAM EXPIRATION:** 7/30/19

Disclosures

- None

Review of Terms

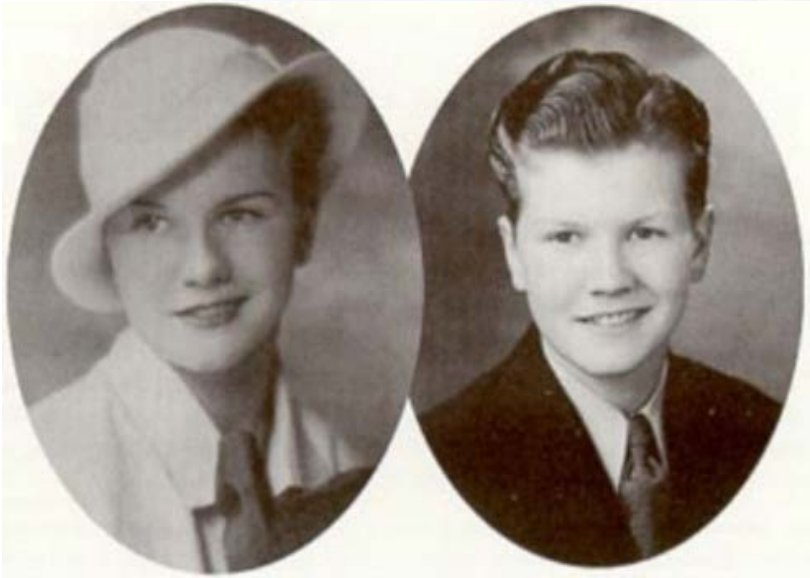
GENDER
GENDER ROLE
GENDER IDENTITY
SEXUAL ORIENTATION

Definitions

- **Gender Dysphoria= Gender Identity Disorder**
  - The desire to live and be accepted as a member of the opposite sex usually accompanied by the wish to make the body as congruent as possible with the preferred sex through surgery and hormone treatment. (WHO)
  - Discomfort or stress from the discrepancy in gender identity an assigned sex at birth (DSM)

    (Fisk, 1974; Knudson, DeCuypere, & Bockting, 2010b).

Transgender History



The World of Transgender Today

Epidemiology

- Difficult assessing due to cultural differences
- Most studies performed in Europe
- De Cuypere and colleagues (2007)
  - range from 1:11,900 to 1:45,000 for male-to-female individuals (MtF)
  - 1:30,400 to 1:200,000 for female-to-male(FtM) individuals.
- Likely underestimated
- Direct comparisons across studies are difficult

Treatment

- Improve quality of life
  - Psychological
    - Explore gender identity role
    - Impact of gender dysphoria
    - Enhance social and peer support
    - Improve body image
  - Medical
    - Hormone Therapy
  - Surgical
    - Change primary and/or secondary sex characteristics

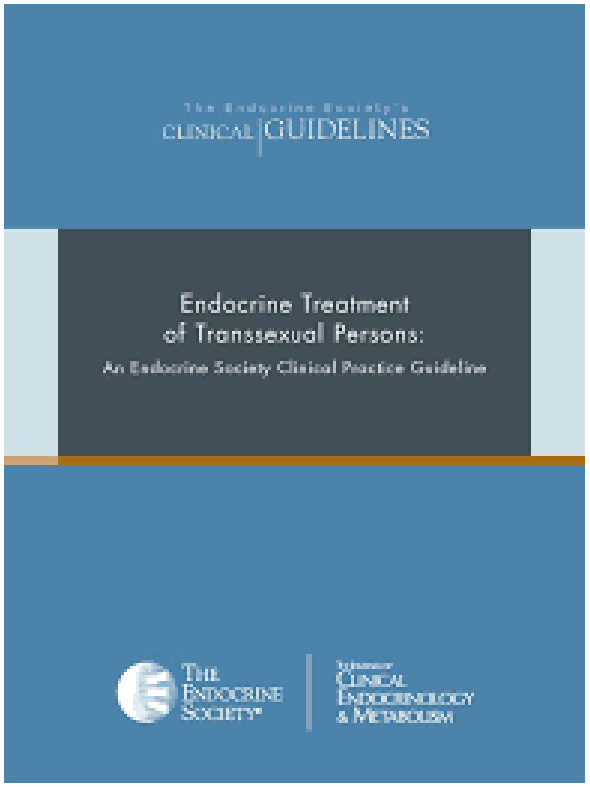
Mental Health Professionals

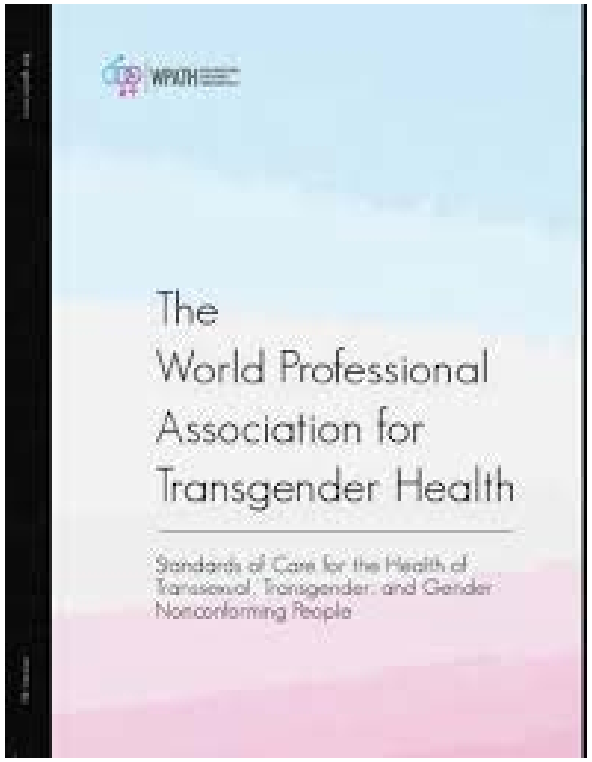
- Competency
- Assess Gender Dysphoria
- Information for various options
- Assess and treat co-existing diagnoses
  - "Minority Stress"(Meyer, 2003)
- Prepare and refer for hormone treatment and/or surgery
- Referral for peer support
- Access to care issues

Hormonal Therapy

- Individualized
  - Goals
  - Risk vs. Benefits
  - Other medical conditions
  - Social factors
  - Economic issues

Guidelines





GLMA
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Hormonal Regimens

- No randomized clinical trials comparing safety and efficacy
- Observational and Anecdotal

Feminizing Hormone Therapy

- Estrogens
  - Oral
  - Transdermal
  - Parenteral
- Antiandrogens
  - Spironolactone
  - Cyproterone acetate
  - 5-alpha reductase inhibitors
- GnRH Analogs

Physical Effects of Hormonal Therapy

Effect	Expected onset[b]	Expected maximum effect [b]
Body fat redistribution	3–6 months	2–5 years
Decreased muscle mass/strength	3–6 months	1–2 years[c]
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	1–2 years
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 years
Decreased testicular volume	3–6 months	2–3 years
Decreased sperm production	Variable	Variable
Thinning and slowed growth of body and facial hair	6–12 months	> 3 years[d]
Male pattern baldness	No regrowth, loss stops 1–3 months	1–2 years

Masculinizing Hormone Therapy

- Testosterone
  - Oral*
  - Transdermal
  - Parenteral
  - Buccal
  - Implantable

Table 1. Testosterone Replacement Therapies Approved for Use in the U.S.[1]

Delivery System (Drug)	Route of Delivery	Standard Dosage for Androgen Deficiency	Advantages	Disadvantages	Estimated Monthly Cost
Testosterone esters					
Testosterone enanthate	IM	100 mg every week or 200 mg every 2 weeks	Inexpensive; administered every 2 weeks	Roller-coaster pharmacokinetics; requires injection	$100
Testosterone cypionate					
Testosterone pellets	SC	Two to six 75-mg pellets every 3 to 6 months	Convenient 6-month biological duration	Expensive; requires small incision; high rate of extrusion; available only through manufacturer	$150
Buccal testosterone	Buccal	30 mg BID	Testosterone levels within physiologic range	Expensive; twice-daily dosing; possible oral irritation	$250
Testosterone patch	Nonscrotal topical	5 mg/day	Mimics circadian rhythm	Expensive, daily administration; skin irritation	$250
Testosterone gel	Topical	5 g/day	Testosterone levels within physiologic range	Expensive; daily administration; possible transference to intimate contacts	$300

Adapted with permission from Edelstein D, Dobs A, Basaria S. Emerging drugs for hypogonadism. *Expert Opin Emerg Drugs*. 2006;11(4):685-707.[1]

Subcutaneous Testosterone

CLINICAL RESEARCH ARTICLE

Subcutaneous Injection of Testosterone Is an Effective and Preferred Alternative to Intramuscular Injection: Demonstration in Female-to-Male Transgender Patients

Daniel I. Spratt,[1] India I. Stewart,[1] Clara Savage,[1] Wendy Craig,[2] Norman P. Spack,[3] Donald Walt Chandler,[4] Lindsey V. Spratt,[1] Toni Eimicke,[5] and Jerrold S. Olshan[5]

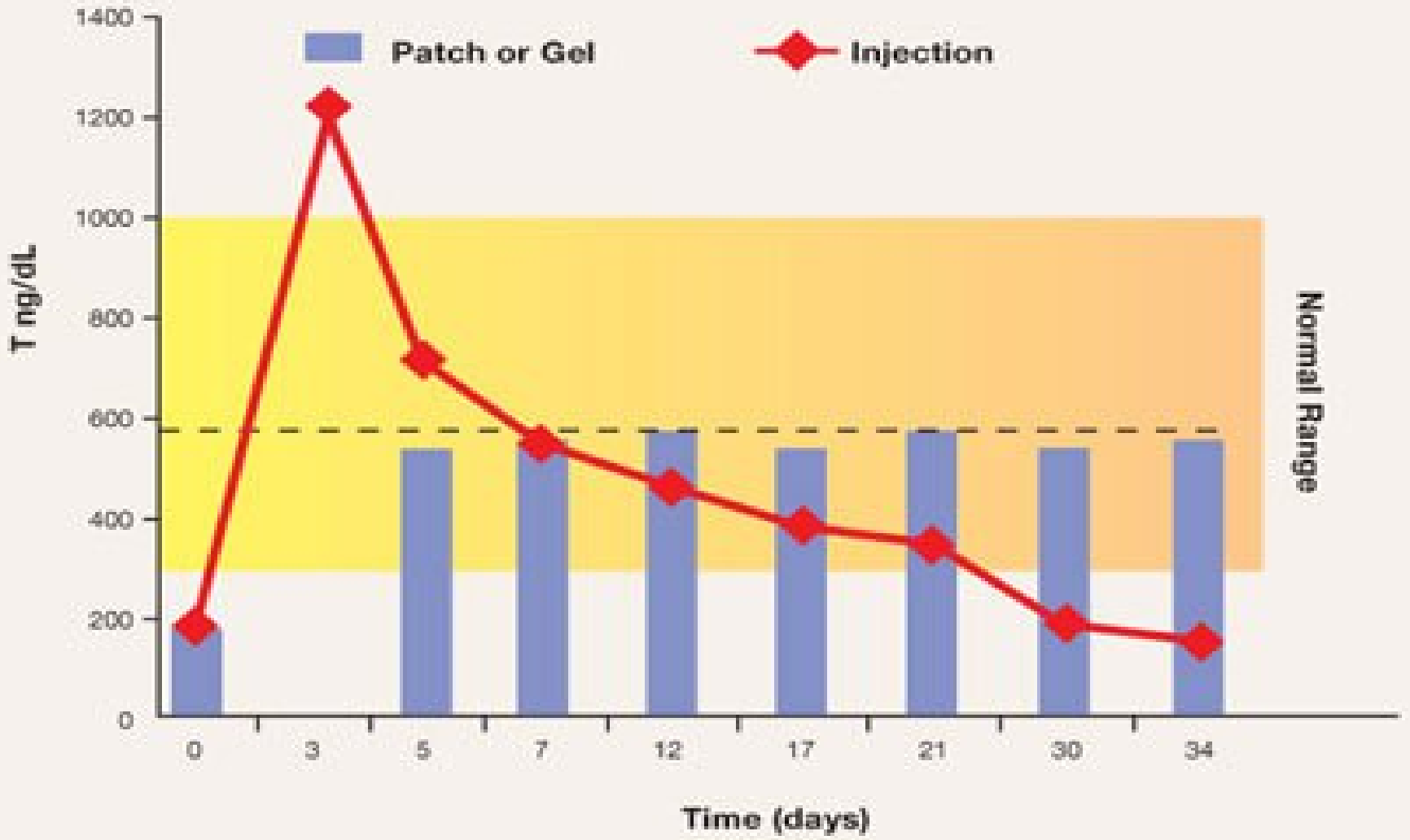
[1]Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Maine Medical Center, Portland, Maine 04102; [2]Maine Medical Center Research Institute, Scarborough, Maine 04704; [3]Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts 02115; [4]LabCorp, Calabasas, California 91301; and [5]Department of Pediatrics, Division of Pediatric Endocrinology, Maine Medical Center, Portland, Maine 04102

Physical Effects of Hormone Therapy

TABLE 1a. Effects and Expected Time Course of Masculinizing Hormones[a]

Effect	Expected onset[b]	Expected maximum effect[b]
Skin oiliness/acne	1–6 months	1–2 years
Facial/body hair growth	3–6 months	3–5 years
Scalp hair loss	>12 months[c]	Variable
Increased muscle mass/strength	6–12 months	2–5 years[d]
Body fat redistribution	3–6 months	2–5 years
Cessation of menses	2–6 months	n/a
Clitoral enlargement	3–6 months	1–2 years
Vaginal atrophy	3–6 months	1–2 years
Deepened voice	3–12 months	1–2 years

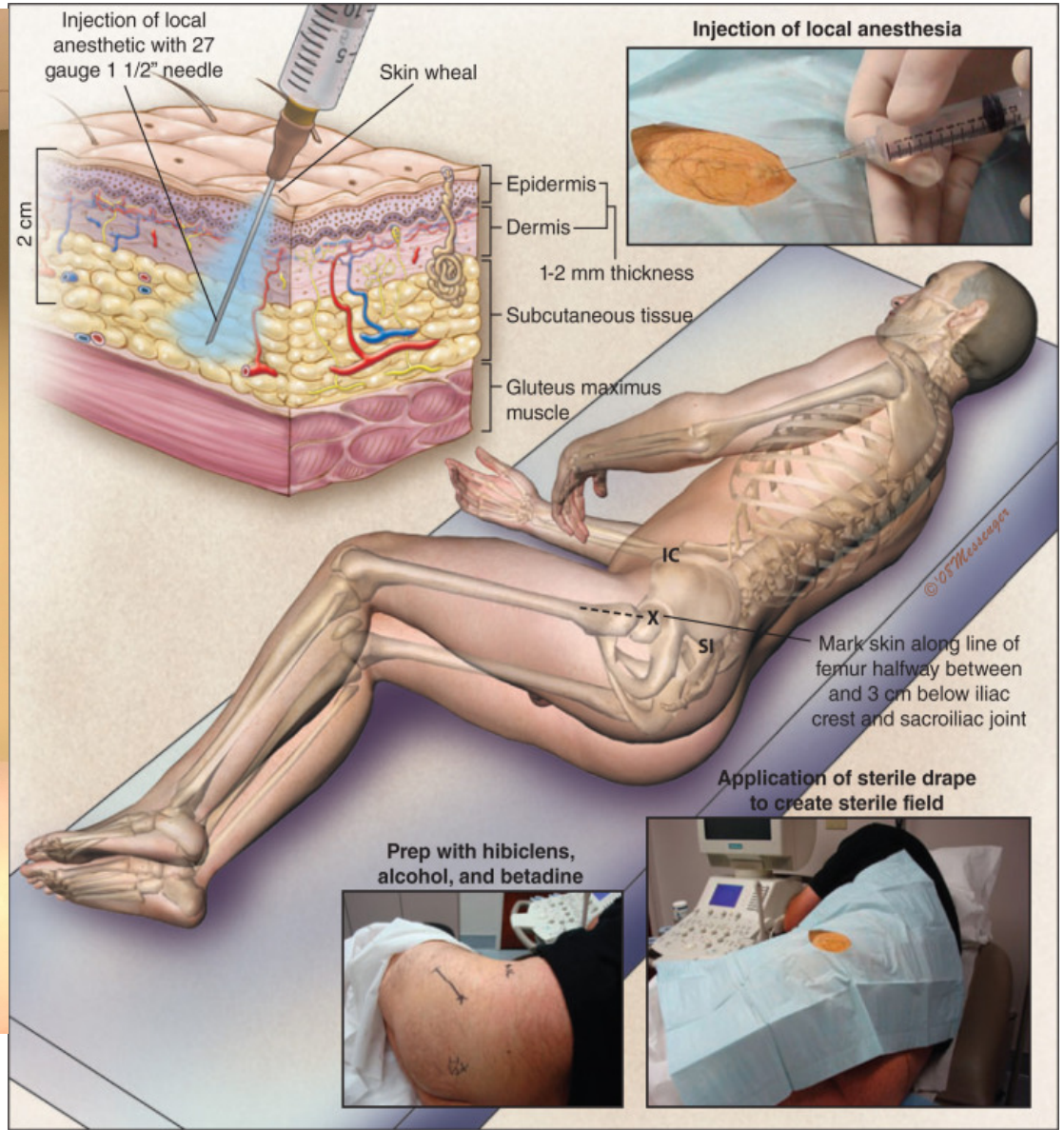
[a] Adapted with permission from Hembree et al. (2009). Copyright 2009, The Endocrine Society.
[b] Estimates represent published and unpublished clinical observations.
[c] Highly dependent on age and inheritance; may be minimal.
[d] Significantly dependent on amount of exercise.



Data derived from Meikle AW, et al. *J Clin Endocrinol Metab.* 1992[11]; Snyder PJ, et al. *J Clin Endocrinol Metab.* 1980[12]; Swerdloff RS, et al. *J Clin Endocrinol Metab.* 2000.[13]

Figure 1. Testosterone levels after replacement with gel, patch, or injection.

Testosterone Pellets (Testopel)



Contraindications

Table 1. Absolute and relative contraindications to cross sex hormone therapy in transsexual people (Futterweit, 1998).

1. Severe hypertension
2. Ischaemic heart disease and other cardiac diseases
3. Thrombophlebitis or thromboembolic disease
4. Cerebrovascular disease
5. Hepatic dysfunction
6. Renal impairment
7. Refractory migraine, seizures, or retinal lesions
8. Brittle or poorly controlled diabetes
9. Hyperprolactinaemia
10. Strong family history of breast cancer
11. Heavy cigarette consumption
12. Marked obesity
13. Hypertriglyceridaemia or hypercholesterolemia in genetic females

Risks of Hormonal Treatment

TABLE 2. Risks Associated with Hormone Therapy

Risk level	Feminizing hormones	Masculinizing hormones
Likely increased risk	• **Venous thromboembolic disease**[a] • Gallstones • Elevated liver enzymes • Weight gain • **Hypertriglyceridemia**	• **Polycythemia** • Weight gain • Acne • Androgenic alopecia (balding) • Sleep apnea
Likely increased risk with presence of additional risk factors[b]	• **Cardiovascular disease**	
Possible increased risk	• **Hypertension** • Hyperprolactinemia or prolactinoma	• Elevated liver enzymes • **Hyperlipidemia**
Possible increased risk with presence of additional risk factors [b]	• **Type 2 diabetes**[a]	• **Destabilization of certain psychiatric disorders**[c] • **Cardiovascular disease** • **Hypertension** • **Type 2 diabetes**
No increased risk or inconclusive	• **Breast cancer**	• Loss of bone density • **Breast cancer** • **Cervical cancer** • **Ovarian cancer** • **Uterine cancer**

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

Background: Venous thromboembolism (VTE), ischemic stroke, and myocardial infarction in transgender persons may be related to hormone use.

Objective: To examine the incidence of these events in a cohort of transgender persons.

Design: Electronic medical record–based cohort study of transgender members of integrated health care systems who had an index date (first evidence of transgender status) from 2006 through 2014. Ten male and 10 female cisgender enrollees were matched to each transgender participant by year of birth, race/ethnicity, study site, and index date enrollment.

Setting: Kaiser Permanente in Georgia and northern and southern California.

Patients: 2842 transfeminine and 2118 transmasculine members with a mean follow-up of 4.0 and 3.6 years, respectively, matched to 48 686 cisgender men and 48 775 cisgender women.

Measurements: VTE, ischemic stroke, and myocardial infarction events ascertained from diagnostic codes through the end of 2016 in transgender and reference cohorts.

Results: Transfeminine participants had a higher incidence of VTE, with 2- and 8-year risk differences of 4.1 (95% CI, 1.6 to 6.7) and 16.7 (CI, 6.4 to 27.5) per 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. The overall analyses for ischemic stroke and myocardial infarction demonstrated similar incidence across groups. More pronounced differences for VTE and ischemic stroke were observed among transfeminine participants who initiated hormone therapy during follow-up. The evidence was insufficient to allow conclusions regarding risk among transmasculine participants.

Limitation: Inability to determine which transgender members received hormones elsewhere.

Conclusion: The patterns of increases in VTE and ischemic stroke rates among transfeminine persons are not consistent with those observed in cisgender women. These results may indicate the need for long-term vigilance in identifying vascular side effects of cross-sex estrogen.

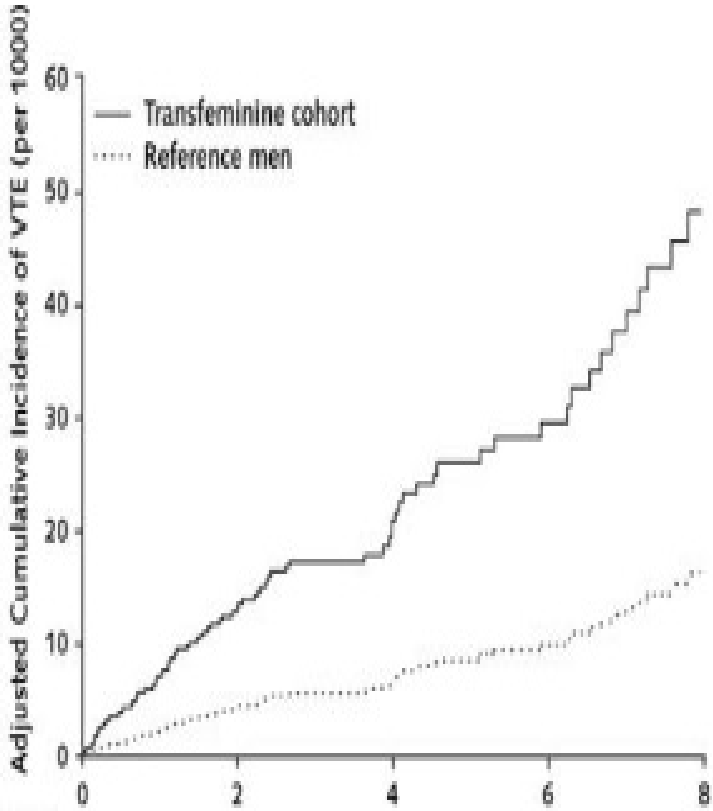
Primary Funding Source: Patient-Centered Outcomes Research Institute and Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Ann Intern Med. 2018;169:205-213. doi:10.7326/M17-2785 Annals.org

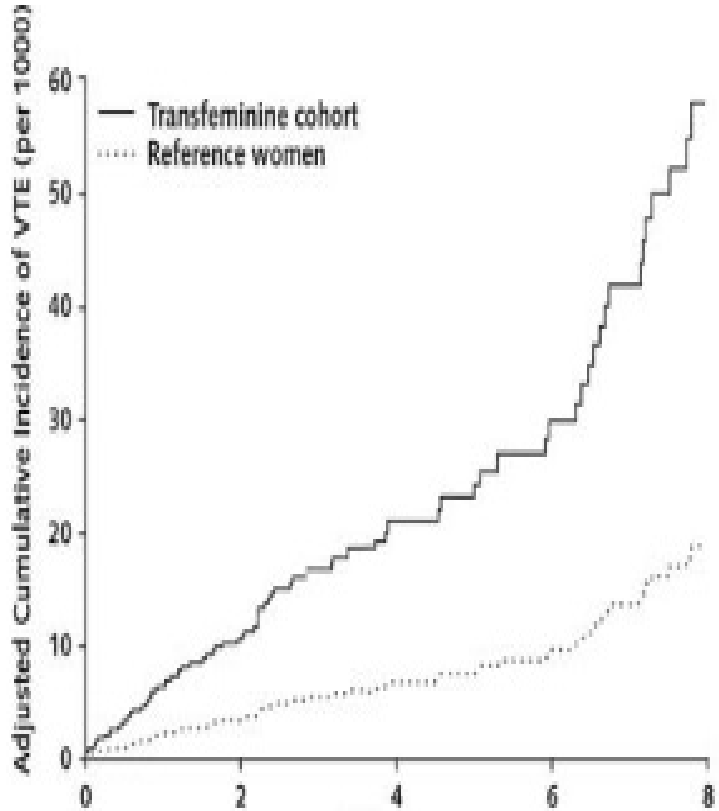
For author affiliations, see end of text.

This article was published at Annals.org on 10 July 2018.

VTE Incidence

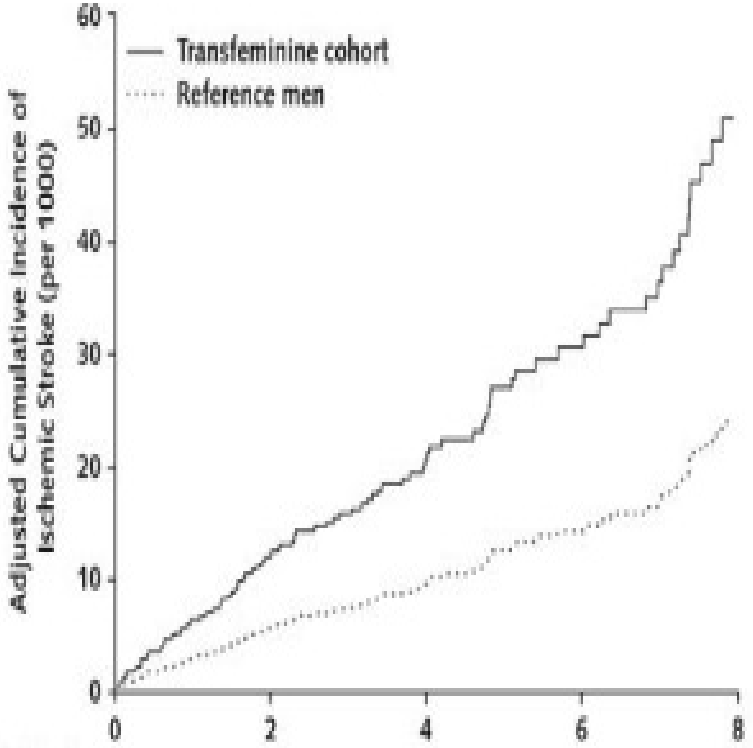


Events/patients at risk, *n/n*					
Transfeminine cohort	0/853	6/517	4/209	3/105	4/48
Reference men	0/7619	41/4951	11/2342	6/1252	6/633
RD (95% CI)*		8.8 (2.9 to 15.4)	14.0 (3.7 to 24.5)	19.8 (2.5 to 34.7)	32.1 (3.5 to 56.4)

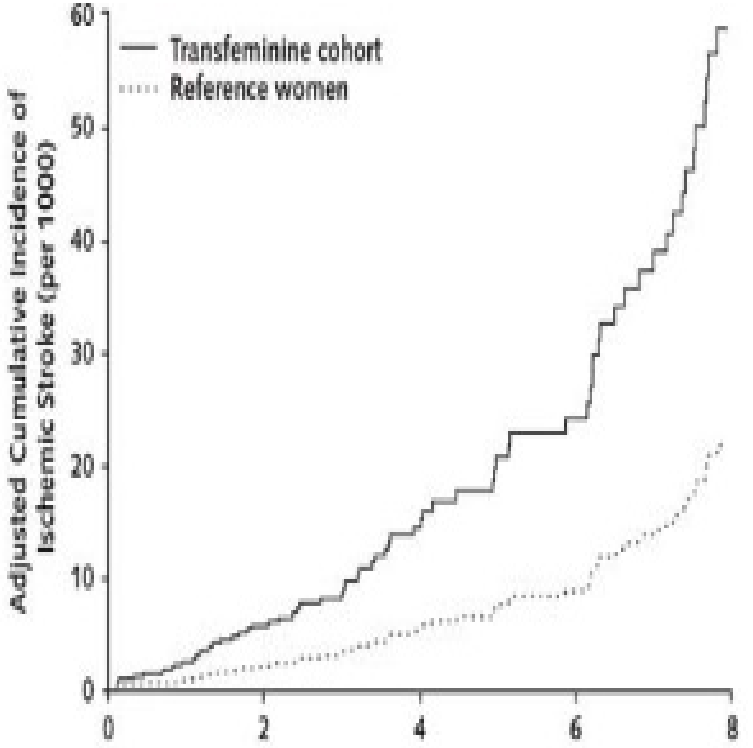


Events/patients at risk, *n/n*					
Transfeminine cohort	0/853	6/517	4/209	3/105	4/48
Reference women	0/7678	29/5093	17/2429	4/1330	10/695
RD (95% CI)*		6.9 (1.2 to 11.9)	13.5 (3.7 to 23.4)	19.1 (5.8 to 33.3)	37.0 (7.9 to 63.4)

Ischemic Stroke Incidence

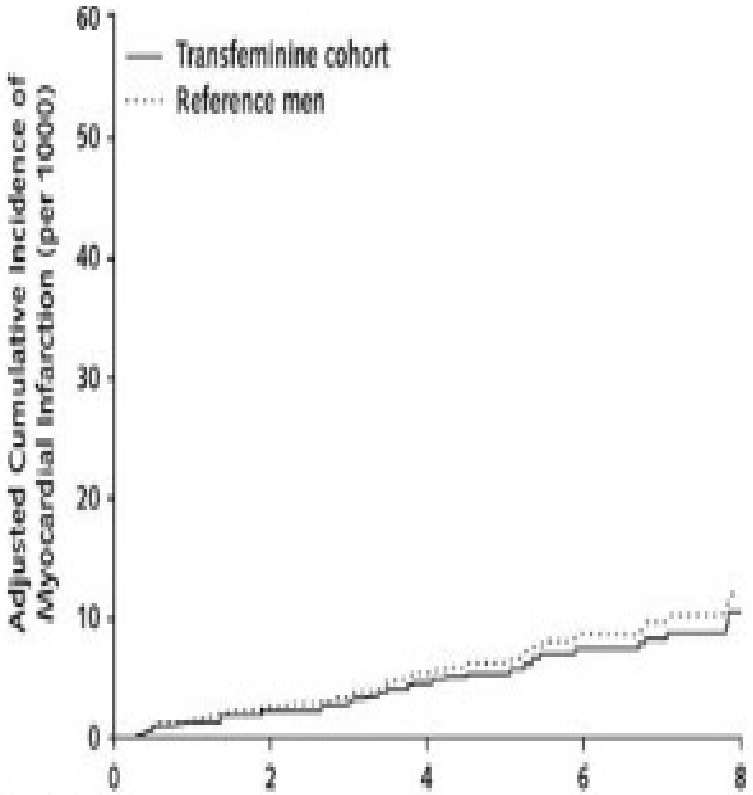


Events/patients at risk, *n/n*					
Transfeminine cohort	0/853	7/515	1/211	1/109	6/51
Reference men	0/7619	49/4945	19/2337	12/1246	8/625
RD (95% CI)*		6.7 (0.5 to 12.3)	11.0 (0.8 to 20.2)	16.3 (0.4 to 30.3)	27.2 (-2.7 to 50.7)

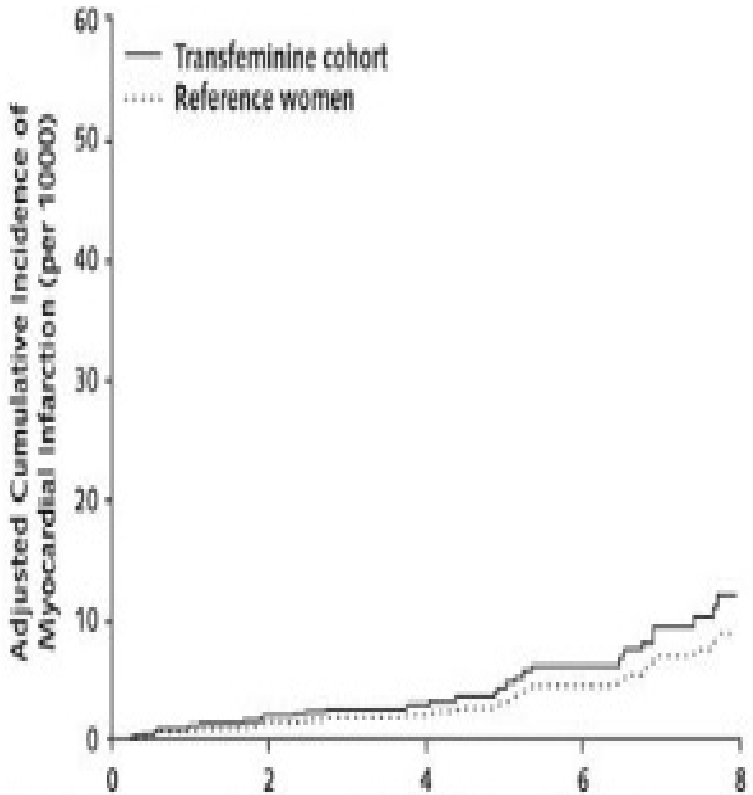


Events/patients at risk, *n/n*					
Transfeminine cohort	0/853	7/515	1/211	1/109	6/51
Reference women	0/7678	14/5104	16/2431	9/1332	14/695
RD (95% CI)*		3.6 (-0.5 to 6.3)	9.2 (0.4 to 6.3)	15.3 (1.1 to 26.3)	37.2 (2.1 to 62.8)

Myocardial Infarction Incidence



Events/patients at risk, *n/n*					
Transfeminine cohort	0/853	1/519	1/210	1/107	1/53
Reference men	0/7619	28/4963	15/2345	8/1251	4/631
RD (95% CI)*		-0.4 (-3.0 to 1.8)	-0.7 (-6.8 to 3.8)	-1.2 (-10.4 to 5.8)	-1.6 (-14.7 to 8.1)



Events/patients at risk, *n/n*					
Transfeminine cohort	0/853	1/519	1/210	1/107	1/53
Reference women	0/7678	16/5105	3/2439	7/1339	7/702
RD (95% CI)*		0.5 (-1.4 to 2.4)	0.7 (-2.2 to 3.3)	1.6 (-4.6 to 7.2)	3.1 (-9.1 to 13.8)

Side effects of cross sex hormone administration in transsexuals

Clin Endocrinol, 47 (1997), p. 337
P. Van Kestern, J.A. Megens, H. Asscheman, *et al.*

- *Increase in activated protein C resistance*
- *Increase in plasma protein C*
- *Decrease in total and free plasma protein S*

Women Fear Drug They Used To Halt Puberty Led To Health Problems

By **Christina Jewett** February 2, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment with a Luteinizing Hormone–Releasing Hormone Agonist in Adolescents with Short Stature

Jack A. Yanovski, M.D., Ph.D., Susan R. Rose, M.D., Giovanna Municchi, M.D., Ora H. Pescovitz, M.D., Suvimol C. Hill, M.D., Fernando G. Cassorla, M.D., and Gordon B. Cutler, Jr., M.D.

N Engl J Med 2003; 348:908-917 | March 6, 2003 | DOI: 10.1056/NEJMoa013555

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Gonadotropin-Releasing Hormone Agonists and Fracture Risk: A Claims-Based Cohort Study of Men With Nonmetastatic Prostate Cancer

Matthew R. Smith, Won Chan Lee, Jane Brandman, Qin Wang, Marc Botteman, Chris L. Pashos

Show Affiliations

From the Massachusetts General Hospital, Boston, MA; Abt Associates Clinical Trials, Bethesda, MD; and Novartis Pharmaceutical Corp, East Hanover, NJ

DOI: http://dx.doi.org/10.1200/JCO.2004.00.6908

Transgender and BMD

- Very little data
- Ruetsche, Kneubuehl, Birkhaeuser, Lippuner, et al. (2005)
  - Cross sectional
  - 39 Transsexuals
    - Trans women BMD preserved over 12.5 years with antiandrogen and estrogen therapy
    - Trans men BMD preserved or increased after 7.5 years with androgen treatment.

Reproductive Considerations

- Limitations on fertility
- Make decisions early
- Sperm banking prior to HRT
- Oocyte banking
- Embryo banking

Surgery

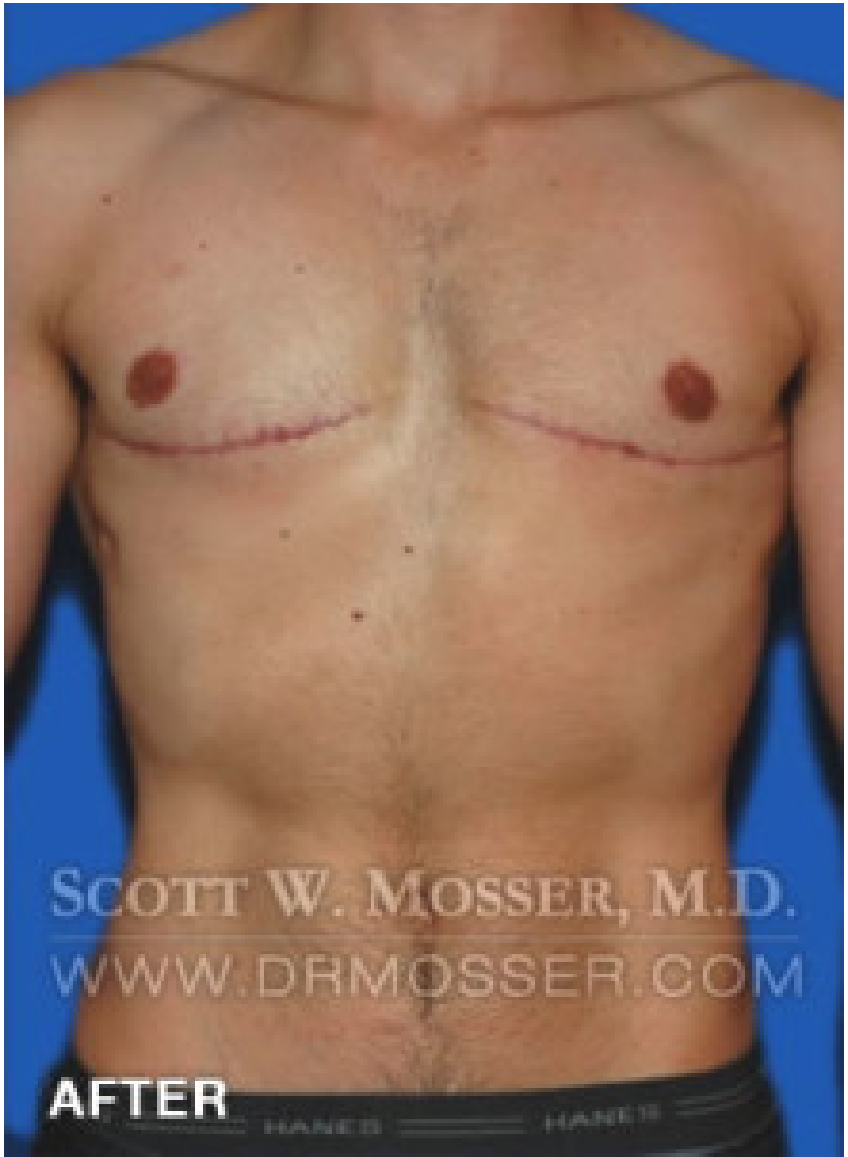
Male to Female

- Breast/chest surgery
  - augmentation mammoplasty (implants/lipofilling);
- Genital surgery
  - penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty;
- Nongenital, nonbreast surgical interventions:
  - facial feminization surgery, liposuction,lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation (implants/lipofilling), hair reconstruction

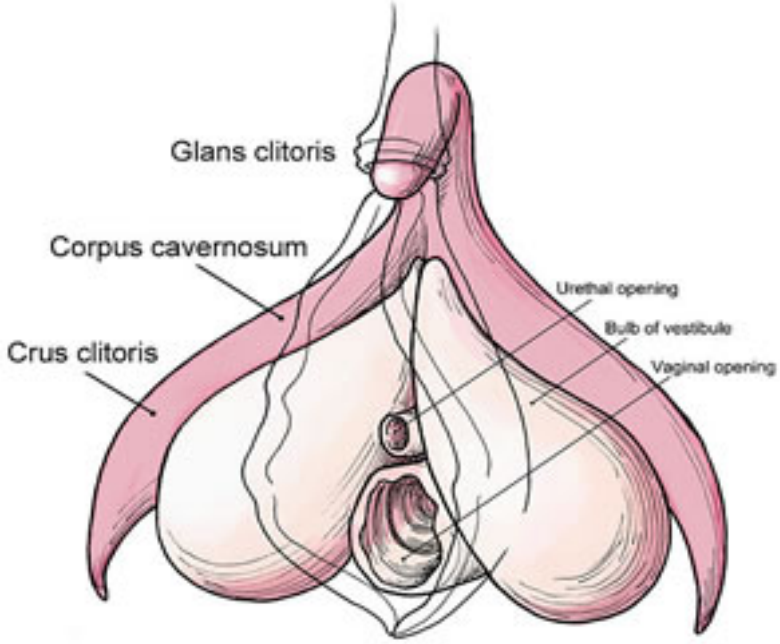
Female to Male

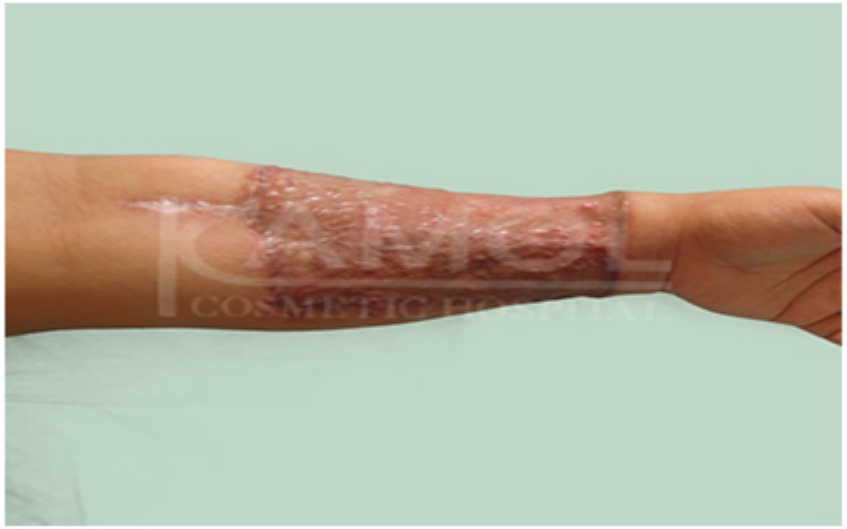
- Breast/chest surgery: subcutaneous mastectomy,
- Genital surgery:
  - hysterectomy/salpingooophorectomy, reconstruction of the fixed part of the urethra, metoidioplasty, phalloplasty, vaginectomy, scrotoplasty, testicular prostheses;
- Nongenital, nonbreast surgical interventions
  - voice surgery, liposuction, lipofilling, pectoral implants

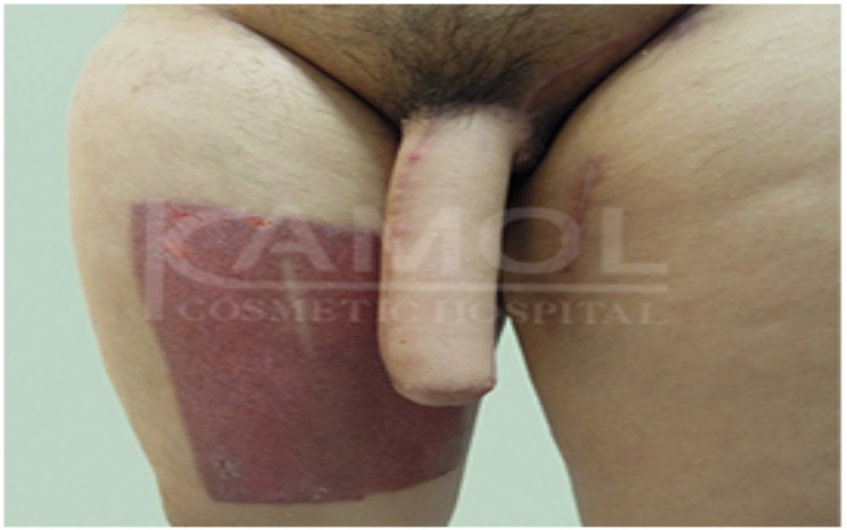
Chest/Breast Surgery



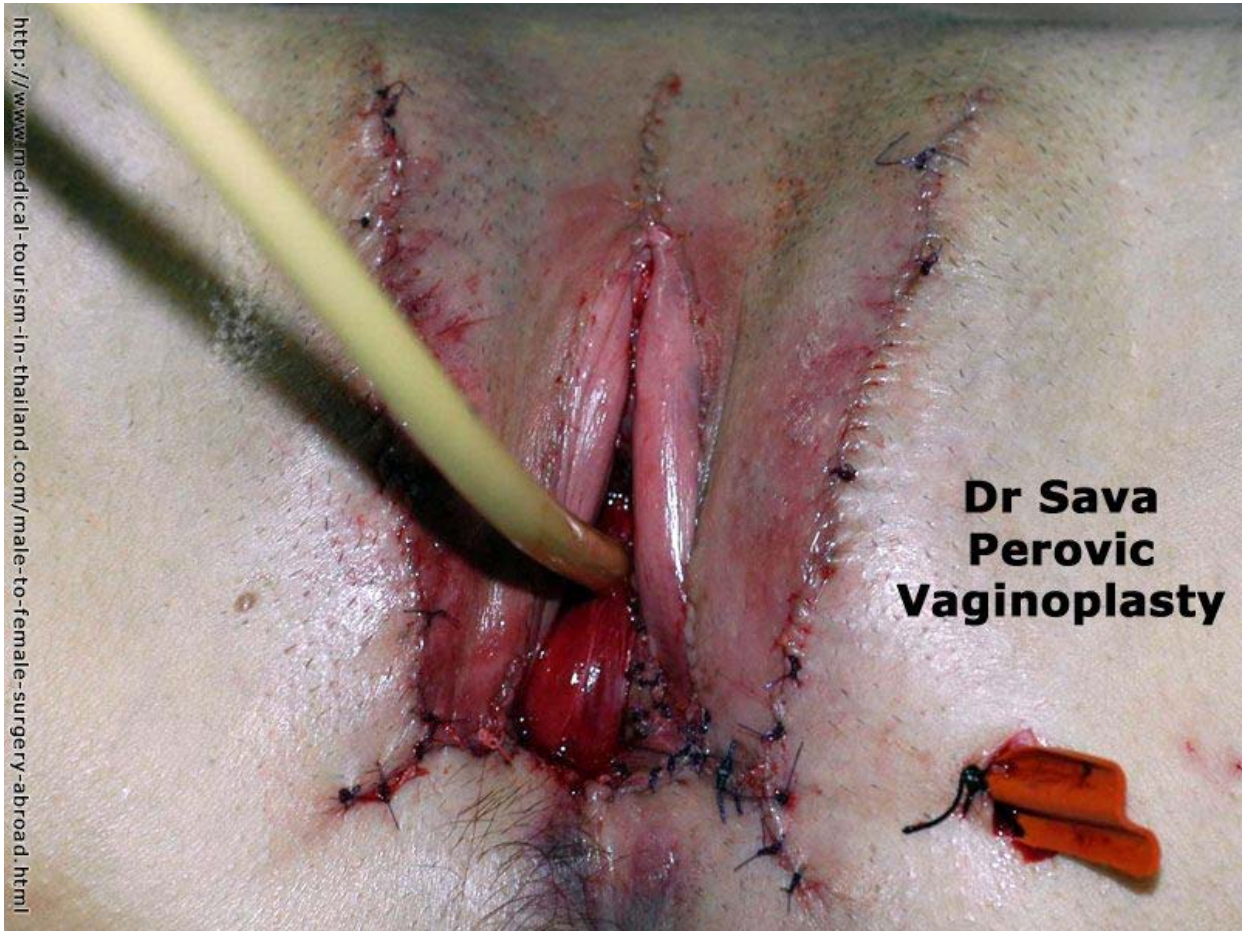
Trans Male Genital Surgery







Trans Female Genital Surgery



Other Therapies

- Speech Therapy
- Reduction thyroid chondroplasty
- Voice modification
- Lipoplasty, rhinoplasty,
- Facial bone reduction, face-lift, and blepharoplasty
- Pectoral implants.

Cancer Screening

- Not enough evidence to determine appropriate type and frequency of cancer screenings.
- MtF- Mammogram, PSA/Prostate, Testicular, Colonoscopy
- FtM- Mammogram, PAP/Pelvic, Colonoscopy

Transgender Care at Northwell Endocrinology

Northwell Health

Our Patient Experiences

- https://vimeo.com/217715465

My Patient Cohort

- 125 Patients. 84 under my care
  - 44 FtM
  - 40 MtF
    - 37 on prior treatment
- Underlying Psychiatric Disorder- 99%
- Hypogonadism (MtF)- 25%
- PCOS (FtM)- 30%
- ADHD/OCD- 16%
- Autism/Spectrum- 4%

What Do I Do?
Initial Visit

- Discuss patient's history and their "story."
- Discuss physical transition and goals
- Obtain health history and exam
- Discuss the expected effects of feminizing/masculinizing medications
- Risks vs. Benefits
- Confirm capacity to understand the risks and benefits of treatment
- STI awareness and prevention
- Smoking Cessation

What Do I Do?
Initial Workup

- CBC
- CMP
- Testosterone/Estradiol
- LH and FSH
- 17-OHP
- DHEA-S
- TFTs
- Lipids
- A1c
- Prolactin
- HIV
- STD Screen

What Do I Do?
Cross-Gender Treatment

- Male to Female
  - Estradiol 1mg oral BID or Injectable 0.3ml weekly
  - Transdermal if >40; 0.1mg 2x/ week
    - ? Withdrawal for surgery
  - Spironolactone 100mg daily (up to 400mg daily)
    - Goal Testosterone <50
  - Micronized Progesterone if needed
  - Can use GnRH analogs
  - Increase doses in 4 weeks based on results
  - Consider Aspirin 81mg

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Progesterone

- Progesterone
  - Breast Growth? Libido? Mood?
  - Controversial
    - "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women" JAMA 2002

Follow-up

- Male to Female
  - Monitor for feminization or adverse reactions
  - Goal serum testosterone <50
  - Estradiol levels should not exceed peak physiologic range (250-300)
  - Check Testosterone, Estradiol, LFTs, Lipids, Prolactin, Lytes (especially if on spironolactone)
  - Post-op- dose adjustment may be needed.

What Do I Do?
Cross-Gender Treatment

- Female to Male
  - Testosterone Cypionate 100mg every 2 weeks or lower if SQ
  - Gels, Transdermal or Pellets if covered
  - Repeat in 4 weeks to increase dose as needed then again 4 weeks later.

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Follow-up

- Female to Male
  - Monitor testosterone
    - Goal male range (500-600 ug/dl)
  - Check Lipids, CBC, LFTs, Testosterone
  - Check estradiol until no uterine bleeding x 6 months
  - Post-op- dose adjustment may be needed

Managing Abnormalities

- Anemia
- Erythrocytosis
- Hyperprolactinemia
- Elevated Transaminases
- Hair Loss

Research On The Horizon

- How to effectively dose hormones?
- Testosterone Pellets
- Egg Banking/Freezing
- What side effects are we noticing?
- Demographic Data

Take Home Points

- Treatment involves a multidisciplinary approach
- Estrogen treatment goal of suppressing testosterone and maintain estrogen at feminine levels.
- Anti-androgen esp. if testosterone difficult to suppress with estrogen alone
- Testosterone for goal of mid-male range
- Close monitoring and yearly reevaluation
- Further studies are needed


THANK
YOU!

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