

Cross-Sex Hormone Therapy

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Continuing Medical Education Disclosure

- Program Faculty: Tim Cavanaugh, MD
- Current Position: Medical Director, Transgender Health Program, Fenway Health
- Disclosure: No relevant financial relationships. All hormone therapy for transgender people is off-label.

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Transgender

- Refers to a person who is born with the genetic traits of one gender but has the internalized identity of another gender
- This is an umbrella term that can encompass a wide range of gender identities: tranny boy, pre-op, post-op, gender queer, gender outlaw

Etiology of Transgender Identity

- Research into genetics, brain anatomy and function, hormonal influences, but, the fact is, we just don't know.
- Recent review of twin studies shows an approximate 30% concordance in MtF monozygotic twins and an approximate 23% concordance in FtM monozygotic twins

Transgender Demographics

- Data from the Netherlands
 - 1 in 11,900 males
 - 1 in 30,400 females
- Some researchers challenge these estimates and estimate that the prevalence is closer to 1/500

Transgender Demographics

- Massachusetts Behavioral Risk Factor Surveillance Survey (2007, 2009)
 - 0.5% of population between ages 18-64
- California LGBT Tobacco Survey
 - 0.1% of adult population
- Estimate in U.S. from the Williams Institute
 - 0.3% of adults
 - Approximately 700,000 people

DSM 5

- December 2012, American Psychiatric Association formally announces that the diagnosis “Gender Identity Disorder” will be dropped and replaced with diagnosis “Gender Dysphoria”

Gender Dysphoria

- The discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and secondary sex characteristics)
Coleman, SOC, V 7 p168
- The focus of health care engagement is alleviating the distress.

Gender Dysphoria

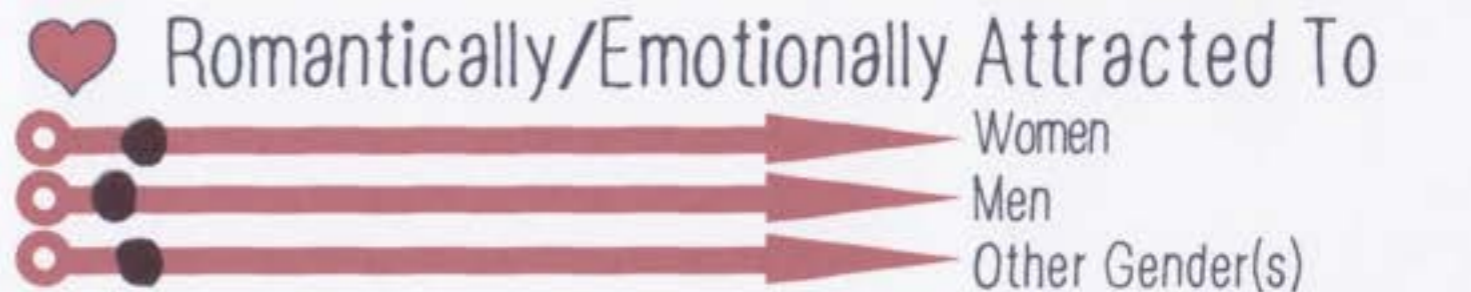
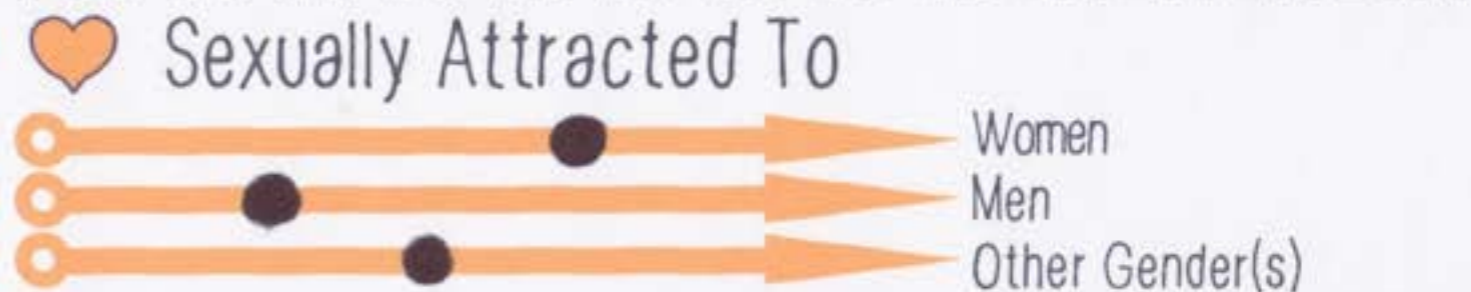
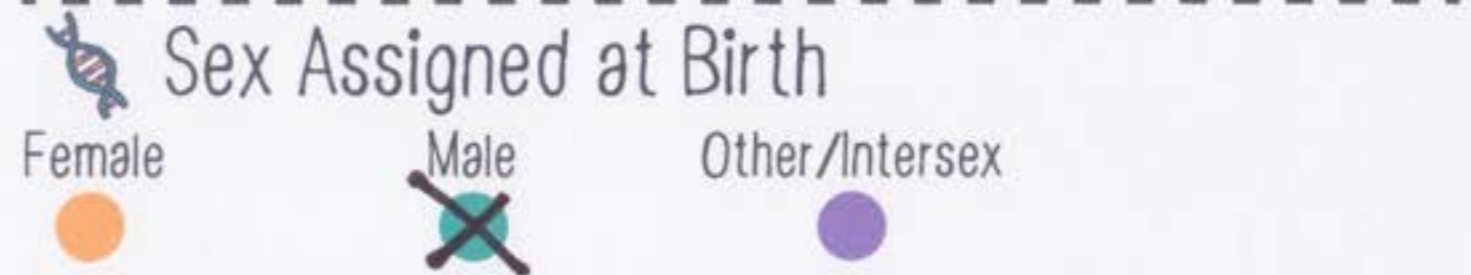
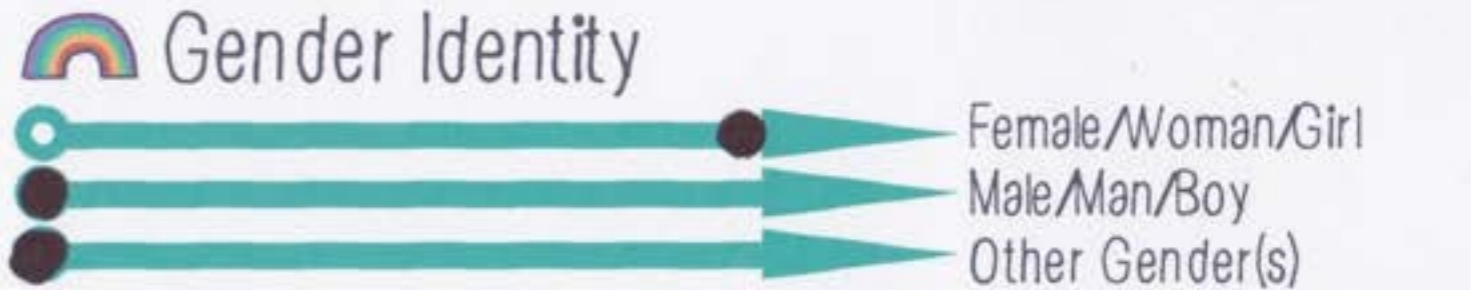
- The goal of treatment for transgender people is to improve their quality of life by facilitating their transition to a physical state that more closely represents their sense of themselves.

Alternative Constructs of Gender Identity:

- If gender is determined by anatomic sex/the genitals...then binary understanding of gender...gender “reassignment” or “transition”
- If gender is determined by the brain/ one’s internal identity...then spectrum of gender identity...gender “affirmation”

The Gender Unicorn

Graphic by:
TSER
Trans Student Equality Resources



To learn more go to:
www.transstudent.org/gender

Design by Landyn Pan

Terminology: Understanding “Transition” or “Affirmation”

- The process of changing from living and being perceived as the gender assigned at birth according to the anatomical sex (M or F) to living and being perceived as the individual sees and understands themselves
- Goes beyond medical treatment with mental health, medical and surgical treatment and includes social affirmation, and legal changes.
- Many prefer the term “gender affirmation” or “gender confirmation” over “transition”

Transgender Standards of Care

The image shows a screenshot of the UCSF Center of Excellence for Transgender Health website. The website header includes the UCSF logo and navigation links: "University of California, San Francisco | About UCSF | Search UCSF | UCSF Medical Center". The main navigation bar features "About Us", "Programs & Services", "Learning Center", and "Cal". The "Learning Center" section is active, displaying a list of resources under the heading "Learning Center".

Overlaid on the website are two documents:

- The Endocrine Society's CLINICAL GUIDELINES**: A blue document titled "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline". The logo of The Endocrine Society is visible at the bottom.
- Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People**: A white document with a rainbow gradient background, published by "The World Professional Association for Transgender Health" (WPATH). The WPATH logo is at the top left.

The website content includes a search bar labeled "Search CoE" and a list of resources under "Learning Center":

- Primary Care Protocols**
- Professional Literature**
- Guidelines & Reports**
- Conferences, Lectures, Online Training**
- Community Education**
- Audiences**
 - Health Care Providers
 - Researchers
 - Community Organizers
 - Individuals

The "Learning Center" list includes:

- Primary Care Protocol for Transsexual Persons**: Practical reference for clinicians.
- The Health of Lesbian, Gay, Bisexual, and Transgender People: Promoting Better Understanding**: Institute of Medicine Consensus Report.
- Healthy People 2020: Lesbian, Gay, Bisexual, and Transgender Health Initiative**: Overview, objectives and data, and health initiative. This is the first time in the history of the People campaign.
- Feldman, JL and Goldberg, J. (2006). *Guidelines for clinicians in British Columbia***: Transgender Health Program. Accessed [date].
- Williams, AR. (2009). *Transgender Consensus Report: Working with Trans and LGB patients***. Accessed [date].

WPATH SOC 2011

- This is the seventh version of the Standards of Care. The original SOC were published in 1979. Previous revisions occurred in 1980, 1981, 1990, 1998 and 2001.
- “The latest 2011 revisions to the SOC realize that transgender, transsexual, and gender nonconforming people have unique health care needs to promote their overall health and well-being, and that those needs extend beyond hormonal treatment and surgical intervention.”
- Eli Coleman, PhD, SOC Committee Chair, Professor and Director at Program in Human Sexuality, University of Minnesota.
- “The previous versions of the SOC were always perceived to be about the things that a trans person must do to satisfy clinicians, this version is much more clearly about every aspect of what clinicians ought to do in order to properly serve their clients. That is a truly radical reversal . . . one that serves both parties very well.”
- Christine Burns, SOC International Advisory Committee Member.
- “More than any other version, 2011 revisions also recognize that gender nonconformity in and of itself is not a disorder and that many people live comfortable lives without having to seek therapy or medical interventions for gender confusion or unhappiness.”

WPATH

- The medical provider who provides hormonal therapy need not be an endocrinologist but should become well-versed in the relevant medical and psychological aspects of treating persons with gender identity disorders

September 2011: WPATH Standards of Care

The criteria for hormone therapy are as follows:

- Persistent, well-documented gender dysphoria;
- Capacity to make a fully informed decision and to consent for treatment;
- Age of majority in a given country (if younger, follow the Standards of Care outlined in section VI);
- If significant medical or mental health concerns are present, they must be reasonably well controlled.

Cross-Gender Hormone Therapy

- Many patients have taken self-prescribed hormones
 - 2013 Ontario survey: 25% had ever used and 6.4% were currently using
 - 2009 NYC study: 23% of transwomen currently using
 - 2007 Virginia Trans Health Initiative Survey: 60% of transwomen and 23% of transmen had ever used
 - 2001 San Francisco Study: 29% of transwomen and 3% of transmen in the past 6 months
 - 2000 Washington, DC Transgender Needs Assessment Study: 58% had used at some time in the past

Cross-Sex Hormone Therapy

Not universally desired nor necessary

Standard vs. Informed Consent Model (WPATH SOC7)

Standard

- Initiation of hormone Rx after psychosocial assessment by “qualified mental health professional”
- Recommendation for team care or collaborative model
- Psychotherapy not required
- Experienced hormone prescribing medical provider may meet requirement
- Informed consent

Informed Consent Model

- Requires healthcare provider to effectively communicate benefits, risks and alternatives of treatment to patient
- Requires healthcare provider to judge that the patient is able to understand and consent to the treatment
- WPATH SOC7 states protocols using informed consent model are consistent with SOC7
 - Applies to hormone therapy
- Informed consent model does not preclude mental health care
- Recognizes that prescribing decision ultimately rests with clinical judgment of provider working together with the patient
 - Informed consent is not equivalent to treatment on demand

(Deutsch, 2012)

Initial Visits

- Review history of gender experience
- Document prior hormone use
- Obtain sexual history
- Review patient goals
- Address safety concerns
- Assess social support system
- Assess readiness for gender transition
- Review risks and benefits of hormone therapy
- Obtain informed consent
- Order screening laboratory studies
- Provide referrals

Transgender Hormone Therapy

- Heredity and age limit the tissue response to hormones
- More is not always better

Female to Male Treatment Options

- **Injectable Testosterone**

- Testosterone Enanthate or Cypionate 100-200 mg IM q 2 wks (20 -22g x 1 ½" needles)

- **Transdermal Testosterone**

- Androderm TTS 2-8mg daily
- Topical testosterone gels in packets and pumps, multiple formulations (Testim, Androgel) 5 to 10 gm (50 to 100 mg of testosterone) applied topically daily
- Axiron 2% pump gel for axillary application 1 pump to each axilla daily

- **Testosterone Pellet**

- Testopel- implant 6-10 pellets q 3 to 6 months

- **Buccal Testosterone**

- Striant 30 mg buccal system q 12 hours

Other Treatment Considerations for FTMs

- Testosterone cream in aquaphor for clitoral enlargement
- Estrogen vaginal cream for atrophy
- Rogaine or Finasteride for male pattern baldness
- Use of Progesterone – may help to reduce estrogen levels and aid in cessation of menses before or after starting testosterone therapy.

Masculinizing Effects of Testosterone

Effect	Onset (months)	Maximum (years)
Skin oiliness/acne	1-6	1-2
Fat redistribution	1-6	2-5
Cessation of Menses	2-6	
Clitoral enlargement	3-6	1-2
Vaginal atrophy	3-6	1-2
Emotional changes		
Increased sex drive		

Masculinizing Effects of Testosterone

Effect	Onset (months)	Maximum (years)
Deepening of voice	3-12	1-2
Facial/Body Hair Growth	6-12	4-5
Scalp Hair Loss	6-12	
Increased Muscle Mass & Strength	6-12	2-5
Coarser Skin/ Increased Sweating		
Weight Gain/Fluid Retention		
Mild Breast Atrophy		
Weakening of Tendons		

Risks of Testosterone Therapy

- Lower HDL and Elevated triglycerides
- Increased homocysteine levels
- Hepatotoxicity ?
- Polycythemia
- Unknown effects on breast, endometrial, ovarian tissues
- Increased risk of sleep apnea
- (Insulin resistance)
- Infertility
- Chronic pelvic pain
- Mental health effects

Drug Interactions - Testosterone

- Increases the anticoagulant effect of warfarin
- Increases clearance of propranolol
- Increases the hypoglycemic effects of sulfonylureas

Laboratory Monitoring for FTM Patients On Testosterone

- Baseline:
 - CBC/Hgb
 - Lipid Profile
 - Liver Enzymes
 - Renal Panel
 - Fasting Glucose
 - ? Screen for PCOS

Laboratory Monitoring For FTM Patients On Testosterone

- After 3 months, then every 6 to 12 months
 - CBC
 - (-Liver Enzymes)
- Every 6 to 12 months
 - Lipid Profile
 - Fasting Glucose or HbA1c

Laboratory Monitoring For FTM Patients On Testosterone

- Serum testosterone levels: checked 2 to 12 weeks after dose start/change, then every 6 to 12 months
- (350-700 ng/dl)
- Estradiol levels? (should be less than 50 pg/ml)

Male to Female Treatment Options

- **Oral Estrogens**

- Estradiol (estrace) 2-6mg PO or SL daily (can be divided into BID dosing)
- Premarin (conjugated estrogens) 1.25-10mg PO daily (can be divided into BID dosing)

- **Transdermal Estrogens**

- Estradiol patch 0.1-0.4mg twice weekly

- **Injectable Estrogens**

- Estradiol valerate 5-20mg IM q2 weeks
- Estradiol cypionate 2-10mg IM weekly

- **Antiandrogens**

- Spironolactone (aldactone) 50-400mg PO daily (can be divided into BID dosing)
- Finasteride (Proscar) 2.5-5mg PO daily

Male to Female Treatment Options

- Cyproterone Acetate (not available in US)
- GnRH agonist: Goserelin Acetate
- Flutamide an androgen receptor blocker, associated with severe liver toxicity

Male to Female Treatment Options

- Progestins: ??? Benefit on breast development, associated with increased risk of cardiovascular events and breast cancer in WHI, also risk of weight gain and depression
 - Depo-Provera 150 mg IM q 3 months
 - Provera 2.5 to 10 mg PO daily*
 - Prometrium 100 mg – 200 mg po daily*
- * Consider dosing 10 days each month cyclically with po form to minimize risk

Cosmetic Therapies

- **Hydroquinone**

- Topical treatment for pigmentation caused by estrogen therapy

- **Hair Removal**

- Eflornithine (Vaniqa) cream
- Electrolysis
- Laser hair removal

MTF Over 40 Years Old

- Add ASA to regimen
- Transdermal estradiol therapy is recommended to reduce the risk of venous thromboembolism

Feminizing Effects of Estrogens & Antiandrogens

Effect	Onset (months)	Maximum (months)
Decreased Libido	1-3	3-6
Decreased Spontaneous Erections		
Breast Growth	3-6	24-36
Decreased Testicular Volume	3-6	24-36
Decreased Sperm Production	Unknown	Unknown
Redistribution of Body Fat	3-6	24-36
Decrease in Muscle Mass	3-6	12-24
Softening of Skin	3-6	Unknown
Decreased Terminal Hair	6-12	>36

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

Risks of Estrogen Therapy

- Venous thrombosis/
thromboembolism
- Increased risk of
cardiovascular disease
- Weight gain
- Decreased libido
- Hypertriglyceridemia
- Elevated blood pressure
- Decreased glucose tolerance
- Gallbladder disease
- Benign pituitary
prolactinoma
- Breast cancer(?)
- Infertility
- Mental health effects

Risks of Spironolactone Therapy

- Hyperkalemia
- Hypotension
- Renal insufficiency

Drug Interactions

Estradiol, Ethinyl Estradiol, Testosterone levels are DECREASED by:

- Lopinavir
- Rifampin
- Phenytoin
- Carbamazepine
- Progesterone
- Phenobarbital
- Dexamethasone
- Phenylbutazone
- Naphthoflavone
- Benzoflavone
- Sulfamide
- Sulfinpyrazone

Drug Interactions

Estradiol, Ethinyl Estradiol, Testosterone levels are **INCREASED** by:

- Nefazodone
- Fluvoxamine
- Indinavir
- Sertraline
- Diltiazem
- Cimetidine
- Itraconazole
- Fluconazole
- Clarithromycin
- Grapefruit
- Isoniazid
- Fluoxetine
- Efavirenz
- Paroxetine
- Verapamil
- Astemizole
- Ketoconazole
- Miconazole
- Erythromycin
- Triacetyloleandomycin

Drug Interactions

Estrogen levels are DECREASED by:

- Smoking cigarettes
- Nelfinavir
- Nevirapine
- Ritonavir

Drug Interactions

Estrogen levels are **INCREASED** by:

- Vitamin C

Lab Monitoring for MTF Patients

- Baseline:
 - Renal panel
 - Lipids
 - Fasting Glucose
 - CBC
 - Testosterone level
 - Prolactin level
 - (Liver Enzymes)

Lab Monitoring for MTF Patients

- If on spironolactone, serum electrolytes 1 to 6 weeks after start/dosage change, then every 3 months in first year
- Lipids, lytes, creatinine, glucose yearly
- Prolactin level annually for 3 years (and beyond??)

Lab Monitoring for MTF Patients

- Serum testosterone level (at 6 to 12 months)
 - Should be less than 55 ng/dl
- Serum Estradiol Levels (?)
 - Ideal level is the mean daily level for premenopausal women (about 100 to 200 pg/ml)

Follow-Up Care on CSHT

- Assess masculinization or feminization
- Review medication use
- Monitor mood cycles and adjust medication as indicated
- Discuss social impact of transition
- Counsel regarding sexual activity
- Review surgical options
- Plans change of name and gender marker on legal forms
- Review CAD risk factors
- ASSESS SAFETY

More on Hormone Safety

Testosterone Treatment for FTM

- Despite changes in CAD risk factors, no increase in cardiovascular morbidity and mortality in 876 FTM patients. Gooren, et al, 2008
- Asscherman, et al (2011): 365 FtM, 18 years median follow-up.
 - No difference in overall or cause-specific mortality
 - Only 1 MI in 72 yo patient on T for 42 years
 - No increase in over-all cancer mortality. No breast CA
 - 1 death by illicit drug use

Estrogen Therapy for MTF

- Women's Health Initiative:

	Odds Ratio	Increased Incidence
CHD event	1.29	7/10,000
Non-fatal MI	1.32	7/10,000
CHD death	1.18	1/10,000
PE	2.13	8/10,000
CVA	1.41	8/10,000
DVT	2.07	13/10,000

- Total mortality not increased, but increase in breast cancer.

Estrogen Therapy for MTF

- HERS (HRT in patients with prior coronary event)
 - Treatment with Premarin and Provera
 - 1380 patients in treatment and control groups
 - No significant difference in primary outcomes
 - Lower LDL and higher HDL in treatment group
 - More events in treatment group in year 1, but fewer in years 4 and 5
 - Increased risk of VT (32 vs 12 cases)

Estrogen Therapy for MTF

- Coronary Drug Project, 1966 – 1975:
 - Men aged 30 to 64 with previous MI
 - Treated with high-dose conjugated estrogen, 2.5 or 5 mg
 - High-dose group discontinued after 5 years because of increased coronary events
 - Low-dose group discontinued because of increased risk of cancers

Estrogen Therapy for MTF

- ESPRIT (Estrogen for the Prevention of Re-Infarction Trial)
 - 1017 women ages 50 to 69, after first MI, randomised to 2 mg estradiol po daily or placebo, between 1996 and 2000
 - Oral estradiol provided neither a beneficial nor a detrimental effect in the incidence of ischemic heart disease, any heart disease or stroke

Estrogen Therapy for MTF

- Gooren, et al (2008), 2236 MTF patients
 - Increased weight, visceral fat, impaired glucose sensitivity, small increase in BP; increased HDL, decreased LDL
 - NO increased in cardiovascular morbidity or mortality
 - Increased incidence of VT (6-8%) but only in patients treated with ethinyl estradiol

Estrogen Therapy for MTF

- Asscherman, et al (2011)
 - 996 MtF patients, 18.5 years follow-up
 - current but not past use of EE associated with 3x risk of CV death
 - about 2x rate of CV death in 40-64 yo
 - Ischemic HD death in 18 subjects, 11, had been using EE, 5 had suffered previous MI
 - stroke in 5 subjects, in younger subjects, all had used EE
 - in over 65 yo, total mortality was not increased
 - higher lipid levels and higher rates of smoking in MtF

Estrogen Therapy for MTF

- Elamin, et al (2010)
 - Meta-analysis of 16 eligible studies, 1471 MTF
 - Very few reported cardiovascular events
 - Quality of evidence is very low
 - No meaningful assessment of clinical outcomes like death, stroke, MI or VT. SUGGESTS a higher incidence in MtF, BUT most were from one center using “fairly high estrogen dose”

Estrogen Therapy for MTF

- Venous thromboembolism
- In the Dutch cohorts, rates of 2.6% annually in first year, falling to 0.4 % thereafter, with 1 – 2% risk of death from PE, BUT all but 1 of these patients was using oral ethinyl estradiol.

Estrogen Therapy for MTF

- Ott, et al (2010)
 - NO occurrence of VT with a mean follow-up of 64.2 months

Estrogen Therapy for MTF

- Wilson, et al (2006 and 2009)
 - MTF patients treated with Premarin
 - increased levels of anti-oxidant and decreased levels of inflammatory markers suggesting cardiovascular BENEFIT
 - Oral estrogen resulted in a transient increase in inflammatory markers and clotting factors(within 2 to 4 months but returning to baseline by 6 months); transdermal estrogen showed no such changes

Estrogen Therapy for MTF

- Toorians, et al (2003)
 - Chemical markers of coagulability in MTF patients on EE, oral estradiol and transdermal estradiol
 - Oral and transdermal estradiol groups were similar in all measures of pro-thrombotic variables, and did not differ in the baseline levels seen in natal females
 - An earlier study had shown the incidence of VT was 20 x higher in oral EE versus transdermal estradiol

Estrogen Therapy for MTF

- Unfortunately, there are no studies that compare injectable estradiol with any other forms of estrogen

Resources

- Transgender Medical Consultation Service
 - <https://transline.zendesk.com/home>
- WPATH SOC v.7
 - <http://www.wpath.org/documents/Standards%20of%20Care%20V7%20-%202011%20WPATH.pdf>
- Endocrine Society Clinical guidelines
 - cem.endojournals.org J Clin Endocrinol Metab. September 2009, 94(9):3132-3154
- UCSF Center of Excellence for Transgender Health
 - <http://transhealth.ucsf.edu/trans?page=protocol-00-00>
- British Columbia TG guidelines and resources
 - <http://www.vch.ca/transhealth/resources/careguidelines.html>

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