Medical Management of the Transgender Patient

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Disclosures

Nothing to Disclose

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Learning Objectives

At the conclusion of this presentation, attendees should be able to
1. To list the guidelines and available resources for the diagnosis and treatment of patients with transgender
2. To describe the initiation and monitoring of hormonal therapy in patients with transgender
3. To identify potential risks of hormone therapy in patients with transgender
Transgender Medicine
~90 years old

1923 transsexual coined by Hirschfeld
1931 first surgery in Germany
First gender identity clinic established at Johns Hopkins 1966
2009 Endocrine Society Clinical Practice Guidelines
Department of Veterans Affairs Memo on Transgender in 2011

- Veterans Administration directive to provide hormonal therapies to veterans and allow veterans to gave gender marker changed
NIH sets aside funds for LGBT health in 2012

NIH invites broad range of research on LGBTI health

New grant solicitations are sponsored by multiple NIH institutes.

The National Institutes of Health (NIH) has released a set of three program announcements inviting grant applications for Research on the Health of LGBTI Populations. These announcements are the broadest and clearest solicitations for research on lesbian, gay, bisexual, transgender and intersex populations that NIH has ever issued. (See links to the announcements below.)

The announcements help to satisfy a major recommendation of a 2011 report from the Institute of Medicine (IOM) for NIH to develop a comprehensive research agenda to guide its future funding of research on sexual minority populations.

In contrast to previous program announcements on LGBTI topics, these announcements are sponsored by a wide range of relevant NIH institutes and offices and they support a variety of grant mechanisms, including R01 (regular grants), R03 (small grants), and R21 (exploratory/developmental grants). Significantly, the shared title of the announcements refers directly to LGBTI populations rather than using the vague term "diverse populations" of previous announcements.
Medicare Ban on Sex-Reassignment Surgery Lifted
Decisions on Procedure Now Will be Made on Case-by-Case Basis

WASHINGTON—Transgender people who receive Medicare benefits will no longer be automatically denied coverage for sex-reassignment surgery, a federal review board ruled Friday.

By STEPHANIE ARMOUR
Updated May 30, 2014 5:04 p.m. ET

CMS.gov
Centers for Medicare & Medicaid Services

National Coverage Determination (NCD) for Transsexual Surgery (140.3)
Select the 'Print Record', 'Add to Basket' or 'Email Record' buttons to print the record, to add it to your basket or to email the record.
NIH convenes expert panel to set research priorities for transgender
May 7-8, 2015

Grants funded so far from NIH

- R21 (Goodman- Emory) Cohort study of mortality and morbidity in transgender persons
- R01 (Bockting- Columbia) Identity development, risk and resilience among gender diverse populations
- R01 (Olson-UCLA) The impact of early medical treatment in transgender youth
“I am Jazz” TLC July 2015
Ban against discrimination for being Trans
Prevalence Estimates of Transgender in the U.S.A.


Figure 5. Percent and number of adults who identify as LGBT in the United States.
Prevalence of Transsexualism in the USA

VA Cohort study

VA data based on ICD9 codes for gender identity disorder in adults, adolescents, and NOS(302.85, 302.6, 302.5)

Searched VA database from 2006-2013

Patients were considered transgender if they had 1 out of the 3 codes

Prevalence of Transgender in the VA

~33 patients out of 100,000 or \(0.03\%\) of the VA population


<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>New Transgender Diagnoses</th>
<th>Deaths</th>
<th>Total Transgender Diagnoses</th>
<th>VHA Population</th>
<th>Incidence$^a$ (95% CI)</th>
<th>Prevalence$^a$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>226</td>
<td>3</td>
<td>226</td>
<td>6,438,734</td>
<td>3.5 (0.0, 7.2)</td>
<td>3.5 (0.0, 7.2)</td>
</tr>
<tr>
<td>2007</td>
<td>223</td>
<td>4</td>
<td>446</td>
<td>6,574,157</td>
<td>3.4 (0.0, 7.0)</td>
<td>6.8 (1.7, 11.9)</td>
</tr>
<tr>
<td>2008</td>
<td>231</td>
<td>9</td>
<td>673</td>
<td>6,846,503</td>
<td>3.4 (0.0, 7.0)</td>
<td>9.8 (3.7, 16.0)</td>
</tr>
<tr>
<td>2009</td>
<td>272</td>
<td>10</td>
<td>936</td>
<td>7,147,546</td>
<td>3.8 (0.0, 7.6)</td>
<td>13.1 (6.0, 20.2)</td>
</tr>
<tr>
<td>2010</td>
<td>341</td>
<td>15</td>
<td>1267</td>
<td>7,381,314</td>
<td>4.6 (0.4, 8.8)</td>
<td>17.2 (9.0, 25.3)</td>
</tr>
<tr>
<td>2011</td>
<td>384</td>
<td>26</td>
<td>1636</td>
<td>7,552,783</td>
<td>5.1 (0.7, 9.5)</td>
<td>21.7 (12.5, 30.8)</td>
</tr>
<tr>
<td>2012</td>
<td>463</td>
<td>28</td>
<td>2073</td>
<td>7,666,940</td>
<td>6.0 (1.2, 10.9)</td>
<td>27.0 (16.8, 37.2)</td>
</tr>
<tr>
<td>2013</td>
<td>522</td>
<td>16</td>
<td>2567</td>
<td>7,809,269</td>
<td>6.7 (1.6, 11.8)</td>
<td>32.9 (21.6, 44.1)</td>
</tr>
</tbody>
</table>

$^a$Per 100,000 patients.

Note: CI = confidence interval; VHA = Veterans Health Administration.
Number of veterans seeking transgender care is increasing

The prevalence of transgender depends on the definition

### Number of transgender people per 100,000

<table>
<thead>
<tr>
<th>Transgender defined as...</th>
<th>Male to Female</th>
<th>Female to Male</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requests for surgery</td>
<td>10-30</td>
<td>1-15</td>
<td>5-10</td>
</tr>
<tr>
<td>Diagnostic codes (i.e. ICD9)</td>
<td>5-30</td>
<td>1-10</td>
<td>2-10</td>
</tr>
<tr>
<td>Self report</td>
<td>500-700</td>
<td>200-500</td>
<td>500-750</td>
</tr>
</tbody>
</table>

Collin et al. Unpublished
Transgender is an umbrella term for gender dysphoric conditions.
Cardinal Feature of Transgender:
Gender Dysphoria

“Gender Dysphoria is the feeling that one’s assigned gender does not match one’s biological sex”

“Mismatch between brain sex and factual anatomy of the body” – Louis Gooren 2003
Gender Identity Disorders in Adults

DSM V

A marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by 2* or more of the following indicators:

1. a marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics

2. a strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender

3. a strong desire for the primary and/or secondary sex characteristics of the other gender

4. a strong desire to be of the other gender

5. a strong desire to be treated as the other gender

6. a strong conviction that one has the typical feelings and reactions of the other gender
Etiology for Transgender is unknown

Cultural, genetic, biological, hormonal and psychological factors likely all contribute
Twin studies suggest some genetic component

40% of monozygotic twins were concordant for transgender
0% of dizygotic twins were concordant for transgender

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Female twin pairs concordant/discordant for gender identity disorder (GID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Zygosity</td>
</tr>
<tr>
<td>Knoblauch et al. [15]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Heylens and De Cuyper [16]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Green and Stoller [16]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Garden and Rotheny [17]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Segal [18]</td>
<td>Two monozygotic</td>
</tr>
<tr>
<td>Zucker [19]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Heylens and De Cuyper [19]</td>
<td>Dizygotic</td>
</tr>
<tr>
<td>Zucker [19]</td>
<td>Dizygotic</td>
</tr>
<tr>
<td>Segal [20]</td>
<td>Dizygotic</td>
</tr>
<tr>
<td>Zucker et al. [21]</td>
<td>Dizygotic</td>
</tr>
<tr>
<td>Vujovic et al. [22]</td>
<td>Dizygotic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Male twin pairs concordant/discordant for gender identity disorder (GID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Zygosity</td>
</tr>
<tr>
<td>Heylens and De Cuyper</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Green and Stoller [16]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Zucker [19]</td>
<td>Three monozygotic</td>
</tr>
<tr>
<td>Hyde and Kenna [23]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Tsur et al. [24]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Ancherson [26]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Stoller and Baker [27]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Gooren et al. [28]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Gooren et al. [28]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Stoller [29]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Hepp et al. [30]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Segal [31]</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>Heylens and De Cuyper</td>
<td>Three dizygotic</td>
</tr>
<tr>
<td>Zucker [19]</td>
<td>12 dizygotic</td>
</tr>
<tr>
<td>Vujovic et al. [22]</td>
<td>Dizygotic</td>
</tr>
</tbody>
</table>

Heylens et al. Journal of Sexual Medicine 2011
Polymorphisms in genes associated with transgender

ERβ (FTM, Fernandez et al, JSM 2014)

AR (MTF, Hare et al, Biol Psyschiatry 2009)

CYP19A1 (no association, Fernández R et al, JSM, 2014)
Neuron Numbers in the BST May Predict Gender Orientation

In men there are twice as many neurons than women in the central part of the bed nucleus of the stria terminalis (BSTc)

The number of neurons in the BSTc in a MTF TS is similar to a female

Frank PM. JCEM. Vol. 85, No. 5 2034-2041
Standards of Care by the World Professional Association for Transgender Health

Largest professional organization for providers of individuals with gender dysphoria

First published “Standards of Care” in 1979

Guidelines for medical and surgical treatment of patients with gender identity disorders
New WPATH guidelines 2011

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

Highlights of the new standards

• “Disorder” is **not** a preferred term. Now “gender non-conformity”. Being transgender or having different gender expression is not pathologic
• Psychotherapy is not an absolute requirement
• More accepting of other forms of gender variance
• An expanded section addressing gender non-conformance in children and reproductive health
• Better definitions of which professionals are “gender experts”
Endocrine Society Guidelines: Hormonal Therapies Male to Female

- Estrogen
- Anti-Androgens
Estrogens

Inhibit LH secretion at the pituitary to decrease testosterone secretion

Has steroid hormone effects at target organs

Also may directly inhibit gonadal production of testosterone

Estrogens

Conjugated Estrogens
- Premarin 2.5 - 5.0 mg daily

Steroidal Estrogens
- Estradiol (2 to 6 mg) oral daily
- Estradiol transdermal patches 0.1 – 0.4 mg/day
- Estradiol valerate IM 40-80 mg/month

Tangpricha et al. Endocrine Pract 2002
Endocrine Society Guidelines 2009
Anti-Androgens

Spironolactone
- 100-400mg/day
- Anti-androgen at the androgen receptor and decreases androgen production
- Often required to reduce testosterone levels

Cyproterone
- Not available in US
- Some progestin activity

Tangpricha et al. Endocrine Pract 2002 Endocrine Society Guidelines 2009
Initial Evaluation

Male to Female Transsexual
Complete physical examination
Blood pressure, height, weight
Extent of masculinization/feminization
Palpation of liver and breasts for tumors
Examination of venous system for thromboembolism
Examination and measurement of genitalia (glans penis, testes)

Tangpricha et al. Endocrine Pract 2002 Endocrine Society Guidelines 2009
Initial Laboratory Tests

Electrolytes, BUN/creatinine
Liver function tests
Fasting glucose and lipid profile
Estradiol and free or total testosterone
Serum Prolactin*

Tangpricha et al. Endocrine Pract 2002 Endocrine Society Guidelines 2009
Monitoring of MTF on hormone therapy

1. Evaluate patient every 2-3 months in first year then every annually or semi-annually
2. Measure estradiol and testosterone until appropriate levels achieved (T<55 ng/dl, estradiol ~ 200 pg/ml)
3. Monitor electrolytes on spironolactone
4. Cancer screening per age appropriate guidelines based on remaining hormone sensitive organs
5. Consider BMD if risk factors for osteoporosis

Endocrine Society Guidelines 2009
# Effects of Hormonal Feminization

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>ONSET±</th>
<th>MAXIMUM±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redistribution of body fat</td>
<td>3 – 6 months</td>
<td>2 – 3 years</td>
</tr>
<tr>
<td>Decrease in muscle mass and strength</td>
<td>3 – 6 months</td>
<td>1 – 2 years</td>
</tr>
<tr>
<td>Softening of skin/decreased oiliness</td>
<td>3 – 6 months</td>
<td>Unknown</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1 – 3 months</td>
<td>3 – 6 months</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
<td>1 – 3 months</td>
<td>3 – 6 months</td>
</tr>
<tr>
<td>Male sexual dysfunction</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Breast growth</td>
<td>3 – 6 months</td>
<td>2 – 3 years</td>
</tr>
<tr>
<td>Decreased testicular volume</td>
<td>3 – 6 months</td>
<td>2 – 3 years</td>
</tr>
<tr>
<td>Decreased sperm production</td>
<td>Unknown</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>Decreased terminal hair growth</td>
<td>6 – 12 months</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>Scalp hair</td>
<td>No regrowth</td>
<td>c</td>
</tr>
<tr>
<td>Voice changes</td>
<td>None</td>
<td>d</td>
</tr>
</tbody>
</table>

± Estimates represent clinical observations. See Refs 81, 92, 93.

b Complete removal of male sexual hair requires electrolysis or laser treatment or both.

c Familial scalp hair loss may occur if estrogens are stopped.

d Treatment by speech pathologists for voice training is most effective.
# Estrogen Contraindications

<table>
<thead>
<tr>
<th>Very High Risk</th>
<th>Moderate High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Thrombosis</td>
<td>Macroprolactinoma</td>
</tr>
<tr>
<td></td>
<td>Hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Breast Ca</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Migraine headaches</td>
</tr>
</tbody>
</table>

Endocrine Society Guidelines 2009
Endocrine Society Guidelines: Hormonal Therapies
Female to Male

- Testosterone
Initiation of Testosterone Therapy

Complete history and physical
CBC, LFTs, fasting glucose and lipids, estradiol and free or total testosterone
Bone mineral density
Sleep study if sx of OSA

Start IM testosterone 50-75 mg q2weeks

Tangpricha et al. Endocrine Pract 2002 Endocrine Society Guidelines 2009
Testosterone Regimens

Testosterone Esters
- Testosterone enanthate 100 to 200 mg IM q2 wk
- Testosterone cypionate 100 to 200 mg IM q2 wk

Transdermal patches
- 2.5 - 5 mg/day transdermally

Oral Testosterone (not 17α) – Only available in Europe
- Testosterone undecanoate 40mg QID

Testosterone gel (AndroGel or Testim)
- 2.5 - 5 g packet daily

Tangpricha et al. Endocrine Pract 2002 Endocrine Society Guidelines 2009
Effects of Testosterone in FTM

TABLE 13. Masculinizing effects in FTM transsexual persons

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>ONSET° (months)</th>
<th>MAXIMUM° (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin oiliness/acne</td>
<td>1 – 6</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Facial/body hair growth</td>
<td>6 – 12</td>
<td>4 – 5</td>
</tr>
<tr>
<td>Scalp hair loss</td>
<td>6 – 12</td>
<td>b</td>
</tr>
<tr>
<td>Increased muscle mass/strength</td>
<td>6 – 12</td>
<td>2 – 5</td>
</tr>
<tr>
<td>Fat redistribution</td>
<td>1 – 6</td>
<td>2 – 5</td>
</tr>
<tr>
<td>Cessation of menses</td>
<td>2 – 6</td>
<td>c</td>
</tr>
<tr>
<td>Clitoral enlargement</td>
<td>3 – 6</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>3 – 6</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Deepening of voice</td>
<td>6 – 12</td>
<td>1 – 2</td>
</tr>
</tbody>
</table>

a Estimates represent clinical observations. See Refs 81, 92, 93.
b Prevention and treatment as recommended for biological men.
c Menorrhagia requires diagnosis and treatment by a gynecologist.
Monitoring Testosterone Therapy

1. Evaluate patient every 2-3 months in the first year and annually and semi-annually

2. Measure serum T every 2-3 months until levels in the physiologic male range

3. Measure estradiol during first 6 months or until there has not been any uterine bleeding. Should be < 50 pg/ml

4. Measure CBC and LFTs at baseball and every 3 months for the first year then 1-2 times a year

5. Consider BMD, mammogram if breast tissue

6. If cervical tissue present, pap smear recommended
Testosterone Contraindications

Very high risk
- Pregnancy
- Breast or Uterine Cancer
- Erythrocytosis (HCT>50)

Moderate High Risk
- Hepatic

Tangpricha et al. Endocrine Pract 2002 Endocrine Society Guidelines 2009
Testosterone Complications

Abnormal liver function Tests (15%)
Hepatic adenomas, peliosis hepatitis (rare)
Increase in visceral fat
Elevation of total cholesterol, triglycerides and LDL and lowering of HDL cholesterol

Endometrial hyperplasia

Tangpricha et al. Endocrine Pract 2002 Endocrine Society Guidelines 2009
Surgical Treatment

Chest

Genital/Reproductive

Cosmetic
Criteria for chest surgery: MTF and FTM

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.
Criteria for hysterectomy and ovariectomy in FTM patients and for orchiectomy in MTF patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled.
5. 12 continuous months of hormone therapy as appropriate to the patient’s gender goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones).
Criteria for genital reconstruction surgery

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient’s gender goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones).
6. 12 continuous months of living in a gender role that is congruent with their gender identity;
Surgical Therapies
Male to Female

Genital
- Penectomy
- Orchietomy
- Clitoroplasty
- Vaginoplasty
  - Penile Inversion
  - Rectosigmoid
  - Neocolpopoiesis

Non-Genital
- Breast Augmentation
- Rhinoplasty
- Chondrolaryngoplasty
Surgical Therapies
Female to Male

Genital
- Phalloplasty
- Abdominal Flap
- Free Flap
- Metaidoioplasty
- Scrotum Reconstruction

Non-Genital
- Mastectomy
- Hysterectomy
- Bilateral Salpingo-oophorectomy
Challenging Cases
Case 1: 50 year old transgender female referred from gender specialist for hormone therapy

Referral letter

- Cross gender identification feelings started in childhood.
- Dressed in feminine clothing and played with dolls.
- Never quite fit in socially with peers during adolescence.
- Grew up in a religious family and has suppressed cross gender feelings.
- Married a woman and has 2 children.
Referral letter

- Recently, the patient has been suffering from depression over the cross gender feelings
- Patient has worked with her therapist for about 1 year and is deemed to meet criteria for cross hormone therapy for treatment for transgender.
PMHx: Asthma

Medications
- sertraline (Zoloft) for depression
- minoxidil topical solution for male pattern balding
- inhaled corticosteroids for asthma
- antihistamines for seasonal allergies

SocHx: No ETOH, Tobacco, illicit drugs

FamHx: Mother with CVA, Father with prostate cancer
Physical Examination

Patient dressed in feminine clothing
Male breast with minimal breast tissue
Normal liver examination
Normal male genitalia
No evidence of edema
**Laboratory tests**

Comprehensive metabolic panel including electrolytes, liver and kidney function normal

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>1.29 ng/mL</td>
</tr>
<tr>
<td>Estradiol</td>
<td>33 pg/mL (99 pmol/L)</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>402 ng/dL (13.9 nmol/L)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>12 ng/mL (0.52 nmol/L)</td>
</tr>
</tbody>
</table>
Cross Sex Hormone Management

Discussed risks and benefits of hormone therapy including thromboembolism and liver disease. Suggested initiation of anti-androgen therapy first followed by estrogen therapy.

Initiated spironolactone 50 mg BID and increased to 100 mg BID after 4 months

Added estrogel 0.06% transdermal cream (2 pumps daily) after 4 months
6 months into hormone therapy
Spironolactone 100 mg BID and estrogel 0.06% transdermal cream 2 pumps daily

Laboratory values
Normal electrolytes, liver, kidney

Estradiol
124 pg/mL (455 pmol/L)

Total testosterone
2 ng/dL (0.07 nmol/L)
1 year into hormone therapy
Patient dissatisfied with breast development (only minimal tissue under areolae)

Changed transdermal estrogen to estradiol valerate 20 mg IM every 2 weeks

After three months still unsatisfied estradiol valerate increased to 30 mg IM every 2 weeks
Pre-Surgical Management

Patient scheduled for orchiectomy (covered by insurance for preexisting hydrocele). Instructed to hold estrogen 2 weeks prior to surgery.

Patient underwent successful orchiectomy. The operation time was 1 hour without any immediate post-op complications. Discharged home without any overnight stay.

After surgery she was very immobile and only was able to ambulate to the bathroom.
Post-Operative Course

Patient had not yet restarted estrogen. 1 week after surgery patient developed pleuritic chest pain while at home.

Lower extremity ultrasound was negative for DVT. V/Q scan demonstrated filling defect in the right lower lobe consistent with a pulmonary embolus.

Patient started on anti-coagulation therapy. All estrogens discontinued.
Hematology Consult

Hypercoagulable workup which is negative including normal protein C, protein S, anti-thrombin III, homocysteine, anti-cardiolipin antibodies and factor V Leiden mutation.

Patient recommended to remain off estrogen for 1 year and continue on life long coumadin therapy.
## Risk of DVT/PE (cohort studies)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>DVT/PE</th>
<th>Follow-up</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Kesteren et al</td>
<td>1997</td>
<td>The Netherlands</td>
<td>45 out of 816 (~5%)</td>
<td>7734 patient years</td>
<td>Regimen of ethinyl estradiol and cyproterone</td>
</tr>
<tr>
<td>Dittrich et al</td>
<td>2005</td>
<td>Germany</td>
<td>1* out of 60</td>
<td>24 months</td>
<td>Oral estradiol Patient with DVT had predisposing mutation</td>
</tr>
<tr>
<td>Ott et al</td>
<td>2010</td>
<td>Austria</td>
<td>0 out of 162</td>
<td>64 months</td>
<td>Regimen of transdermal E2, cyproterone and finasteride</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 patients had APC mutation</td>
</tr>
<tr>
<td>Wierckx et al</td>
<td>2012</td>
<td>Belgium</td>
<td>3 out of 50</td>
<td>10 years</td>
<td>1 DVT and 2 cerebral thrombosis aged 46-58. 2 out of 3 were smokers</td>
</tr>
<tr>
<td>Asschemen et al</td>
<td>2014</td>
<td>Multi-National</td>
<td>10 out of 1073</td>
<td>5 years</td>
<td>9 European and 6 US sites</td>
</tr>
</tbody>
</table>

van Kesteren PJ et al. PMID 9373456  
Dittrich R et al. PMID 16320157  
Ott J et al. PMID 19200981  
Wierckx K et al. PMID 22906135  
Asschemen Endo 2014
Risk Factors for DVT/PE in MTF Transgender Patients  
(Review of Published Cases)

1. Formulation of Estrogen (ethinyl estradiol, ↑ risk)
2. First year of therapy (Dutch Cohort: 77% of cases in 1989, 58% in 1997)
3. Post-operative state/Immobile state (1.7% in 1989, <1% in 1997 due to use of LMWH)
4. Age (2% risk age <40, 12% risk age >40)

Asscheman et al. Andrologia. 2014
Recommendations to prevent PE/DVT in MTF Transgender Patients

- Avoid use of ethinyl estradiol
- Hold estrogen therapy 2 weeks prior and 3 weeks after surgery
- Prophylaxis for DVT post surgery
- Transdermal estrogens especially in older individuals
- Avoid supra-physiologic dosing with estrogen

Asscheman et al. Andrologia. 2014
Case 1 (Part 2)
## Bone Mineral Density Testing

Since patient is deficient of both sex steroids, patient undergoes bone mineral density testing

<table>
<thead>
<tr>
<th>Location</th>
<th>T-Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine (L1-L4)</td>
<td>-2.9</td>
</tr>
<tr>
<td>Left Femoral Neck</td>
<td>-2.3</td>
</tr>
<tr>
<td>Left Total Hip</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

* Female reference ranges
Bone Mineral Density May be Lower in MTF Transsexuals Prior to the Start of Estrogen

European Network for the Investigation of Gender Incongruence (ENIGI)

Cross-sectional study of 25 MTF, 25 age matched and a reference population of 941 men

Measured Bone Mineral Density prior to initiation of cross section hormones

Median age 37 (range 28-42)

<table>
<thead>
<tr>
<th></th>
<th>Transsexual Women</th>
<th>Age Matched Control Males</th>
<th>Male Reference Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine BMD (g/cm²)</td>
<td>0.97 ± 0.13</td>
<td>1.05 ± 0.10</td>
<td>1.06 ± 0.13</td>
</tr>
<tr>
<td>Femoral Neck BMD (g/cm²)</td>
<td>0.78 ± 0.12*</td>
<td>0.92 ± 0.13</td>
<td>0.88 ± 0.13</td>
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<tr>
<td>Total Hip BMD (g/cm²)</td>
<td>0.94 ± 0.14*</td>
<td>1.11 ± 0.14</td>
<td>1.07 ± 0.13</td>
</tr>
<tr>
<td>Whole Body BMD (g/cm²)</td>
<td>1.09 ± 0.07*</td>
<td>1.23 ± 0.09</td>
<td>1.22 ± 0.10</td>
</tr>
<tr>
<td>Spine T-score &lt;-1.0 and &gt;-2.5</td>
<td>32%*</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Total Hip T-score &lt;-1.0 and &gt;-2.5</td>
<td>36%*</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Spine T-score &lt;-2.5</td>
<td>16%**</td>
<td>4%</td>
<td>2.1%</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/ml)</td>
<td>15 ± 7</td>
<td>23 ± 7</td>
<td>21 ± 8</td>
</tr>
</tbody>
</table>

Bone Density is preserved during follow-up with estrogen

49 transwomen on oral estradiol valerate 4 mg daily or transdermal 17-β estradiol 100 µg/24 h (age >45 years) plus oral cyproterone acetate 50 mg daily

E. Van Caenegem et al. Osteoporosis Int. 2015.
Case 1: Treatment of Osteoporosis

Treated with vitamin D 1,500 IU and calcium 1,000 mg daily

After 1 year of anti-coagulation, patient re-initiated on estroderm patch 0.5 mg/day to 1.5 mg/day.
Case 1: Bone Mineral Density after re-initiation of estrogen

T-score -2.9
+ 13% fr baseline
Case 2: 20 year old male undergraduate art student referred for cross hormone therapy

Referral letter

- Cross gender identification feelings since age 6.
- Previously in a relationship with a female but broke up after issues surrounding gender
- No previous psychiatric history
- Deemed eligible and ready to start cross hormone therapy
- No medical problems
- Normal exam
Excerpts from mental health letter

• “She regularly took clothes from her sister and did not return them”

• “She began an online relationship during the summer of her freshman year. She eventually told this woman that she liked to dress in women’s clothing. When she revealed that it was more than cross dressing, the girlfriend reacted negatively”
Cross Sex Hormone Management

The risks and benefits of cross hormone therapy was discussed. Patient declines sperm banking at this time.

Patient was started on estradiol 1 mg bid and spironolactone 50 mg BID.
Cross Sex Hormone Management (years 1-4)

Patient was on cross hormone therapy for 2 years then discontinued because she was not ready to fully transition in college.

Patient returned after being off hormones for 1 year to reinitiate cross hormones. Started estradiol 1 mg daily and spironolactone 50 mg QD. Patient is very happy. Patient is having physical changes and doing very well socially in school. Dose eventually titrated to estradiol 2 mg BID and spironolactone 100 mg BID.
Discontinuation of Cross Sex Hormones

1.5 years after re-initiation of hormones patient concludes that he is much happier as a male. He stops all hormone therapy. He has been going to the gym to build muscle mass and has grown a beard. He states that he misses the libido when he was a male. His breasts have regressed but there is still some residual breast tissue. Patient states that there were no regrets about the transition and it was necessary for him to work out his gender identity.
Laboratory Tests after Discontinuation of Cross Sex Hormones

Laboratory Tests

Total Testosterone: 403 ng/dL
Estradiol: 18.4 pg/mL
Regret in Post-Op Transsexuals

111 Canadian postoperative transsexuals followed for at least 1 year

0 out of 61 FTM regretted surgery
0 out of 36 MTF transsexuals who prefer men regretted surgery
4 out of 14 MTF transsexuals who prefer women regretted surgery

Regret in Post-Op Transsexuals

1998 Study - Case Control

218 Swedish post op transsexuals
Overall rate of regret 3.8%

3 Factors associated with regret
1. Poor support by family and friends
2. Diagnosis of transsexualism with atypical features
3. Prior history of psychiatric disorder

Quality of Life in Transgender Patients

28 studies (n=1833 with GID)

80% improvement in gender dysphoria with hormones ± surgery

80% improvement in quality of life

72% improvement in sexual function

Case 3: 16 ½ male presents with gender dysphoria.

- Uncomfortable with secondary characteristics such as increased body hair and muscle mass.
- Does want to delay puberty until he can figure out gender identity.
- PMH: Asperger’s and ADD
- Medications: Methylphenidate Hydrochloride 10 mg daily
- Physical Exam: normal with tanner stage 5 genitalia
Laboratory Tests

- Estradiol: 18.7 pg/mL
- Testosterone: 581 ng/dL
- LH: 6 mIU/mL
- FSH: 3 mIU/mL
- TSH: 1.9 uIU/mL
- Prolactin: 6 ng/mL
Impression DDx transsexual vs gender non-conformity.

Cross Sex Hormone Management
After discussion with parent and patient, decided to start spironolactone 50 mg BID as a trial. Testosterone 127, estradiol <20

6 months later
Patient continues to do well. Therapist supports trial of low dose estradiol 0.5 mg QD
Re-consideration of reproduction options

After 1 year of starting anti-androgens and 4 months of low dose estrogen, patient wants to bank sperm. All hormone therapy was discontinued

3 months after holding all therapy patient collects a semen specimen
Semen Analysis

Volume: 2.2 ml (>1.5 ml), pH 7.6 (>7.2)
Concentration: 35 million/mL
Motility: 28%
  Score 3
  (>40%, 1=slight, 4=rapid linear)
Morphology: 2% normal (>4%)

Patient banks sperm and resumes estradiol and spironolactone therapy.
Case 3b

Fertility in Transgender
Case 3b: 44 yo MTF seeking fertility options

- Has been on cross hormone therapy with estradiol and spironolactone for 3 years
- Current dose of estradiol is 6 mg total daily. No longer on spironolactone.
- Wishes to bank semen for future fertility.
Laboratory
On estradiol 2 mg PO TID, no spironolactone
Testosterone 64, Estradiol 234

3 months later
Off estradiol and spironolactone
Testosterone 534, Estradiol 29
**First Collection**
Motility 0
Sperm count 0
Volume 0.5ml
Ph 9

**Second Collection**
Motility 0
Sperm count 0
Volume 1.0 ml
Ph 8.0
Re-initiation of cross hormone therapy

Patient is very uncomfortable being off of hormone therapy and wishes to restart treatment. Patient not interested in pursuing further evaluation for Azoospermia.
Fertility in MTF Transgender

Survey of 50 MTF transgender patients in Belgium indicate 54% desire children

However, ~15% bank their sperm before initiation of therapy

The duration of hormone therapy irreversible infertility is not known

Wierckx K Hum Reprod. 2012
Wierckx K. Arch Sex Behav. 2012 Oct;41(5):1069-71
Fertility in MTF Transgender

Younger patients are seeking gender reassignment surgery and reproductive options should be discussed.
WPATH Standards of Care

Providers should discuss reproductive options prior to initiation of hormone therapy

Transsexual women may be offered sperm banking

Transsexual men may be offered egg cryopreservation
WPATH Standards of Care

Providers should discuss reproductive options prior to initiation of hormone therapy

Transsexual women may be offered sperm banking

Transsexual men may be offered egg cryopreservation
Case 4: 19 year old transmale seeking hormone therapy

- Has been working with a therapist and a support group for about a year and deemed ready for hormones
- History of migraines
- Meds: amitriptyline prn HA
- SocHx: college student, no ETOH, tobacco
- FamHx: negative
Case 4: 19 year old transmale seeking hormone therapy

Physical Exam
BMI 27
Otherwise normal

Labs: Normal electrolytes, kidney and liver function

Hematocrit 44 %, Hemoglobin 14.8 g/dL
Testosterone 31 ng/dL
Case 4: 19 year old transmale seeking hormone therapy

• Patient started on testosterone enanthate 100 mg IM every 2 weeks. Has been taking it for 4 months now with some mild acne, no abdominal pain, noticed increase in muscle mass and cessation of menses. Voice is deepening and fair hair has started.
Case 4: 19 year old transmale seeking hormone therapy

Laboratory tests (after 4 months of testosterone)
Trough Testosterone value 192
Hematocrit 50.3 %, hemoglobin 16.6 g/dL
Testosterone Dose/Levels

100 mg IM q2 weeks  200 mg IM q2 weeks  Testosterone 150 mg IM q2 weeks
Hematocrit response

100 mg IM q2 weeks
200 mg IM q2 weeks
150 mg IM q2 weeks

Hematocrit

Blood donation quarterly
Testosterone and Erythrocytosis

- Single center study of 50 transmen found that about 30% of subjects had HCT >50% and 16% had HCT >52% (Wierckx et al J Sex Med 2012)
- European multi center study of 53 transmen found that hematocrit increased from 40.8 ± 2.9% to 45.8 ± 3.0 % after 1 year of testosterone therapy
- No reported case of a serious adverse event resulting from erythrocytosis has been reported
Testosterone and Erythrocytosis

• Lowering the testosterone dose will generally result in lowering of the hematocrit/hemoglobin concentrations

• Consider routine phlebotomy (blood donation) if HCT does not return to under 50%
Long Term Data in Transsexuals

- Belgium - Short term (1 year) no increase mortality

- Netherlands (n=966) - 18 year follow-up: MTF about 50% increase mortality compared to control not related to hormones (suicide, HIV, drug abuse, CVD). No difference in FTM.

- Sweden (n=324) 10 year follow-up: MTF and FTM increased mortality. Increased CVD, suicide, psychiatric hospitalizations

- USA (VA) (n=5117) – Increase rates of suicide

Blosnich et al. LGBT Health 2014
Wierckx K et al. J Sexual Medicine 2014
Summary of Cases

• Case 1: Thromboembolism can occur as a result of long term estrogen therapy but is relatively rare in larger cohort studies. Risk for thromboembolism include age, formulation of estrogen, post-op state. Osteoporosis screening could be considered especially if estrogen is adequately dosed or discontinued.

• Case 2: Gender identity is sometimes fluid. There is a spectrum of gender dysphoria.
Summary of Cases

• Case 3: Prior to initiation of cross hormone therapy, options for fertility should be discussed.

• Case 4: Hematocrit/hemoglobin should be monitored in transmen and the dose of testosterone should be reduced if HCT > 50%.
Summary

• The prevalence of gender variance is unknown in the United States but in the range of 10-30 per 100,000.

• Patients with gender variance require support from mental health, endocrinology and surgery.

• Physicians need to have a basic understanding of some of the health care issues facing gender variant patients.

• The long term safety of hormonal therapies appears safe in the short term but long term data are needed.
Thank you for your attention!

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