Endocrine Considerations in Transgender Youth

Deanna W. Adkins, MD
Duke Children’s
Disclosure

• I have no relevant financial relationship with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.
Learning Objectives

- Review the determinants of gender
- Discuss gender identity and potential determinants
- Provide current treatment protocols for gender dysphoria
- Describe the unique risks of treatment in this population
Determinants of Gender

- Chromosomes
- HPG axis and Gonads
- External genitalia
Chromosomes

- XX
- XY
- XO Turner
- Mosaic-tissue specific
- XXY Klinefelter
- XYY
- XXYY
### Genes known to be involved in disorders of sex development (DSD)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>OMIM No.</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Gonad</th>
<th>Mullerian structures</th>
<th>External genitalia</th>
<th>Associated features/variant phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WT1</strong></td>
<td>TF</td>
<td>607102</td>
<td>11q13</td>
<td>AD</td>
<td>+/-</td>
<td>Dysgenic testes</td>
<td>Female or ambiguous</td>
<td>Wilm's tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash and Fraser syndromes)</td>
</tr>
<tr>
<td><strong>NKX3.1 (D1F1)</strong></td>
<td>Nuclear receptor Ty1</td>
<td>184737</td>
<td>9q33</td>
<td>AR,UR</td>
<td>+/-</td>
<td>Dysgenic testes</td>
<td>Female or ambiguous</td>
<td>Multiple severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial genital dysgenesis</td>
</tr>
<tr>
<td><strong>SRY</strong></td>
<td>TF</td>
<td>460000</td>
<td>Yp11.3</td>
<td>Y</td>
<td>+/-</td>
<td>Dysgenic testes or ovotesticular</td>
<td>Female or ambiguous</td>
<td>The severe phenotype of a patient included masculinization of the external genitalia; other patients have isolated genital dysgenesis</td>
</tr>
<tr>
<td><strong>SOX9</strong></td>
<td>TF</td>
<td>608560</td>
<td>17q24.25</td>
<td>AD</td>
<td>+/-</td>
<td>Dysgenic testes or ovotesticular</td>
<td>Female or ambiguous</td>
<td>Complete gonadal dysgenesis (17q24 rearrangements; milder phenotype than point mutations)</td>
</tr>
<tr>
<td><strong>DHH</strong></td>
<td>Signaling molecule</td>
<td>605423</td>
<td>12q13.1</td>
<td>AR</td>
<td>+/-</td>
<td>Dysgenic testes</td>
<td>Female</td>
<td>The severe phenotype of a patient included masculinization of the external genitalia; other patients have isolated genital dysgenesis</td>
</tr>
<tr>
<td><strong>AMX2</strong></td>
<td>Mullerin (? chronoblastomlying)</td>
<td>300932</td>
<td>Xq11.3</td>
<td>X</td>
<td>+/-</td>
<td>Dysgenic testes</td>
<td>Female, ambiguous, or male</td>
<td>Partial gonadal dysgenesis, mental retardation</td>
</tr>
<tr>
<td><strong>ARX</strong></td>
<td>TF</td>
<td>200302</td>
<td>Xq22.12</td>
<td>X</td>
<td>+/-</td>
<td>Dysgenic testes</td>
<td>Ambiguous</td>
<td>X-linked lissencephaly, epilepsy, temperature instability</td>
</tr>
</tbody>
</table>

#### Disorders of gonadal (testicular) development: single-gene disorders

**DMDR1**
- **Gene:** Transcription factor; **OMIM:** 602424; **Locus:** Xq24.3; **Inheritance:** Autosomal dominant; **Gonad:** Dysgenic testes; **Associated features/variant phenotypes:** Female or ambiguous; Mental retardation

**NROB1 (CAIS)**
- **Gene:** Nuclear receptor; **OMIM:** 300018; **Locus:** Xq21.3; **Inheritance:** Autosomal dominant; **Gonad:** Dysgenic testes or ovotesticular; **Associated features/variant phenotypes:** Female or ambiguous; Mental retardation

**WNT4**
- **Gene:** Signaling molecule; **OMIM:** 603490; **Locus:** Xp15; **Inheritance:** Autosomal dominant; **Gonad:** Dysgenic testes; **Associated features/variant phenotypes:** Ambiguous; Mental retardation

**WWOX**
- **Gene:** Steroid metabolism; **OMIM:** 603133; **Locus:** Xq23; **Inheritance:** Autosomal dominant; **Gonad:** Ambiguous; 46,XY mother of index case had normal female genitalia and late menarche

#### Disorders in hormone synthesis or action

**LMNA**
- **Gene:** Lamins; **OMIM:** 152790; **Locus:** 2q21; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Laryngeal cleft hypoplasia

**DHCR7**
- **Gene:** Enzyme; **OMIM:** 600850; **Locus:** 11q12-13; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Variable; Sotos-Lucri-Quintana syndrome; coarse faces, second-third ray syndactyly, failure to thrive, developmental delays, cardiac and visceral abnormalities

**SARM1**
- **Gene:** Steroid oestrogen receptor; **OMIM:** 609517; **Locus:** Xq11.2; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female; Congenital adrenal hypoplasia (primary adrenal failure); partial failure

**CPY11A1**
- **Gene:** Enzyme; **OMIM:** 118485; **Locus:** 15q23-24; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Congenital adrenal hypoplasia (primary adrenal failure), partial failure

**HSDB2**
- **Gene:** Enzyme; **OMIM:** 201810; **Locus:** 10q11.2; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Congenital adrenal hypoplasia (primary adrenal failure), partial failure

**CYP17**
- **Gene:** Enzyme; **OMIM:** 202100; **Locus:** 10q11.23; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Congenital adrenal hypoplasia (primary adrenal failure), partial failure

**POR (P450 oxidoreductase)**
- **Gene:** Enzyme; **OMIM:** 124015; **Locus:** 7q11.2; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Male or ambiguous; Mixed features of 21-hydroxylase deficiency, 17a-hydroxylase deficiency, and androgen deficiency; sometimes associated with solitary testicular Leydig cell tumor

**HSOD1**
- **Gene:** Enzyme; **OMIM:** 605573; **Locus:** 8q22; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Partial gonadal dysgenesis at puberty, and androgen/testosterone ratio

**SRD5A2**
- **Gene:** Enzyme; **OMIM:** 607305; **Locus:** Xp23; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Male or ambiguous; Partial gonadal dysgenesis at puberty, testosterone/dihydrotestosterone ratio

**Anti-Mullerian hormone (AMH)**
- **Gene:** Enzyme; **OMIM:** 600957; **Locus:** 19p13.2-13.3; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Partial gonadal dysgenesis at puberty, testosterone/dihydrotestosterone ratio

**Androgen receptor (AR)**
- **Gene:** Nuclear receptor; **OMIM:** 312700; **Locus:** Xp11.22; **Inheritance:** Autosomal; **Gonad:** Testes; **Associated features/variant phenotypes:** Female, ambiguous, or mosaic; Phenotypic spectrum from CAIS (female external genitalia) and PAIS (ambiguous) to normal male genitalia/penis
HPG axis

**Hypothalamus**
- MBH GnRH neurons

**Portal vessels**
- GnRH

**Pituitary**
- Gonadotropes
  - FSH LH

**Gonads**
- Testis
- Ovaries
  - Testosterone
  - Estradiol

**Organization**

**Characteristics**
- GnRH Oscillator (Pulse generator):
  - Frequency coded: largely synchronous intermittent discharge
- Hormonal signal: pulsatile
- Frequency and amplitude modulated
- Signal
  - Pulsatile secretion
- Activation of gonadal gonadotropin receptors
- Amplitude modulated
- ACT via gonadal steroid receptor
The molecular and genetic events in mammalian sex determination and differentiation. The bipotential genital ridge is established by several genes including NR5A1 [Wilhelm et al, 2007; Sekido and Lovell-Badge, 2009]. In the XY gonad the activation of SRY expression, possibly initiated by GATA4/FOG2/NR5A1/WT1, leads to the upregulation of SOX9 expression via a synergy with NR5A1 [Sekido and Lovell-Badge 2008, 2009]. In the XX gonad, the supporting cell precursors accumulate β-catenin in response to Rspo1/Wnt4 signaling and repress SOX9 activity [Schlessinger, et al, 2010]. Once SOX9 levels reach a critical threshold, several positive regulatory loops are initiated, including autoregulation of its own expression and formation of feed-forward loops via FGF9 or Pdgfr signaling [Sekido and Lovell-Badge, 2009]. At later stages, FOXL2 may repress SOX9 expression [Uhlenhaut, et al, 2009]. In the testis, SOX9 promotes the testis pathway, including AMH activation, and it also probably represses the ovarian genes Wnt4 and FoxL2 [Sekido and Lovell-Badge, 2009; Uhlenhaut, et al, 2009; Schlessinger, et al, 2010]. DMRT1 controls sex determination in some species of fish and may be the master sex-determining switch in birds, but its role in mammalian sexual development is unclear [Wilhelm, et al, 2007; Smith, et al, 2009]. Much of this data has been generated from studies in mice.

Phenotypic differentiation of the female and male urogenital tracts

In females, the Müllerian ducts give rise to the fallopian tubes, uterus, and upper vagina, and the Wolffian ducts persist in vestigial form. In males, the Wolffian ducts give rise to the epididymides, vasa deferentia, seminal vesicles, and ejaculatory ducts, and the Müllerian ducts regress.
Other hormones

- Adrenal
  - CAH
- MIS
- Placenta
- Maternal
- Exogenous
Receptors/Tissue

Schematic representation of grading scheme for clinical classification of androgen insensitivity syndromes (AIS)

Grades are numbered 1-7 in order of increasing severity (more defective masculinization). Grade 1: normal masculinization in utero; grade 2: male phenotype with mild defect in masculinization eg, isolated hypospadias; grade 3: male phenotype with severe defect in masculinization-small penis, perineoscrotal hypospadias, bifid scrotum and/or cryptorchidism; grade 4: severe genital ambiguity-clitoral-like phallus, labioscrotal folds, single perineal orifice; grade 5: female phenotype with posterior labial fusion and clitoromegaly; grade 6/7: female phenotype (grade 6 if pubic hair present in adulthood, grade 7 if no pubic hair in adulthood).

In females, the genital tubercle becomes the clitoris, the genital swellings become the labia majora, and the genital folds become the labia minora. In males, the genital tubercle becomes the glans penis, the genital swellings fuse to become the scrotum, the genital folds elongate and fuse to form the shaft of the penis and the penile urethra, and the prostate forms in the wall of the urogenital sinus.
Gender Identity

- State of being where the sexual differentiation of the brain is not consonant with chromosomal pattern and gonadal sex
Prevalence of gender dysphoria:

- based on data of subjects undergoing sex reassignment treatment in the Netherlands, is 1:11,900 men and 1:30,400 women
- prevalence by self-report in New Zealand is approximately 1:6000
- approximate 3:1 ratio of male-to female versus female-to-male transsexuals is widely encountered in the western world
Prevalence over time

Regression of year on Logit event rate

Logit event rate

Year:
-12.31
-12.02
-11.73
-11.44
-11.15
-10.86
-10.57
-10.28
-10.00
-9.87
-9.54
-9.16
-8.77
-8.35

Year:
1958.30
1963.94
1969.58
1975.22
1980.86
1986.50
1992.14
1997.78
2003.42
2009.06
2014.70
How likely is it that, as a provider I will encounter this population?

• >8 million Americans identify as gay, lesbian, or bisexual
• >700,000 Americans identify as transgender

Source: The Williams Institute
Possible Etiologies

• Prenatal hormone exposure
  ▫ Maternal-luteoma
  ▫ Environmental-DES
  ▫ Placental-aromatase
  ▫ Infant-CAH

• Variants of the androgen receptor
Gender Based Brain Variations

• Overall volume-M>F
  ▫ Similar to natal sex in adolescents
  ▫ Adults are between M and F

• White Matter-M>F
  ▫ Between male and female

• Connectivity profiles-
  ▫ Differ from both male and female
  ▫ MtF more less inter hemispheric connections
  ▫ FtM fewer intra hemispheric connections
Gender Based Brain Variations-2

- Cerebral blood flow
- Hypothalamic response to androgen chemosignals even in prepubertal
  - MtF same as natal female
  - FtM same as natal male
- On GnRH
  - Less activation of the temporal lobe
- Visual spatial activation similar male to FtM and female to MtF pre treatment
Effects of treatment on the brain

- Decreased volume overall on antiandrogen/estrogen combination-7 months
- Increased volume on testosterone total and hypothalamic
- Increased cortical thickness on in FtM
Youth who identify as transgender, gender fluid or gender non-conforming

At high risk for:

- Suicide Ideation (51%)
- Suicide Attempts (9.3-30%)
- Anxiety (25%)
- Depression (35-58.1%)
- Eating Disturbance (7%)

(Khatchadourian, Amed, & Metzger, 2014; Olson et al., 2015; Spack, et al., 2012).
Non TG vs TG

- Lifetime prevalence of psychiatric diagnoses (including mood disorders, anxiety disorders, schizophrenia, substance abuse, and eating disorders) of 71 percent, but a current prevalence of 39 percent [28].
- 6% vs 18% non transgender vs transgender are bullied weekly
- 30% vs 50% been physically injured by someone
- 23% vs 45% self harm in last 12 mos
- 4% vs 20% attempted suicide in last 21 mos
- 17% vs 40% unable to access healthcare
With Regard to healthcare

Source: Lambda Legal “When Health Care Isn’t Caring” study
Treatment
Treatment Guidelines

TRANSGENDER STANDARDS OF CARE

NATIONAL LGBT HEALTH EDUCATION CENTER
A PROGRAM OF THE FENWAY INSTITUTE
Gender Dysphoria and Transition

- **Gender Transition** is the process of changing one’s gender presentation/ expression/ physical characteristics more fully/ permanently to align with their gender identity (inner sense of self).
- Transitioning is one form of treatment for gender dysphoria
- There are varying levels of transition and individuals can engage or disengage from one or several of these levels over their lifespan
Stages of transition: cont

- **Stage 4: Social Transition**: can include any or all of the following—name change, dressing as one’s felt gender, hair, make-up, bathroom use, pronoun change, coming out to friends and family

- **Stage 5: Medical Transition**: Introduction of blockers and/or cross-sex hormones

- **Stage 6: Surgical Transition**: Sex reassignment surgery/surgeries, e.g. masectomy, breast augmentation, hysterectomy, salpingo-oophorectomy, metoidioplasty, phalloplasty, vaginoplasty
Efficacy

- 80% reported significant improvement in gender dysphoria,
- 78% reported significant improvement in psychological symptoms,
- 80% reported improvement in quality of life
- 72% reported significant improvement in sexual function.
### Feminizing effects in male-to-female transsexual persons

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset*</th>
<th>Maximum*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redistribution of body fat</td>
<td>3 to 6 months</td>
<td>2 to 3 years</td>
</tr>
<tr>
<td>Decrease in muscle mass and strength</td>
<td>3 to 6 months</td>
<td>1 to 2 years</td>
</tr>
<tr>
<td>Softening of skin/decreased oiliness</td>
<td>3 to 6 months</td>
<td>Unknown</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1 to 3 months</td>
<td>3 to 6 months</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
<td>1 to 3 months</td>
<td>3 to 6 months</td>
</tr>
<tr>
<td>Male sexual dysfunction</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Breast growth</td>
<td>3 to 6 months</td>
<td>2 to 3 years</td>
</tr>
<tr>
<td>Decreased testicular volume</td>
<td>3 to 6 months</td>
<td>2 to 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 to 12 months</td>
<td>&gt;3 years</td>
</tr>
<tr>
<td>Scalp hair</td>
<td>No regrowth</td>
<td>Δ</td>
</tr>
<tr>
<td>Voice changes</td>
<td>None</td>
<td>◊</td>
</tr>
</tbody>
</table>

* Estimates represent clinical observations.
- Complete removal of male sexual hair requires electrolysis, or laser treatment, or both.
- Familial scalp hair loss may occur if estrogens are stopped.
- Treatment by speech pathologists for voice training is most effective.

Hormone regimens in the transsexual persons: MTF

- **Estrogen:**
  - Oral: estradiol 2.0–6.0 mg/d
  - Transdermal: estradiol patch 0.1–0.4 mg twice weekly
  - Parenteral: estradiol valerate or cypionate
    - 5–20 mg im every 2 wk
    - 2–10 mg im every week

- **Antiandrogens**
  - Spironolactone 100–200 mg/d
  - Cyproterone acetate 50–100 mg/d

- **GnRH agonist** 3.75 mg sc monthly; depot q 3 month
  - Supprelin or vantas yearly
Medical conditions that can be exacerbated by cross-sex hormone therapy: FTM

- Transgender female (MTF): estrogen
  - Very high risk of serious adverse outcomes
  - Thromboembolic disease
  - Moderate to high risk of adverse outcomes
  - Macroprolactinoma
  - Severe liver dysfunction (transaminases 3 upper limit of normal)
  - Breast cancer
  - Coronary artery disease
  - Cerebrovascular disease
  - Severe migraine headaches
Estrogen Formulations and VTE

- pre-1990 frequent use of
  - oral ethinyl estradiol (50–100 lg/day),
  - oral conjugated equine estrogens (5–10 mg/day), and
  - self-procured estradiol (200–800 mg/mo) administered intramuscularly
- the rate of VTE decreased from:
  - 143 cases/10,000 treatment-years between 1972 and 1986
  - 42 to 58 cases/10,000 treatment-years between 1975 and 1994
Increased risk for cardiovascular disease mortality

- 4.1% vs 1.3% for continuous use of ethinyl estradiol vs former use of or never used ethinyl estradiol
- even after adjustment for age and smoking history (HR 3.64, 95% CI 1.52–8.73, p=0.004).
Stroke

- rate of stroke was 7.5/10,000 treatment-years from 1975–1994
- rate of 2.7 cases/10,000 treatment-years during a follow-up period between 1975 and 2007
## Masculinizing effects in female-to-male transsexual persons

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset (months) *</th>
<th>Maximum (yr)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin oiliness/acne</td>
<td>1 to 6</td>
<td>1 to 2</td>
</tr>
<tr>
<td>Facial/body hair growth</td>
<td>6 to 12</td>
<td>4 to 5</td>
</tr>
<tr>
<td>Scalp hair loss</td>
<td>6 to 12</td>
<td></td>
</tr>
<tr>
<td>Increased muscle mass/strength</td>
<td>6 to 12</td>
<td>2 to 5</td>
</tr>
<tr>
<td>Fat redistribution</td>
<td>1 to 6</td>
<td>2 to 5</td>
</tr>
<tr>
<td>Cessation of menses</td>
<td>2 to 6</td>
<td>Δ</td>
</tr>
<tr>
<td>Clitoral enlargement</td>
<td>3 to 6</td>
<td>1 to 2</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>3 to 6</td>
<td>1 to 2</td>
</tr>
<tr>
<td>Deepening of voice</td>
<td>6 to 12</td>
<td>1 to 2</td>
</tr>
</tbody>
</table>

* Estimates represent clinical observations.

Hormone regimens in the transgender persons: FTM

• Parenteral
  ▫ Testosterone enanthate or cypionate
    • 100–200 mg im every (sq 50% of IM)
    • 2 wk or 50% weekly
  ▫ Testosterone undecanoate\(b,c\) 1000 mg every 12 wk

• Transdermal
  ▫ Testosterone gel 1% 2.5–10 g/d
  ▫ Testosterone patch 2.5–7.5 mg/d
Medical conditions that can be exacerbated by cross-sex hormone therapy MTF

- Hyperlipidemia
- Polycythemia
- Male pattern baldness
- Acne
- Infertility
- Elevated liver enzymes
Monitoring

• During the induction of puberty, the following examinations and lab tests are recommended:
  • Height, weight, breast development (in transgender females) – every three months during the first year of treatment
  • Estradiol, testosterone – every three months during the first year of treatment
  • Renal function, liver function, lipids, glucose, insulin, glycosylated hemoglobin – yearly
Gender vs. Sex vs. Sexual Orientation Cont.

- **Transgender** – a person whose gender identity and/or gender expression differs to varying degrees from the gender expected of them based on their sex assigned at birth.

- **Cisgender** – a person whose gender identity and gender expression align with the gender expected of them based on their sex assigned at birth.
Gender vs. Sex vs. Sexual Orientation

Cont.

- **Gender Nonconforming** – someone whose gender identity and/or gender expression breaks societal norms, e.g., a self-identified man, assigned male at birth, who wears skirts and fingernail polish.

- **Gender Conforming** – someone whose gender identity and/or gender expression is consistent with societal norms. e.g., a self-identified woman, assigned female at birth, who wears clothing found in the women’s section of stores.