Endocrine Considerations in Transgender Youth

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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

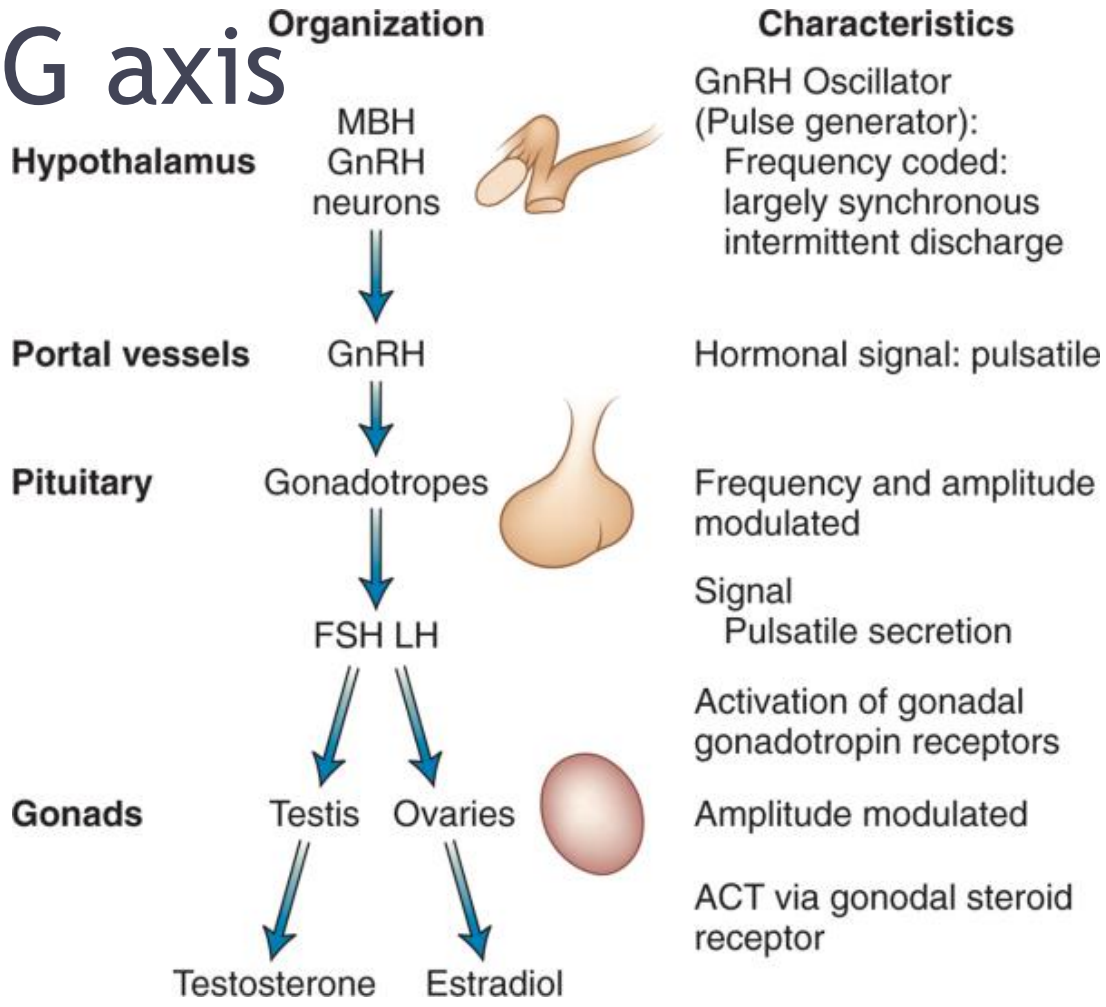
Genes known to be involved in disorders of sex development (DSD)

Gene	Protein	OMIM No.	Locus	Inheritance	Gonad	Mullerian structures	External genitalia	Associated features/variant phenotypes
46,XY DSD								
Disorders of gonadal (testicular) development: single-gene disorders								
WT1	TF	607102	11p13	AD	Dysgenetic testis	+/–	Female or ambiguous	Wilms' tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash and Frasier syndromes)
NR5A1 (SF1)	Nuclear receptor TF	184757	9q33	AD/AR	Dysgenetic testis	+/–	Female or ambiguous	More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis
SRY	TF	480000	Yp11.3	Y	Dysgenetic testis or ovotestis	+/–	Female or ambiguous	
SOX9	TF	608160	17q24-25	AD	Dysgenetic testis or ovotestis	+/–	Female or ambiguous	Camptomelic dysplasia (17q24 rearrangements; milder phenotype than point mutations)
DHH	Signaling molecule	605423	12q13.1	AR	Dysgenetic testis	+	Female	The severe phenotype of 1 patient included minifascicular neuropathy; other patients have isolated gonadal dysgenesis
ATRX	Helicase (? chromatin remodeling)	300032	Xq13.3	X	Dysgenetic testis	–	Female, ambiguous, or male	α-Thalassemia, mental retardation
ARX	TF	300382	Xp22.13	X	Dysgenetic testis	–	Ambiguous	X-linked lissencephaly, epilepsy, temperature instability
Disorders of gonadal (testicular) development: chromosomal changes involving key candidate genes								
DMRT1	TF	602424	9p24.3	Monosomic deletion	Dysgenetic testis	+/–	Female or ambiguous	Mental retardation
NR0B1 (DAX1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Dysgenetic testis or ovary	+/–	Female or ambiguous	
WNT4	Signaling molecule	603490	1p35	dup1p35	Dysgenetic testis	+	Ambiguous	Mental retardation
WWOX	Steroid metabolism	605131	16q23	del16q23	Dysgenetic testis	–	Ambiguous	46,XX mother of index case had normal female genitalia and late menarche
Disorders in hormone synthesis or action								
LHGCR	G-protein receptor	152790	2p21	AR	Testis	–	Female, ambiguous, or micropenis	Leydig cell hypoplasia
DHCR7	Enzyme	602858	11q12-13	AR	Testis	–	Variable	Smith-Lemli-Opitz syndrome: coarse facies, second-third toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities
StAR (steroidogenic acute regulatory protein)	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	–	Female	Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	–	Female or ambiguous	CAH (primary adrenal failure), pubertal failure
HSD3B2	Enzyme	201810	1p13.1	AR	Testis	–	Ambiguous	CAH, primary adrenal failure, partial androgenization caused by dehydroepiandrosterone sulfate
CYP17	Enzyme	202110	10q24.3	AR	Testis	–	Female, ambiguous, or micropenis	CAH, hypertension caused by corticosterone and 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	–	Male or ambiguous	Mixed features of 21-hydroxylase deficiency, 17 α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; sometimes associated with Antley Bixler craniosynostosis
HSD17B3	Enzyme	605573	9q22	AR	Testis	–	Female or ambiguous	Partial androgenization at puberty, androstenedione/testosterone ratio
SRD5A2	Enzyme	607306	2p23	AR	Testis	–	Ambiguous or micropenis	Partial androgenization at puberty, testosterone/dihydrotestosterone ratio
Anti-Mullerian hormone	Signaling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal male	Persistent Mullerian duct syndrome; male external genitalia, bilateral cryptorchidism
Anti-Mullerian hormone receptor	Serine-threonine kinase transmembrane receptor	600956	12q13	AR	Testis	+	Normal male	
Androgen receptor	Nuclear receptor TF	313700	Xq11-12	X	Testis	–	Female, ambiguous, micropenis, or normal male	Phenotypic spectrum from CAIS (female external genitalia) and PAIS (ambiguous) to normal male genitalia/infertility

Chromosomal rearrangements likely to include key genes are included.

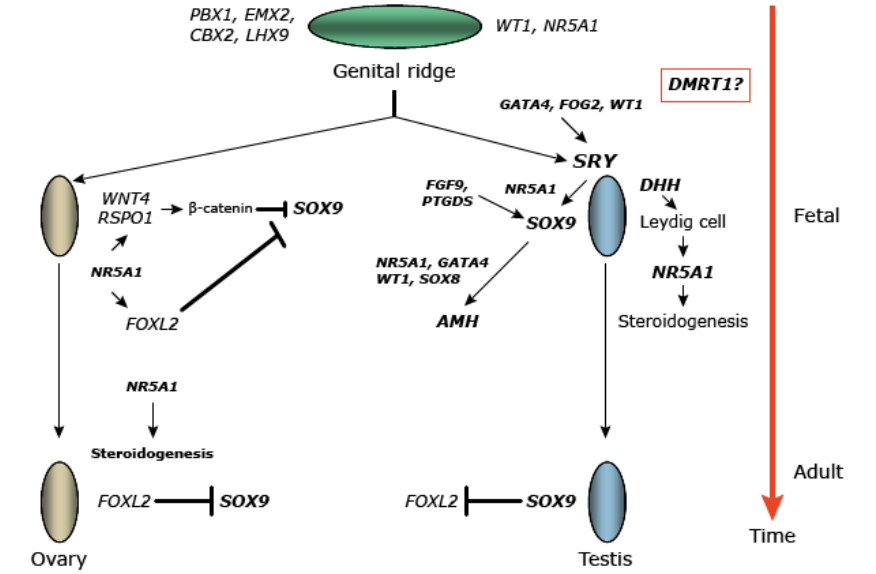
OMIM: Online Mendelian Inheritance in Man; TF: transcription factor; AD: autosomal dominant (often do novo mutation); AR: autosomal recessive; Y: Y-chromosomal; X: X-chromosomal.

HPG axis


Organization
Characteristics
Hypothalamus
MBH
GnRH
neurons
GnRH Oscillator
(Pulse generator):
Frequency coded:
largely synchronous
intermittent discharge
Portal vessels
GnRH
Hormonal signal: pulsatile
Pituitary
Gonadotropes
Frequency and amplitude
modulated
FSH LH
Signal
Pulsatile secretion
Activation of gonadal
gonadotropin receptors
Gonads
Testis
Ovaries
Amplitude modulated
ACT via gonodal steroid
receptor
Testosterone
Estradiol

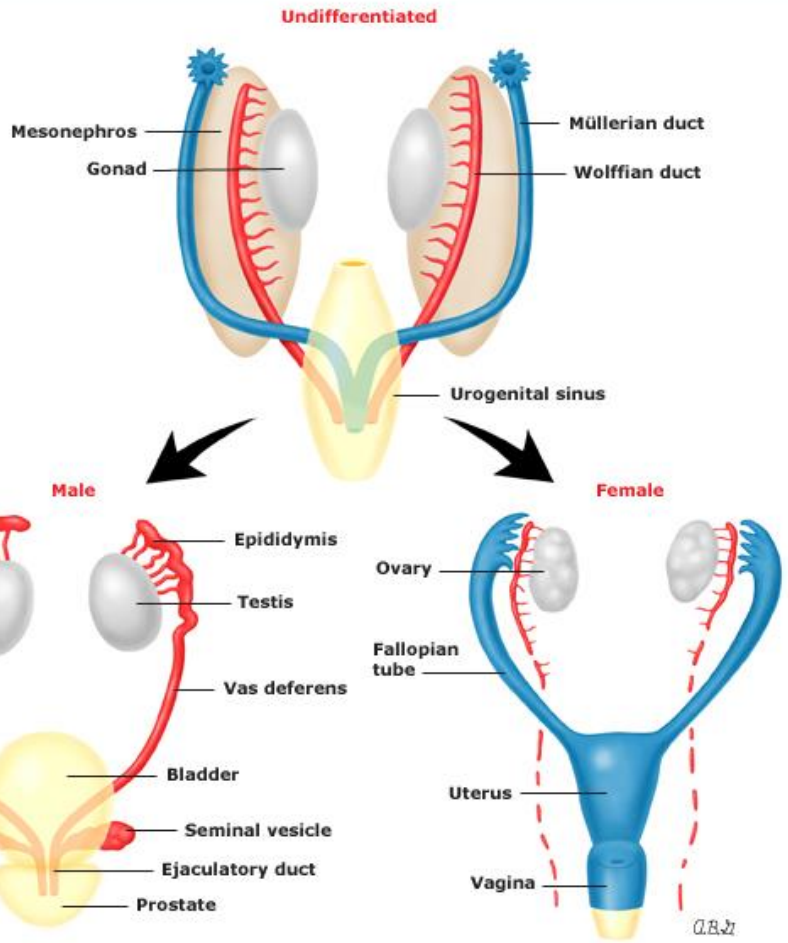
Gonads

Molecular and genetic events in mammalian sex determination and differentiation



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* signalling 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 *PGD2* signalling [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



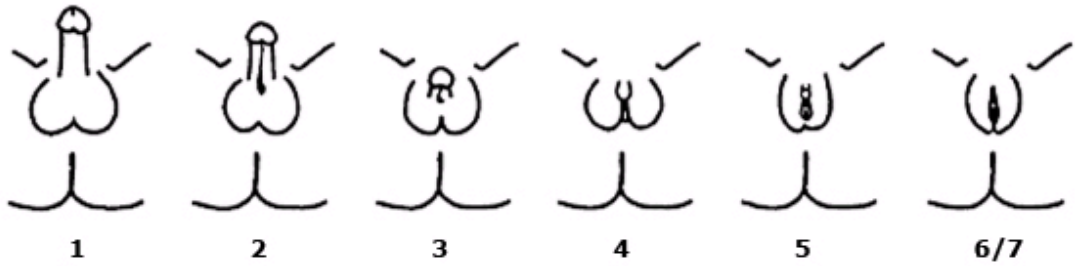
In females, the Müllerian ducts give rise to the fallopian tubes, uterus, and upper vagina, and the Wolffian ducts persist in vestigial form. In males, the Wolffian ducts give rise to the epididymides, vasa deferentia, seminal vesicles, and ejaculatory ducts, and the Müllerian ducts regress.

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).

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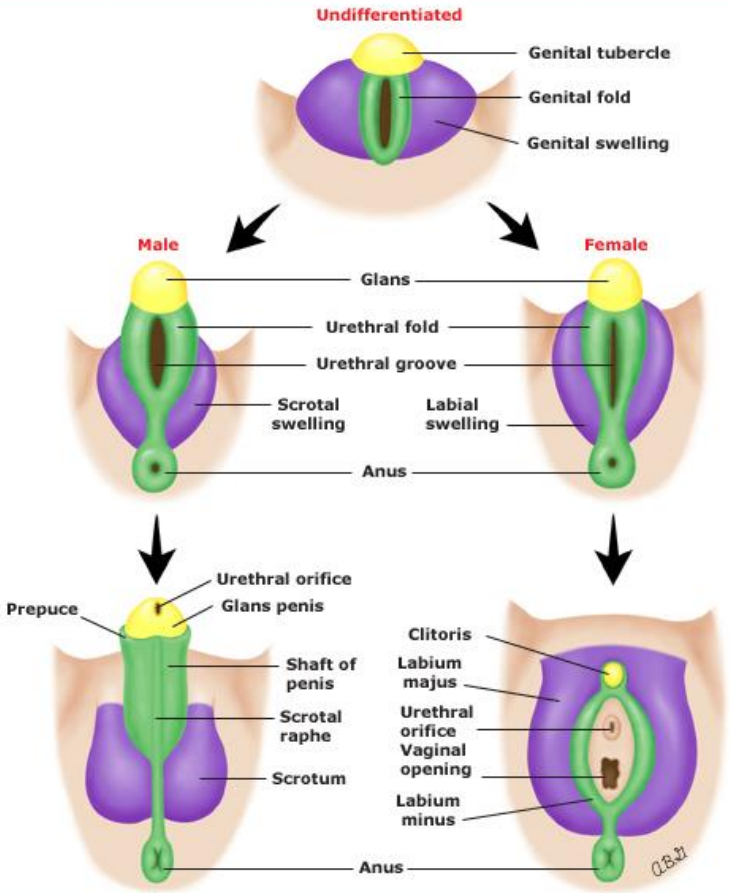
Phenotypic differentiation of the external genitalia in female and male embryos



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.

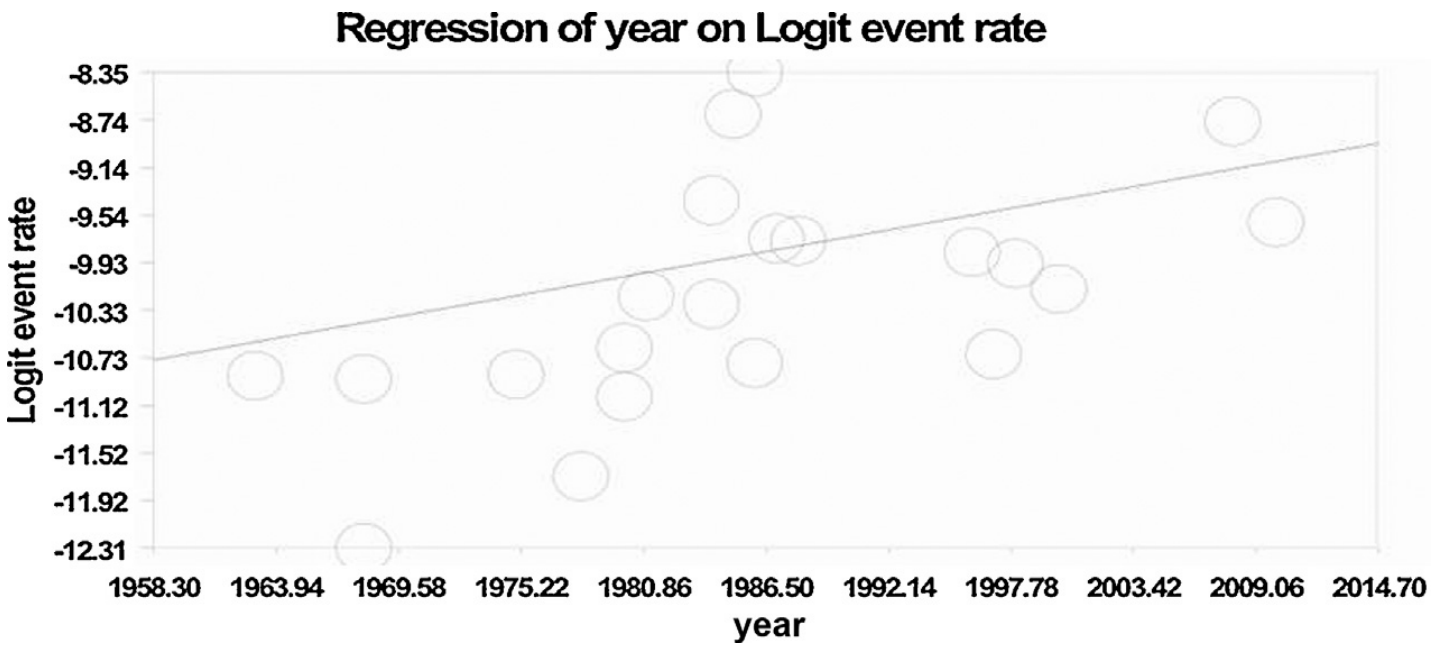
Gender Identity

- 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



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 thickeness on in FtM

Youth who identify as transgender, gender fluid or gender non-conforming

At high risk for:

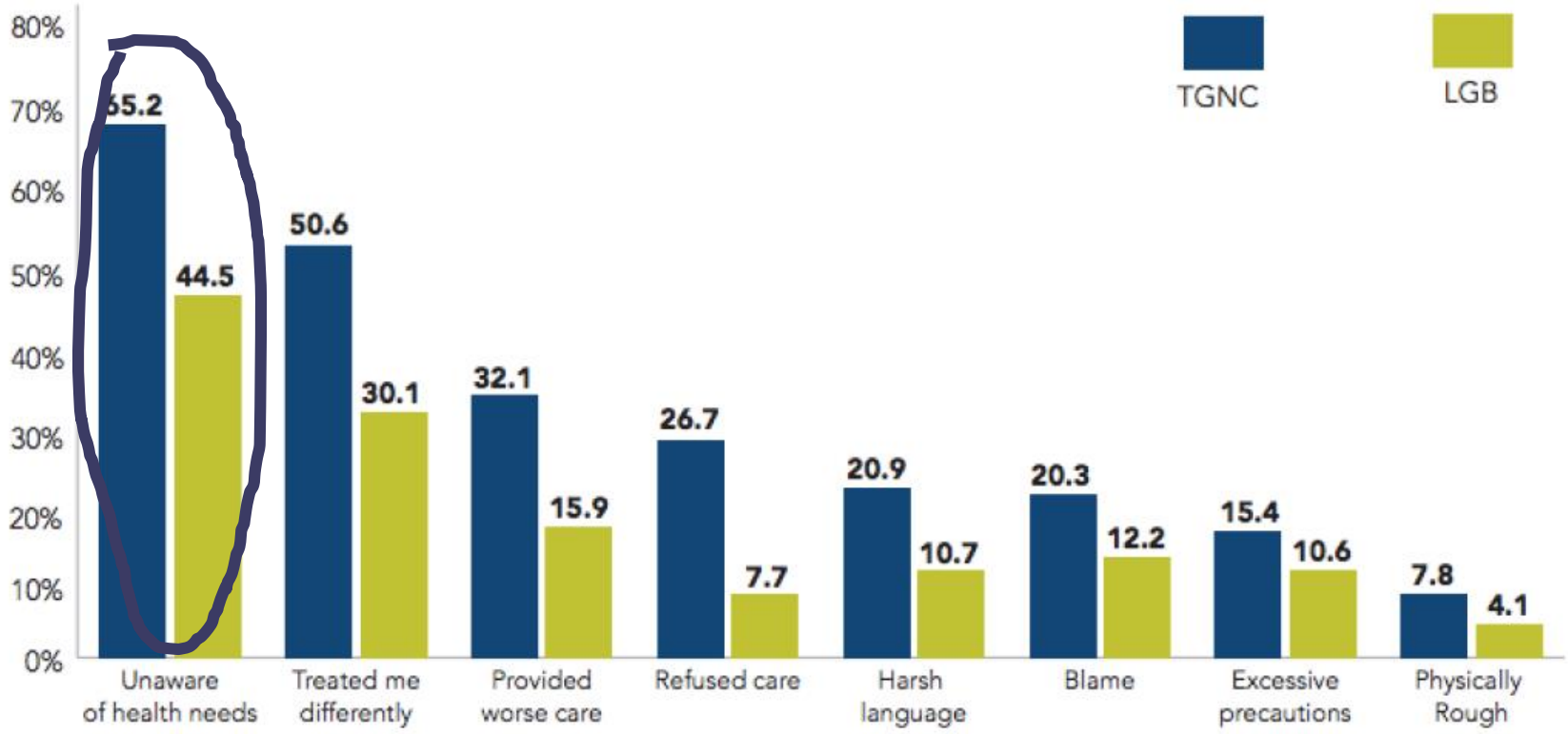
- Suicide Ideation(51%)
- Suicide Attempts (9.3-30%)
- Anxiety (25%)
- Depression (35-58.1%)
- Eating Disturbance (7%)

(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

Resources

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

Effect	Onset*	Maximum*
Redistribution of body fat	3 to 6 months	2 to 3 years
Decrease in muscle mass and strength	3 to 6 months	1 to 2 years
Softening of skin/decreased oiliness	3 to 6 months	Unknown
Decreased libido	1 to 3 months	3 to 6 months
Decreased spontaneous erections	1 to 3 months	3 to 6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3 to 6 months	2 to 3 years
Decreased testicular volume	3 to 6 months	2 to 3 years
Decreased sperm production	Unknown	>3 years
Decreased terminal hair growth	6 to 12 months	>3 years•
Scalp hair	No regrowth	Δ
Voice changes	None	◇

* Estimates represent clinical observations.
• Complete removal of male sexual hair requires electrolysis, or laser treatment, or both.
Δ 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*b* 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 Formulationsand 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

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

* Estimates represent clinical observations.
• Prevention and treatment as recommended for biological men.
Δ Menorhagia requires diagnosis and treatment by a gynecologist.
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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.