Disclosures

Dr. Bethin received research funding from Arbor and Abbvie as local PI
Outline

- Terms
- Prevalence
- Readiness Criteria
- Therapy Part 1
- Therapy Part 2
Relative Terms & Definitions

Related to Gender Care

Rafferty J. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics 2018;142:e20182162
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>An assignment that is made at birth, usually male or female, typically on the basis of external genital anatomy but sometimes on the basis of internal gonads, chromosomes, or hormone levels</td>
</tr>
<tr>
<td>Gender Identity</td>
<td>A person’s deep internal sense of being female, male, a combination of both, somewhere in between, or neither, resulting from a multifaceted interaction of biological traits, environmental factors, self-understanding, and cultural expectations</td>
</tr>
<tr>
<td>Gender Expression</td>
<td>The external way a person expresses their gender, such as with clothing, hair, mannerisms, activities, or social roles</td>
</tr>
<tr>
<td>Gender Perception</td>
<td>The way others interpret a person’s gender expression</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>Gender diverse</td>
<td>A term that is used to describe people with gender behaviors, appearances, or identities that are incongruent with those culturally assigned to their birth sex; gender-diverse individuals may refer to themselves with many different terms, such as transgender, nonbinary, genderqueer, gender fluid, gender creative, gender independent, or noncisgender. “Gender diverse” is used to acknowledge and include the vast diversity of gender identities that exists. It replaces the former term, “gender nonconforming,” which has a negative and exclusionary connotation.</td>
</tr>
<tr>
<td>Transgender</td>
<td>A subset of gender-diverse youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time; the term “transgender” also encompasses many other labels individuals may use to refer to themselves.</td>
</tr>
<tr>
<td>Cisgender</td>
<td>A term that is used to describe a person who identifies and expresses a gender that is consistent with the culturally defined norms of the sex they were assigned at birth.</td>
</tr>
<tr>
<td>Agender</td>
<td>A term that is used to describe a person who does not identify as having a particular gender.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>Affirmed gender</td>
<td>When a person’s true gender identity, or concern about their gender identity, is communicated to and validated from others as authentic</td>
</tr>
<tr>
<td>MTF; affirmed female; trans female</td>
<td>Terms that are used to describe individuals who were assigned male sex at birth but who have a gender identity and/or expression that is asserted to be more feminine</td>
</tr>
<tr>
<td>FTM; affirmed male; trans male</td>
<td>Terms that are used to describe individuals who were assigned female sex at birth but who have a gender identity and/or expression that is asserted to be more masculine</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
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</tr>
<tr>
<td>Gender dysphoria</td>
<td>A clinical symptom that is characterized by a sense of alienation to some or all of the physical characteristics or social roles of one’s assigned gender; also, gender dysphoria is the psychiatric diagnosis in the DSM-5, which has focus on the distress that stems from the incongruence between one’s expressed or experienced (affirmed) gender and the gender assigned at birth</td>
</tr>
<tr>
<td>Gender Identity Disorder</td>
<td>A psychiatric diagnosis defined previously in the DSM-IV (changed to “gender dysphoria” in the DSM-5); the primary criteria include a strong, persistent cross-sex identification and significant distress and social impairment. This diagnosis is no longer appropriate for use and may lead to stigma, but the term may be found in older research</td>
</tr>
<tr>
<td>Sexual Orientation</td>
<td>A person’s sexual identity in relation to the gender(s) to which they are attracted; sexual orientation and gender identity develop separately.</td>
</tr>
</tbody>
</table>
Prevalence of Transitioning Persons

- 0.6% in US (1.6 million)
- 0.3% in ND to 0.8% in Hawaii
- Estimates – 0.7% (150,000) youth ages 13-17 years
Transgender & Gender Diverse Youth

- Traditionally underserved population
- Increasingly presenting to pediatric providers
- Huge need for standardized treatment and more formal training
Gender Identity Development

- 2-3 years general sense of gender
- 6-7 years sense that gender likely does not change
- 12-27% of children with gender dysphoria persist into puberty
- Number of individuals whose GD did not exist until after puberty
Readiness Criteria
- Determine eligibility and readiness criteria
  - Trained Mental Health Counselor
- Suppress pubertal hormones after puberty starts
  - No earlier than Tanner 2
- GnRH analogs are the gold standard
Adolescents are eligible for GnRH agonist treatment if:

- A qualified MHP has confirmed that:
  - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
  - gender dysphoria worsened with the onset of puberty,
  - any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent’s situation and functioning are stable enough to start treatment,
  - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,

Adapted from: Rafferty J. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics 2018;142:e20182162.
And the adolescent:
- has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

And a pediatric endocrinologist or other clinician experienced in pubertal assessment:
- agrees with the indication for GnRH agonist treatment,
- has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2),
- has confirmed that there are no medical contraindications to GnRH agonist treatment.
Adolescents are eligible for subsequent sex hormone treatment if:

- A qualified MHP has confirmed:
  - the persistence of gender dysphoria,
  - any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent’s situation and functioning are stable enough to start sex hormone treatment,
  - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
And the adolescent:

- has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

And a pediatric endocrinologist or other clinician experienced in pubertal induction:

- agrees with the indication for sex hormone treatment,
- has confirmed that there are no medical contraindications to sex hormone treatment.
Readiness Criteria

- Meets DSM-5 or ICD-10 criteria
- Diagnose and treat any psychiatric conditions
- Educated on limitations of sex reassignment treatment and what to expect
- Assessed for psychological or social risk factors
Suppression of Puberty

- Suppress puberty when reach Tanner 2
- Allows exploration of gender identity
- Prevents surgical procedures as adults
  - Laryngeal prominence
  - Muscle mass
  - Voice changes
  - Breasts
  - Menstruation
Hypothalamic-Pituitary-Gonadal Axis

Hypothalamus

GnRH

Pituitary

FSH

LH

Gonadal peptides

Gonad

Sex Steroids

E, P, T

Gametogenesis

Secondary Sex Characteristics

Margaret E. Wierman Advan in Physiol Edu 2007;31:26-33
### Inhibitors of gonadal sex steroid secretion or action

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide acetate</td>
<td>7.5 mg SC</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>22.5 mg SC</td>
<td>Every 3 mo</td>
</tr>
<tr>
<td></td>
<td>40 mg SC</td>
<td>Every 4 mo</td>
</tr>
<tr>
<td></td>
<td>45 mg SC</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>11.25 mg IM</td>
<td>Every 3 mo</td>
</tr>
<tr>
<td></td>
<td>15 mg IM</td>
<td>Every 3 mo</td>
</tr>
<tr>
<td>Histrelin SC implant (50 mg)</td>
<td>65 mcg/d</td>
<td>Every 12 mo (may have longer duration of action)</td>
</tr>
<tr>
<td>Triptorelin (50 mg)</td>
<td>22.5 mg IM</td>
<td>Every 6 mo</td>
</tr>
</tbody>
</table>

HPG, hypothalamic-pituitary-gonadal; IM, intramuscular; SC, subcutaneous.
Alternative Therapies

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate (FTM and MTF)</td>
<td>150 mg IM</td>
<td>Every 3 mo</td>
</tr>
<tr>
<td>Spironolactone (MTF)</td>
<td>100–300 mg/d oral</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Finasteride (MTF)</td>
<td>2.5–5.0 mg/d oral</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

Medroxyprogesterone- inhibits LH/FSH release, inhibits gonadal steroidogenesis

Spironolactone- binds to androgen receptor and inhibits testosterone synthesis

Finasteride- inhibits the conversion of testosterone to 5-alpha DHT
Side Effects of Pubertal Suppression

- Decreased BMD
  - Counteracted by cross-hormone treatment
  - Progesterone in high doses suppress bone growth
- Compromised fertility
- Unknown effects on brain development
- Weight gain
- Depression
## Monitoring

**Every 3–6 mo**

**Anthropometry:** height, weight, sitting height, blood pressure, Tanner stages

**Every 6–12 mo**

- Laboratory: LH, FSH, E2/T, 25OH vitamin D

**Every 1–2 y**

- Bone density using DXA
- Bone age on X-ray of the left hand (if clinically indicated)
Monitoring

- Physical Exam - height, weight, Tanner staging
- LH/FSH, estradiol, testosterone
- Liver enzymes, CBC
- Lipids
- Vitamin D, calcium phosphorus, alkaline phosphatase
- Diabetes screen
- Bone density
Cross-Therapy Treatment

- Have met GID criteria for pubertal suppression
- At least 16 years of age
- Dose should be gradually increased
## Induction of Female Puberty

Induction of female puberty with oral $17\beta$-estradiol, increasing the dose every 6 mo:

<table>
<thead>
<tr>
<th>Dose</th>
<th>mg/kg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Adult dose = 2–6 mg/d

*In postpubertal transgender female adolescents, the dose of $17\beta$-estradiol can be increased more rapidly:*

<table>
<thead>
<tr>
<th>Dose</th>
<th>mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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Jacobs School of Medicine and Biomedical Sciences
University at Buffalo
Patches for Induction

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):

<table>
<thead>
<tr>
<th>Dose</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.25–12.5 μg/24 h</td>
<td>(cut 25-μg patch into quarters, then halves)</td>
</tr>
<tr>
<td>25 μg/24 h</td>
<td></td>
</tr>
<tr>
<td>37.5 μg/24 h</td>
<td></td>
</tr>
<tr>
<td><strong>Adult dose = 50–200 μg/24 h</strong></td>
<td></td>
</tr>
</tbody>
</table>

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).
Other forms of Estrogen

- Oral/sublingual: daily
- Parenteral IM (synthetic esters of 17β-estradiol):
  - estradiol valerate (5–20 mg up to 30–40 mg/2 wk) or
  - estradiol cypionate (2–10 mg/wk)
# Induction of Male Puberty

Testosterone esters increasing the dose every 6 mo (IM or SC):

- **25 mg/m²/2 wk** (or alternatively, half this dose weekly, or double the dose every 4 wk)
- **50 mg/m²/2 wk**
- **75 mg/m²/2 wk**
- **100 mg/m²/2 wk**

**Adult dose = 100–200 mg every 2 wk**
Induction in Postpubertal FTM

Dose of testosterone esters can be increased more rapidly:

- 75 mg/2 wk for 6 mo
- 125 mg/2 wk

Adjust maintenance dose to mimic physiological testosterone levels.
Alternative Testosterones

- Patch
- Gels
- Oral (not in US)
Monitoring

- Physical Exam including blood pressure
- LH/FSH, estradiol, testosterone
- Prolactin (MTF)
- Electrolytes (Spironolactone)
- Liver enzymes, renal function, CBC
- Lipids
- Vitamin D, calcium phosphorus, alkaline phosphatase
- Diabetes screen
- Bone density
MTF Risks

- Thromboembolic disease
- Prolactinoma
- Liver dysfunction
- Breast cancer
- Coronary artery disease
- Cerebrovascular disease
- Severe migraine headaches
- Insulin Resistance
- Hypertension
FTM Risks

- Erythrocytosis
- Liver dysfunction
- Hypertension
- Weight gain
- Lipid changes
- Salt retention
- Acne
- Psychological effects
- Breast or Uterine cancer
Cancer Screening MTF

- Breast cancer
- Prostatic disease and cancer
- Breast cancer
- Uterine cancer
- Consider total hysterectomy and oophorectomy
- Prostate cancer
Gender Reassignment Surgery

- 18 years
- Continuous cross-sex hormones >12 mos
- Continuous RLE >12 mos
- MHP agreement
- Knowledge of all aspects of surgery
  - Cost
  - Hospitalization/ rehabilitation
  - Complications
References


- Rafferty J. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics 2018;142:e20182162.

Thank You!

Questions?