GENDER AFFIRMING MEDICINE

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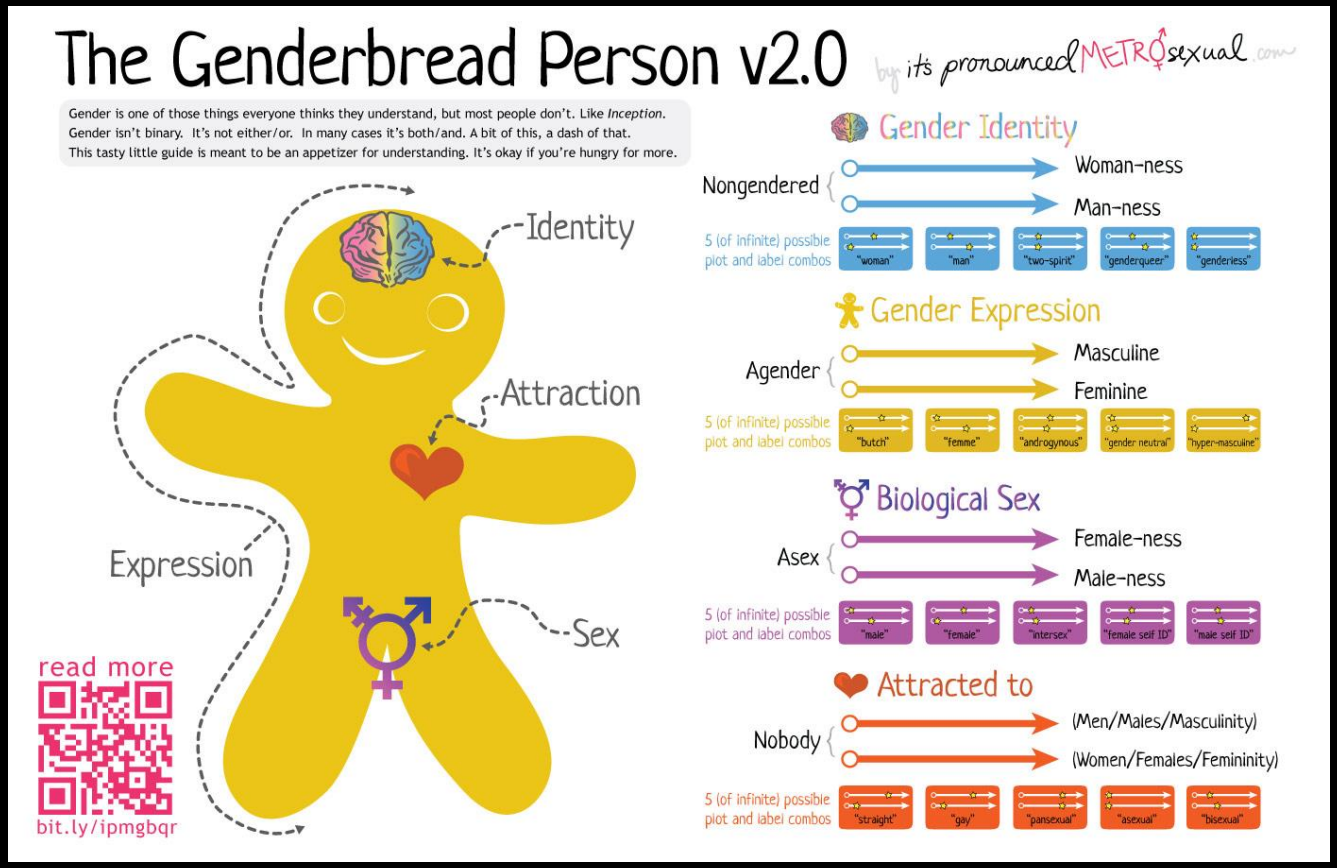
(SHE,HER,HERS)

OBJECTIVES

Recognize	Recognize the medical/social/psychological needs of Gender Diverse Youth
Describe	Describe different pharmacological methods in treating gender related concerns
Develop	Develop comfort in providing an affirming environment for gender diverse youth

BASIC TERMS: OUR PATIENTS



EXAMPLES

COMMONLY USED TERMS

- ***LGBTQ+:*** Acronym commonly used to refer to Lesbian, Gay, Bisexual, Transgender, and Queer/Questioning individuals
- ***Transgender:*** Adjective. Used to describe a person whose gender identity does not "match" the biological sex they were assigned at birth. "trans"
  - FtM (transmasculine)
  - MtF (transfeminine)
- ***Cisgender:*** Adjective. Used to describe a person whose gender identity "matches" the biological sex they were assigned at birth.
- ***Non-Binary:*** A spectrum of gender identities based on the rejection of the gender binary and its assumption that gender is strictly an either/or option of male or female

PRONOUNS

Gendered Pronouns					
He	***He*** laughed	I called ***him***	***His*** shirt	That is ***his***	He likes ***himself***
She	***She*** laughed	I called ***her***	***Her*** shirt	That is ***hers***	She likes ***herself***
All Gender/Gender Neutral Pronouns					
They	***They*** laughed	I called ***them***	***Their*** shirt	That is ***theirs***	They like ***themselves***
Spivak	***Ey*** laughed	I called ***em***	***Eir*** shirt	That is ***eirs***	Ey likes ***emself***
Ze	***Ze*** laughed	I called ***zim***	***Zir*** shirt	That is ***zirs***	Ze likes ***zirself***
Ze/Hir	***Ze*** laughed	I called ***zim***	***Zir*** shirt	That is ***zirs***	Ze likes ***zirself***
Xe	***Xe*** laughed	I called ***xem***	***Xyr*** shirt	That is ***xyrs***	Xe likes ***xemself***
[Name]	***[Name]*** laughed	I called ***[Name]***	***[Name's]*** shirt	That is ***[name's]***	[Name] likes ***[name's] self***

COMMON QUESTIONS

- ***Why are pronouns so important in regards to gender identity?***
  - Everyone has pronouns
  - A way of identifying one's self apart from their name
  - Knowing and using correct pronouns for gender diverse youth is a simple way to let them know that you accept them

COMMON QUESTIONS

- ***What is the right way to find out a person's pronouns?***
  - Start by giving yours!
  - "Hello! My name is Dr. Cole/Crystal , my pronouns are she/her/hers"

COMMON QUESTIONS

- ***Should we be asking everyone their pronouns? Does it depend on the setting?***
  - ***It allows you to have accurate information about another person***
  - ***Gender expression does not equal gender identity***
  - ***Not just a trans issue! (email)***

COMMON QUESTIONS

- ***How is "they" used as a singular pronoun?***
  - ***Prevents you from using gendered language***
  - ***Avoids misgendering an individual***
  - ***Safe choice***

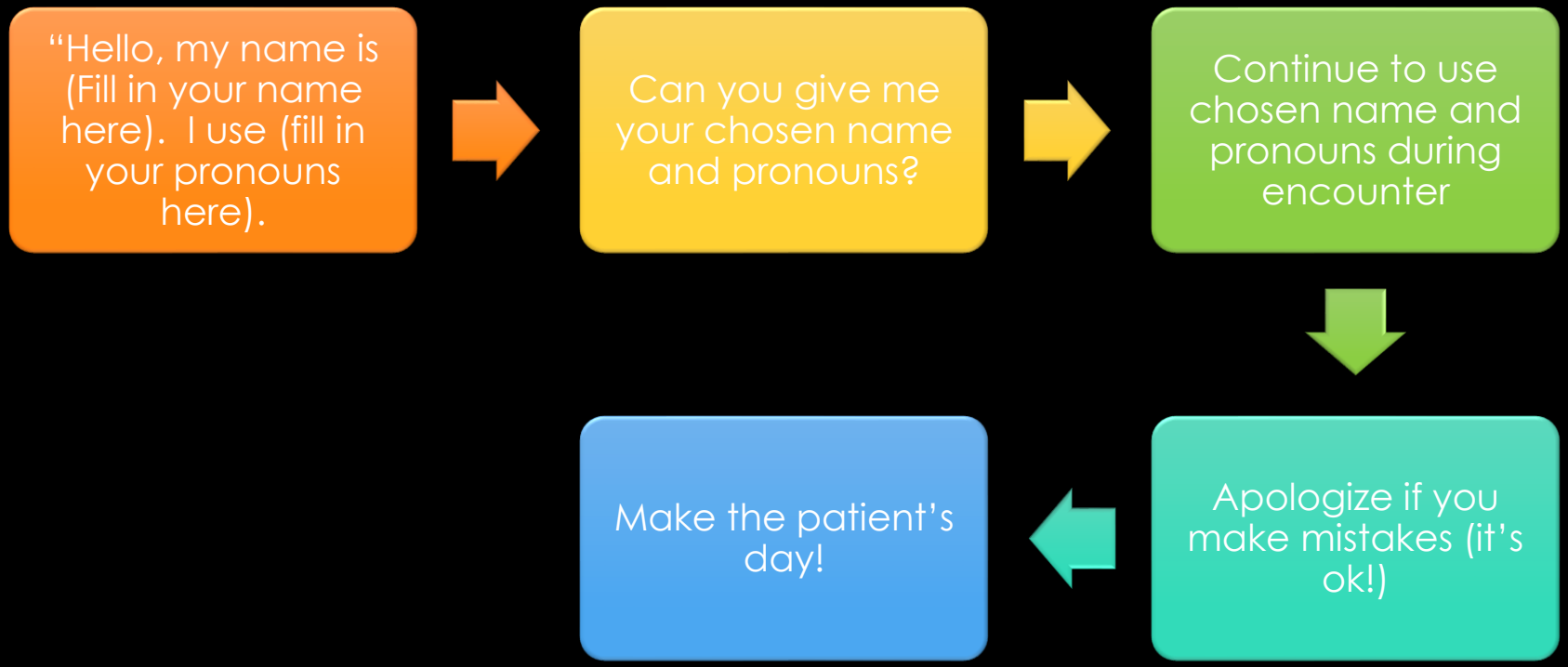
COMMON QUESTIONS

- What do you do if you misgender someone/forget to use their chose name?
  - Apologize and correct

COMMON QUESTIONS

- What if parent and patient are conflicted regarding gender?
  - “your child”
  - Using the patient’s name
  - modeling

FLOWSHEET


"Hello, my name is (Fill in your name here). I use (fill in your pronouns here).
Can you give me your chosen name and pronouns?
Continue to use chosen name and pronouns during encounter
Apologize if you make mistakes (it's ok!)
Make the patient's day!

TREVOR PROJECT 2023 DATA

- 41% of LGBTQ young people seriously considered attempting suicide in the past year—and young people who are transgender, nonbinary, and/or people of color reported higher rates than their peers.
- 56% of LGBTQ young people who wanted mental health care in the past year were not able to get it.
- Transgender and nonbinary young people who reported that all of the people they live with respect their pronouns reported lower rates of attempting suicide.
- Fewer than 40% of LGBTQ young people found their home to be LGBTQ-affirming.

TREVOR PROJECT DATA 2023

Roughly half of transgender and nonbinary young people found their school to be gender-affirming, and those who did reported lower rates of attempting suicide.

A majority of LGBTQ young people reported being verbally harassed at school because people thought they were LGBTQ.

Nearly 1 in 3 LGBTQ young people said their mental health was poor most of the time or always due to anti-LGBTQ policies and legislation.

Nearly 2 in 3 LGBTQ young people said that hearing about potential state or local laws banning people from discussing LGBTQ people at school made their mental health a lot worse.

GENDER DYSPHORIA: CHILDREN (AT LEAST 6 CRITERIA IN 6 MONTHS)

- A strong desire to be of the other gender or an insistence that one is the other gender
- A strong preference for wearing clothes typical of the opposite gender
- A strong preference for cross-gender roles in make-believe play or fantasy play
- A strong preference for the toys, games or activities stereotypically used or engaged in by the other gender
- A strong preference for playmates of the other gender
- A strong rejection of toys, games and activities typical of one's assigned gender
- A strong dislike of one's sexual anatomy
- A strong desire for the physical sex characteristics that match one's experienced gender
- **Causes distress/impairment in school/relationships**

GENDER DYSPHORIA: ADULTS AND ADOLESCENTS

- A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics
- A strong desire to be rid of one's primary and/or secondary sex characteristics
- A strong desire for the primary and/or secondary sex characteristics of the other gender
- A strong desire to be of the other gender
- A strong desire to be treated as the other gender
- A strong conviction that one has the typical feelings and reactions of the other gender
- **Causes distress/impairment in school/work/relationships**

Standards of Care

for the Health of Transsexual, Transgender, and Gender Nonconforming People

The World Professiona Association for Transgender Health

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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TREATMENT

- Completely Reversible
- Partially Reversible
- Irreversible

COMPLETELY REVERSIBLE CARE

- Social Transitioning
  - Clothing
  - Hair
  - Packing/Padding/Binding
  - Name, Pronouns
  - Menstrual management

COMPLETELY REVERSIBLE CARE

- GnRH agonists (puberty blockers)
  - Helps "buy time"
  - "pauses puberty"
  - Tanner stage 2-3?
- Menstrual management
  - Hormonal contraceptives
    - Medroxyprogesterone
    - Norethindrone
- Spironolactone
  - Anti-androgen

GENDER-AFFIRMING HORMONES: CRITERIA

- ***Ideally, made among the patient, the family and the treatment team***
  1. Persistent, well-documented gender dysphoria
  2. Capacity to make 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 reasonably well controlled

GNRH AGONISTS

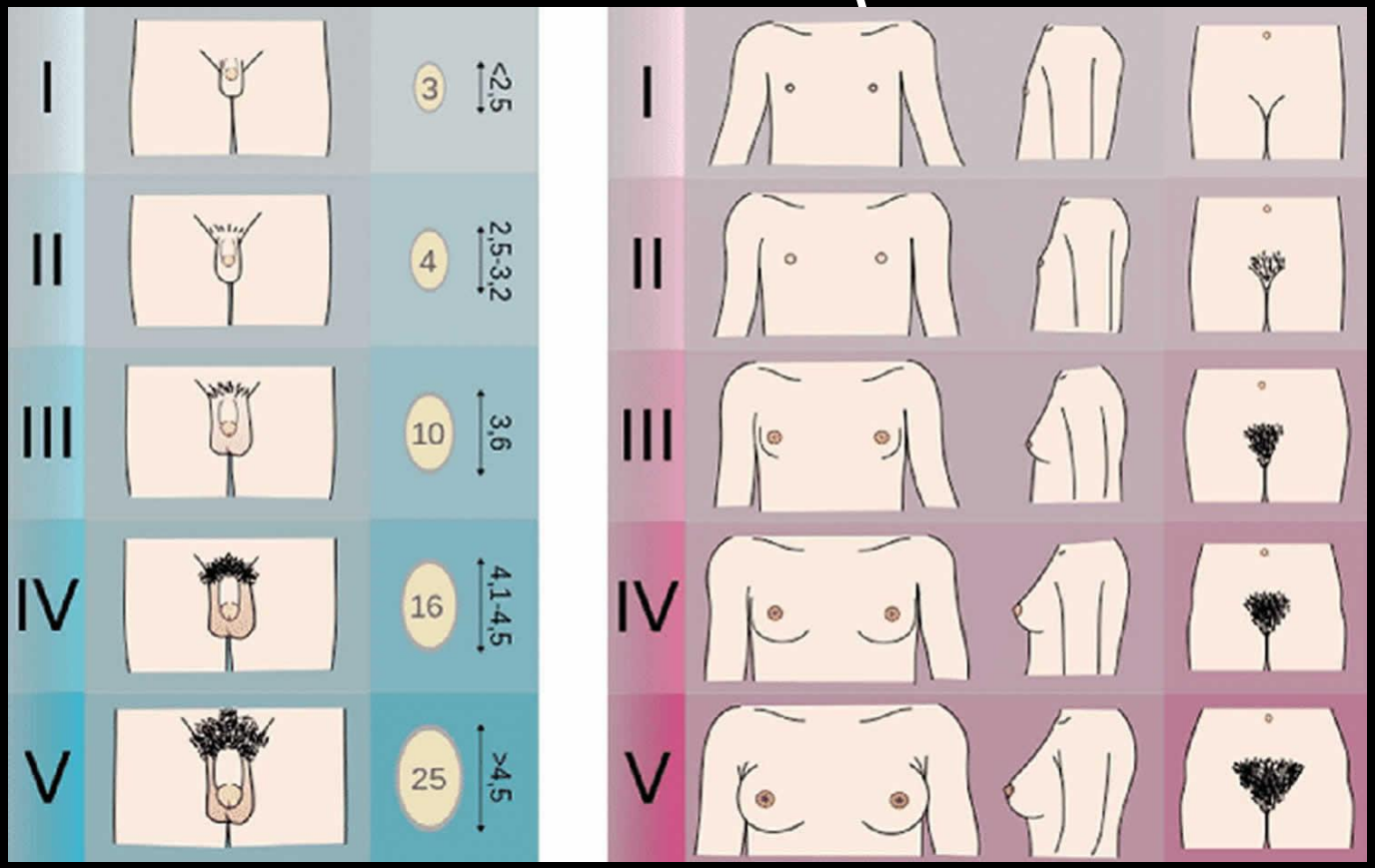
Adolescents are eligible for GnRH agonist treatment if:

1. 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,

2. 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,

3. 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.

SECONDARY SEX CHARACTERISTICS: SEXUAL MATURITY RATING (TANNER



GNRH AGONISTS: HOW DO THEY WORK?

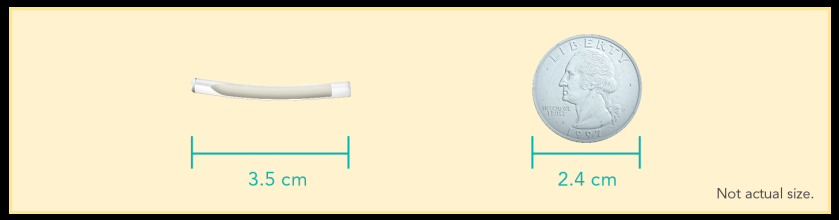
- GnRH agonists: act as agonists of the GnRH receptor, the target of gonadotropin releasing hormone.
  - GnRH causes the release of the pituitary hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
  - Eventually causes downregulation of the GnRH receptors in the pituitary gland.
  - Reduces the secretion of LH and FSH and thus induces a state of hypogonadotropic hypogonadism (reversible)

GNRH AGONISTS: PUBERTY BLOCKERS

- GnRH agonists:
  - Injections
    - Leuprolide acetate
      - Lupron (IM) — 1 or 3 months
      - Eligard (SC) — 3 months
    - Triptorelin acetate
      - Decapeptyl-CR (SC/IM) — 1 or 6 months
  - Implants
    - Histrelin Acetate
      - Supprelin-LA (SC) — 1-2 years

GNRH AGONISTS

Histrelin Acetate SC Implant



Leuprolide Acetate IM Injections

PUBERTAL BLOCKERS: OTHER OPTIONS

- Medroxy-progesterone acetate
  - HPG Axis inhibition
  - Inhibition of Testosterone synthesis, action
- Spironolactone
  - Inhibition of Testosterone synthesis, action

PUBERTAL SUPPRESSION: MONITORING

- Time zero and every 3 months
  - PE: height/weight, Tanner Stage
  - Labs: LH/FSH, estradiol/testosterone
- Time Zero and yearly
  - Metabolic labs: Ca, phos, alk phos, 25-OH Vit D
  - DXA scan: bone density
  - Bone age

PUBERTAL SUPPRESSION: LIMITATIONS AND DISADVANTAGES

- No regression of pubertal development
- Potential side effects
  - Leuprolide-Depot: sterile abscess → Switch to histrelin implant
  - Depression if started in mid-puberty
  - ?? Cognitive and emotional development
- Growth suppression
- Low bone mineral density (BMD)
- Cost

HOW LONG TO STAY ON PUBERTAL SUPPRESSION?

- Depends. ***Patient-specific***
- Often beneficial to continue after starting hormones
  - Youth with ovaries pursuing masculinizing hormones
    - Menstrual cessation can take up to 1-2 years after starting testosterone
    - Preventing chest development
  - Youth with testicles
    - Best options for suppressing testosterone completely
    - Considering orchiectomy

MEDICATIONS FOR INDUCING AMENORRHEA

- Progestogens
  - natural, micronized progesterone and synthetic progestins
  - Post-menarchal adolescent not yet ready for or desiring of masculinizing hormones
  - less effective in inducting amenorrhea than combined oral contraceptive pills
  - oral, injectable, implantable, and intrauterine

PROGESTOGENS: HOW DO THEY WORK?

- exert most of their effects peripherally at the level of the endometrium primarily through changes in angiogenesis
- may also suppress the hypothalamic–pituitary–gonadal axis by inhibiting GnRH activity
- counteract the effects of estrogen by inhibiting the proliferation of the endometrium and reducing the mitotic rate of the glands and stromal tissue, through reduction of the estrogen receptors on the glands

PROGESTOGENS

Table 2.

Select Progestogens Available in the United States

Active ingredient	Trade names	How supplied	Dosing patterns	Comment
Oral				
Norethindrone	Micronor Camila Deblitane Heather Jencycla Jolivette Sharobel	0.35 mg tabs	Once daily	"Mini-pill" for oral contraception. Must be taken at same time of day
Norethindrone acetate	Aygestin	5 mg tabs	Once daily (2.5–15 mg daily)	May titrate up to effect
Medroxyprogesterone acetate	Provera	2.5, 5, 10 mg tabs	Once or twice daily	Dosing has ranged from 20 to 80 mg day[19]
Micronized progesterone	Prometrium	100, 200 mg	100–200 mg nightly	Incipient contains peanut oil
Injectable				
Medroxyprogesterone acetate	Depo-Provera	150 mg/1 mL		Deep IM injection into gluteal or deltoid muscle q 12–14 weeks
	Depo-SubQ Provera 104	104 mg/0.65 mL		Anterior thigh or abdomen q 12–14 weeks
Intradermal				
Etonogestrel	Implanon	68 mg single capsule	Active for 3 years	Breakthrough bleeding common initially
Intrauterine				
Levonorgestrel	Mirena Liletta	52 mg	May be left in for 5 years	Insert within 7 days of onset of menstruation

POTENTIAL ADVERSE EFFECTS/CONSIDERATIONS

- Medroxyprogesterone/Norethindrone: Worsening Depression?
- Depot Medroxyprogesterone acetate: Weight Gain

- Intradermal Etonogestrel: Irregular bleeding
- Intrauterine Levonorgestrel: Requires exam

GENDER-AFFIRMING HORMONES

- Partially Reversible Treatment
- Generally at age 16
  - May start younger depending on patient
  - Minimal published students of gender-affirming hormones started before 13.5-14 years

CRITERIA FOR HORMONES

Adolescents are eligible for subsequent sex hormone treatment if:

1. 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,

2. 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,

3. 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.

GENDER-AFFIRMING HORMONES: WHEN TO START?

Younger Age

- Feelings of isolation worsening as peers undergo puberty
- Worsening anxiety/depression
- BMD in patients with pubertal suppression

Waiting

- Uncertain about fertility implications
- Uncertain about physical changes

GENDER-AFFIRMING HORMONES: BEFORE STARTING

- Comprehensive discussion: expected changes & timeline
- Discuss side effects, including the impact on fertility
- Assess risk factors for complications
  - Medical conditions: clotting disorders, smoking, early CV disease/dyslipidemia
  - Screening labs: CBC, lipids, CMP

GENDER-AFFIRMING HORMONES: GOALS

- Gradual pubertal induction (over approx. 2 years)
  - Start at a low dose
  - Monitor growth closely
  - Minimize risks of side effects
  - Monitor depression/anxiety

GENDER AFFIRMING HORMONES: FERTILITY

- **Discuss reproduction options before initiation of hormones**
- **MTF:** Sperm Banking
- **FTM:** Referral for oocyte cryopreservation

FEMINIZING TREATMENT

- Increasing Estrogen
- Decreasing Testosterone Secretion and Action
- If patient is previously blocked
  - Titrate over 2-3 years
- Not previously blocked
  - OK to start at adult dosing

ANTI-ANDROGEN THERAPY

- GnRH agonists
- Progestogens
- Spironolactone (100-400 mg/day) oral medication
  - antagonist of the androgen receptor (AR), the biological target of androgens like testosterone and dihydrotestosterone (DHT)
  - antagonist of the mineralocorticoid receptor (MR), the biological target mineralocorticoids like aldosterone and 11-deoxycorticosterone → inhibits the effects of mineralocorticoids in the body.
  - Side effects- hyperkalemia, hypotension

ESTROGEN: 17 BETA ESTRADIOL

- Oral
  - Estradiol 2-6 mg/day
  - Conjugated estrogens 2.5-7.5 mg/day
  - Avoid ethinyl estradiol (thrombosis risk)
- Transdermal
  - Gel or patch daily
- Implantable
  - Pellet form
- Injectable
  - Estradiol valerate 5-20 mg IM every 1-2 weeks

EXPECTATIONS?

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

[a] Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b] Familial scalp hair loss may occur if estrogens are stopped.

[c] Treatment by speech pathologists for voice training is most effective.

ESTROGEN: ADVERSE EFFECTS

Transgender female: estrogen

Very high risk of adverse outcomes:

- Thromboembolic disease

Moderate risk of adverse outcomes:

- Macroprolactinoma
- Breast cancer
- Coronary artery disease
- Cerebrovascular disease
- Cholelithiasis
- Hypertriglyceridemia

FEMINIZING THERAPY: MONITORING

- At Time Zero and every 3 months during first year of therapy
  - Serum Testosterone
  - Estradiol levels
  - Prolactin level
  - Potassium
  - Lipid profile
- Bone Density?

FEMINIZING THERAPY: GOALS

- Testosterone in female range (Less than 50 ng/dL)
- Estradiol that is NOT supraphysiologic (No higher than 100-200 pg/mL)

MASCULINIZING THERAPY

- Testosterone
- Injectable
  - Testosterone (Cypionate or enanthate) 50-100 mg (IM or SQ every week
- Other
  - Transdermal (gel or patch) 5-10 g every day
  - Implantable
- Avoid testosterone tablets

EXPECTATIONS?

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a] Prevention and treatment as recommended for biological men.

[b] Menorrhagia requires diagnosis and treatment by a gynecologist.

ADVERSE REACTIONS

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen
- Very high risk of adverse outcomes:
  - Thromboembolic disease
- Moderate risk of adverse outcomes:
  - Macroprolactinoma
  - Breast cancer
  - Coronary artery disease
  - Cerebrovascular disease
  - Cholelithiasis
  - Hypertriglyceridemia

Transgender male: testosterone
- Very high risk of adverse outcomes:
  - Erythrocytosis (hematocrit > 50%)
- Moderate risk of adverse outcomes:
  - Severe liver dysfunction (transaminases > threefold upper limit of normal)
  - Coronary artery disease
  - Cerebrovascular disease
  - Hypertension
  - Breast or uterine cancer

MASCULINIZING THERAPY: MONITORING

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a]Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

LIMITATIONS

EMR

Leadership

Legislation

LEGAL IMPACT ON ABILITY TO PRESCRIBE

- HB68 -> SAFE act

CONCLUSION

- Treatment of Transgender youth is complex and involves both pharmacologic and non-pharmacologic methods
- There are reversible and partially reversible pharmacologic treatments
- Pharmacologic treatments have positive effects on transgender patients
- If any questions, please contact me at ccole@akronchildrens.org

RESOURCES

- *Endocrine treatment of gender dysphoria/gender incongruent persons: An endocrine society practice guideline.The Journal of Clinical Endocrinology & Metabolism*, Volume 102, Issue 11, 1 November 2017, Pages 3869–3903
- Standards of Care for the health of Transsexual, Transgender and gender non-conforming people. 8th version. WPATH, 2022
- Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents Jason Rafferty, COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON ADOLESCENCE and SECTION ON LESBIAN, GAY, BISEXUAL, AND TRANSGENDER HEALTH AND WELLNESS Pediatrics October 2018, 142 (4) e20182162; DOI: https://doi.org/10.1542/peds.2018-2162
- Induction and Maintenance of Amenorrhea in Transmasculine and Nonbinary Adolescents, Jeremi Carwell, Stephanie Roberts. Transgender Health, Volume 2, 2017.