TRANSGENDER MEDICINE

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LEARNING OBJECTIVES

- Understanding terminology in transgender medicine
- Diagnosis
- Treatment
- Monitoring
- complications

CASE QUESTION 1

A 19 yo person comes to you for advice. Male sex assigned at birth. They report that since they were a child, they felt like they were in the wrong body. They loved playing with dolls and felt very at peace when wearing their sister's clothes. The stress over this feeling worsened during teen age years, leading to severe depression, suicidal ideation and intensive therapy. Now depression is controlled. They are active smokers. What is the diagnosis?

- Gender incongruence
- Gender identity disorder
- Intersex
- Congenital adrenal hyperplasia

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Gender identity

Term	Cisgender (cis)	Transgender (trans)	Gender non-binary
Definition	Adjectives for persons whose gender identity and expression align with their sex recorded at birth	Adjectives for persons whose gender identity and/or expression do not align with their sex assigned at birth	
Examples	Cis female = a person with female sex recorded at birth who has female gender identity	Trans female = a person with male sex recorded at birth who has female gender identity	Umbrella term for a broad range of identities along or outside the male-female binary: transfeminine, transmasculine, genderqueer, pangender, agender and many more

Klein DA et al. *Am Fam Physician* 2018. Safer JD, Tangpricha V. *Ann Intern Med* 2019. Safer JD, Tangpricha V. *N Engl J Med* 2019. Adapted from Iwamoto S. Endocrine Society 2020

GENDER IDENTITY UMBRELLA

Men

Non Binary

embraces a diversity of expressions, moving beyond and not confined exclusively to the gender binary categorization

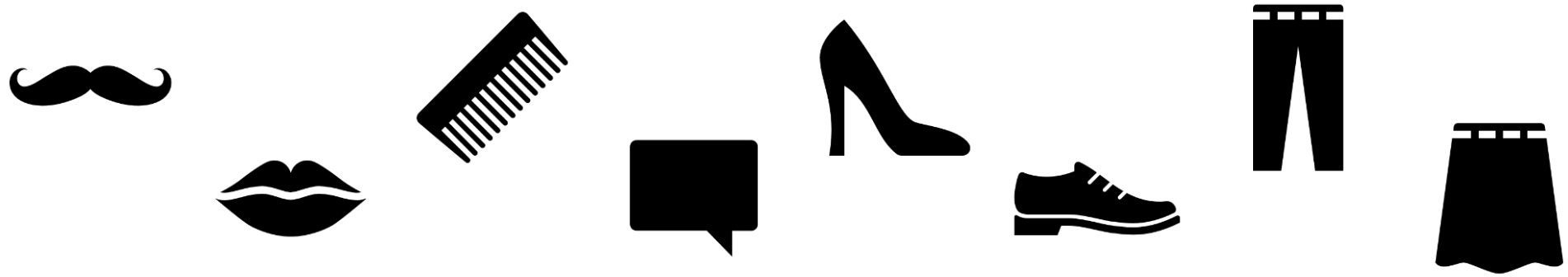
Agender

Does not identify with any gender

Women

Gender expression

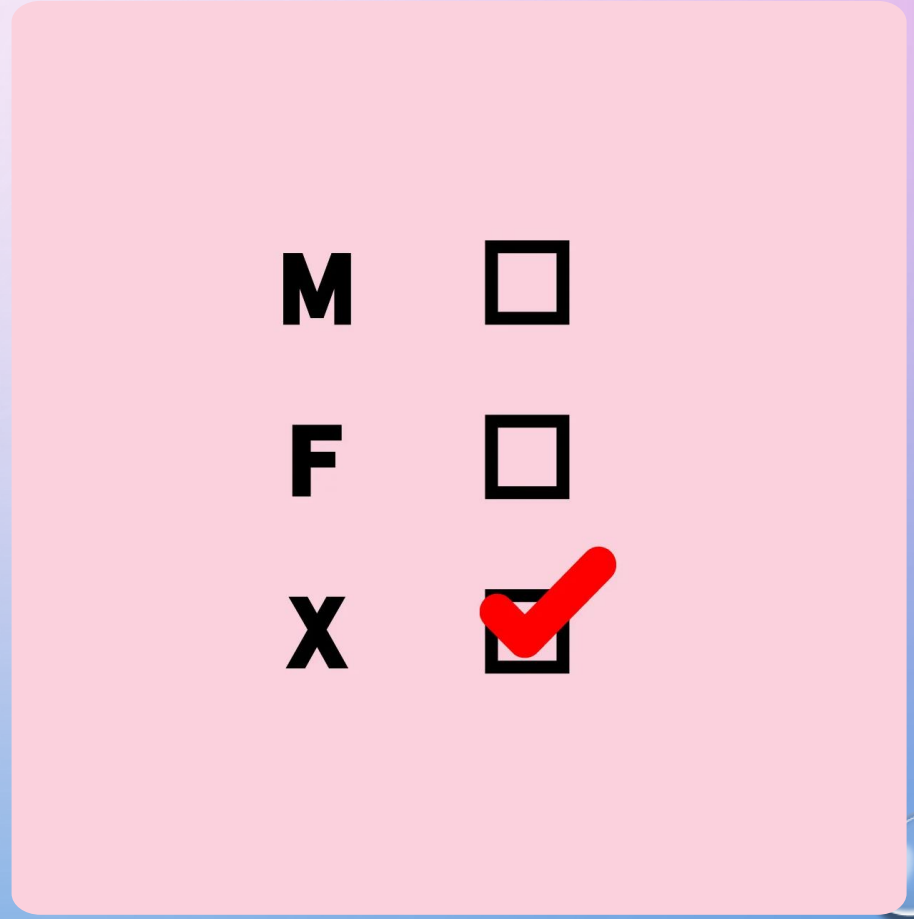
- Ways in which a person communicates gender identity to others
  - Appearance (e.g., clothing, hairstyle), behaviors, mannerisms, speech/voice
  - Name, pronouns
- Gender identity and expression may not align with the gender binary



Klein DA et al. *Am Fam Physician* 2018.; Safer JD, Tangpricha V. *Ann Intern Med* 2019.; Safer JD, Tangpricha V. *N Engl J Med* 2019. Adapted from Iwamoto S. Endocrine Society 2020

Sex recorded at birth

- Female, male or intersex designation primarily based on visible physical anatomy at birth
- *Sex* can also reference biologic characteristics
  - Sex chromosomes, gonads, genitalia, secondary sex characteristics, sex hormones
- *Intersex* or *disorders/differences of sexual differentiation*
  - Conditions in which a person is born with reproductive or sexual anatomy that does not fit typical female or male definitions

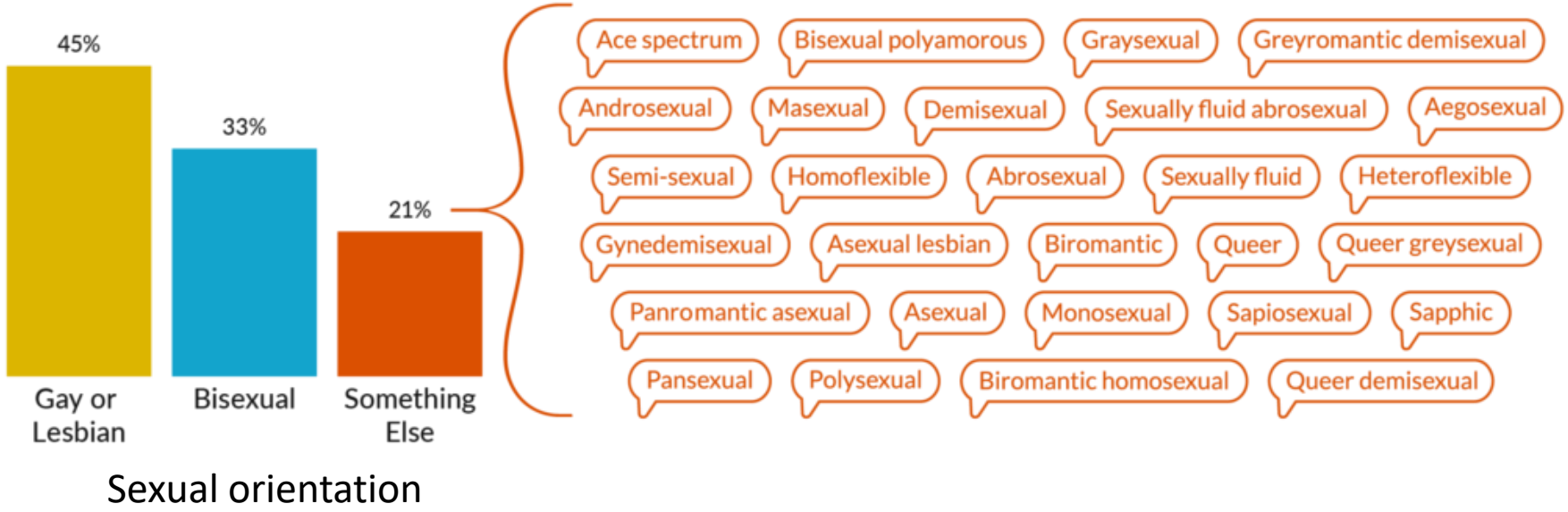


Klein DA et al. *Am Fam Physician* 2018.; Safer JD, Tangpricha V. *N Engl J Med* 2019. Adapted from Iwamoto S. Endocrine Society 2020

Sexual orientation

- Encompasses physical, sexual, emotional, romantic attraction to other people
- Independent of gender identity and defined by the individual

The Trevor Project National Survey on LGBTQ Youth



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TREATMENT TERMINOLOGY

- GENDER AFFIRMING INTERVENTIONS
  - GENDER AFFIRMING HORMONE THERAPY
  - GENDER AFFIRMING SURGERY
    - CHEST SURGERY (FOR TRANS MAN)
    - BREAST SURGERY (FOR TRANS WOMAN)
    - BOTTOM SURGERY (FOR BOTH)
  - OTHER GENDER AFFIRMING INTERVENTIONS

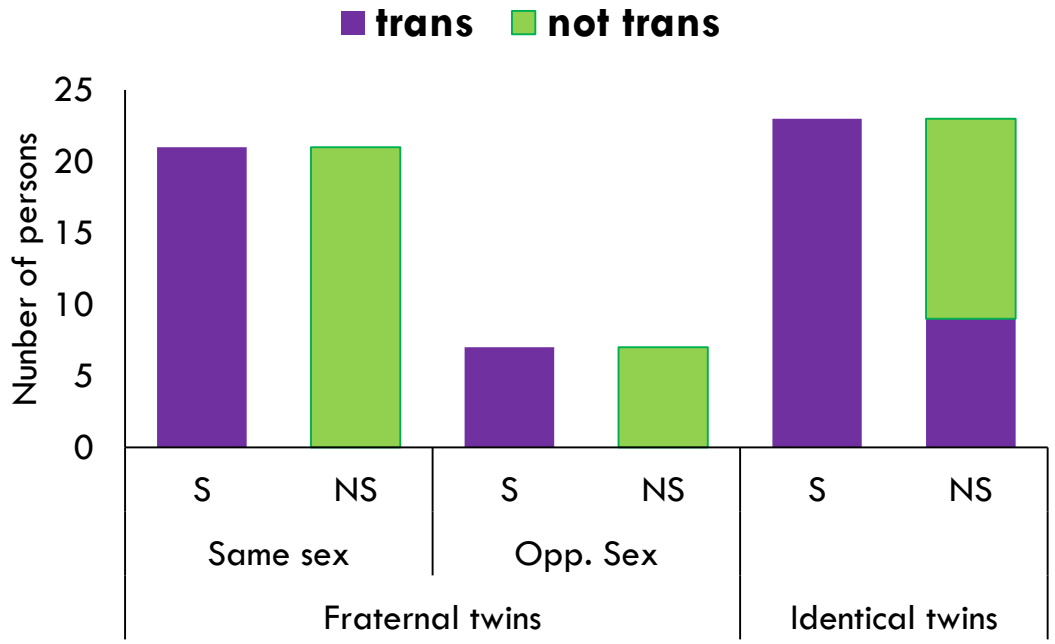
The biology of gender: Genetics

Disorders of sexual development (DSD) – Examples (small cohorts)

- **46 XY individuals with DSD**
  - Raised female, ~20-30% now live as male
  - Raised male, all continue to live as male
- **46 XX individuals with CAH**
  - ↑ androgens, virilization
  - Raised female, ~5% gender dysphoria

Twin studies

Higher concordance for trans identity in monozygotic than dizygotic twins



Saraswat A et al. *Endocr Pract* 2015.; Nguyen HB et al. *Neuropsychopharmacology* 2019.; Heylens G et al. J of Sex Med. 2012. Adapted from Iwamoto S., Endocrine Society, 2020

QUESTION 2

Diagnosis of gender dysphoria is confirmed. Patient is following regularly with mental health professional and feels ready to start on hormonal affirming therapy. What is your first action?

- Start estrogen orally 2 mg daily
- Start spironolactone 100 mg daily
- Order CBC, CMP, lipids, A1c, estradiol and testosterone levels
- Discuss expectations for body changes timelines

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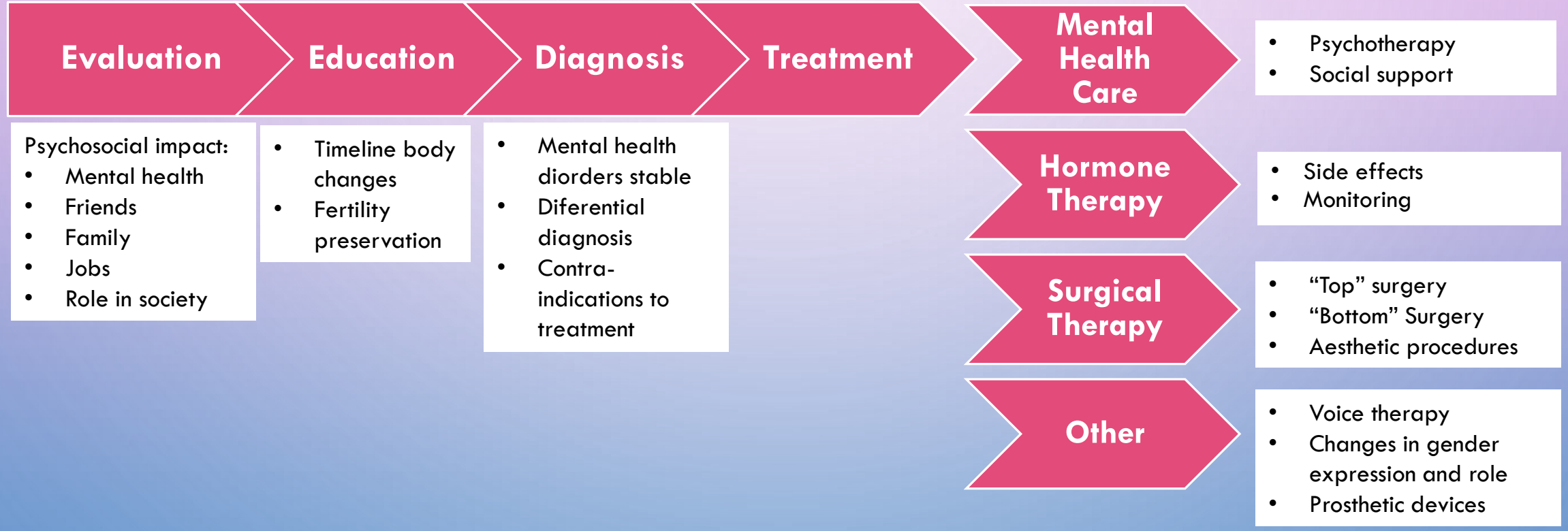
TREATMENT FLOW



a) START ESTROGEN ORALLY 2 MG DAILY – THIS IS ACCEPTABLE OPTION FOR TRANS WOMEN WHEN YOUNG AND NON-SMOKERS

b) START SPIRONOLACTONE 100 MG DAILY – WE USE UP TO 200 MG DAILY AS ANDROGEN RECEPTOR BLOCKER

c) ORDER CBC, CMP, ESTRADIOL AND TESTOSTERONE LEVELS – IMPORTANT TO FOLLOW UP ON SIDE EFFECTS OF THERAPY

d) DISCUSS EXPECTATIONS FOR BODY CHANGES TIMELINES – VERY IMPORTANT TO DISCUSS THIS PRIOR TO START ANY THERAPY

QUESTION 3

What are absolute contraindications for Feminizing hormone therapy?

- Smoking
- Cardiovascular disease
- Cerebrovascular disease
- End-stage liver disease

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RISK ASSESSMENT AND MODIFICATION FOR FEMINIZING HORMONE THERAPY

Absolute contra-indications for Estrogen therapy

- previous venous thrombotic events related to an underlying hypercoagulable condition
- history of estrogen-sensitive neoplasm
- end-stage chronic liver disease

Relative contra-indications for Estrogen therapy

- Smoking
- Established Cardiovascular or cerebrovascular disease

RISK ASSESSMENT AND MODIFICATION FOR MASCULINIZING HORMONE THERAPY

Absolute contra-indications for Testosterone therapy

- Pregnancy
- unstable coronary artery disease
- untreated polycythemia with a hematocrit of 55% or higher

Relative contra-indications for Testosterone therapy

- Breast cancer
- Established Cardiovascular or cerebrovascular disease

CRITERIA FOR GENDER-AFFIRMING HORMONE THERAPY IN ADULTS

- Persistent, well-documented gender dysphoria/gender incongruence
- The capacity to make a fully informed decision and to consent for treatment
- The age of majority in a given country
- Mental health concerns, if present, must be reasonably well controlled

QUESTION 4

After education on expectations of body changes and preserving sperms in bank, patient is ready for therapy. She is not willing to stop smoking at this time. Baseline labs were normal. What gender affirming therapy do you start for her?

- Estradiol 2mg orally daily
- Estradiol patches 0.05 mg daily changed biweekly
- Estradiol patches 0.05 mg daily changed biweekly + Espironolactone 50 mg BID
- Estradiol 2mg orally daily + Espironolactone 50 mg BID

QUESTION 4

After education on expectations of body changes and preserving sperms in bank, patient is ready for therapy. She is not willing to stop smoking at this time. Baseline labs were normal. What regimen do you start for her?

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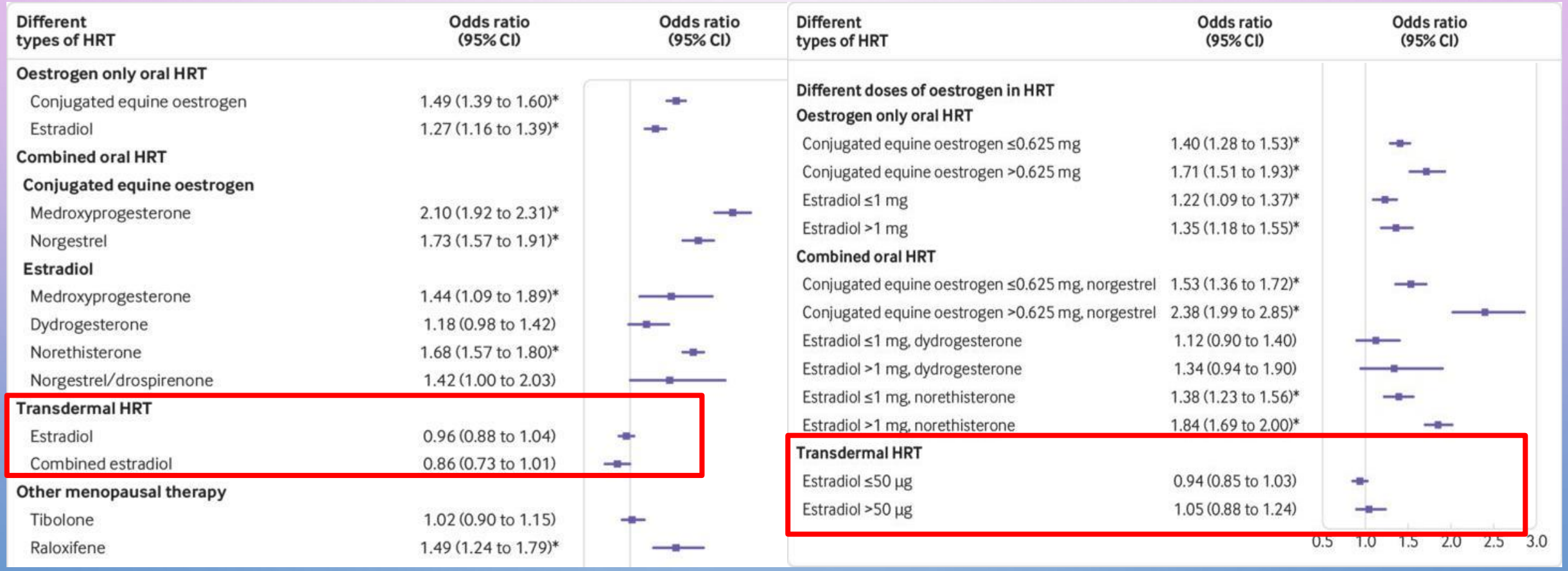
ADJUSTED ODDS RATIOS OF DVT FOR DIFFERENT TYPES OF HRT AND DIFFERENT DOSES OF ESTROGEN IN CISGENDER WOMEN



Different types of HRT	Odds ratio (95% CI)
Oestrogen only oral HRT	
Conjugated equine oestrogen	1.49 (1.39 to 1.60)*
Estradiol	1.27 (1.16 to 1.39)*
Combined oral HRT	
Conjugated equine oestrogen	
Medroxyprogesterone	2.10 (1.92 to 2.31)*
Norgestrel	1.73 (1.57 to 1.91)*
Estradiol	
Medroxyprogesterone	1.44 (1.09 to 1.89)*
Dydrogesterone	1.18 (0.98 to 1.42)
Norethisterone	1.68 (1.57 to 1.80)*
Norgestrel/drospirenone	1.42 (1.00 to 2.03)
Transdermal HRT	
Estradiol	0.96 (0.88 to 1.04)
Combined estradiol	0.86 (0.73 to 1.01)
Other menopausal therapy	
Tibolone	1.02 (0.90 to 1.15)
Raloxifene	1.49 (1.24 to 1.79)*

Different types of HRT	Odds ratio (95% CI)
Different doses of oestrogen in HRT	
Oestrogen only oral HRT	
Conjugated equine oestrogen ≤0.625 mg	1.40 (1.28 to 1.53)*
Conjugated equine oestrogen >0.625 mg	1.71 (1.51 to 1.93)*
Estradiol ≤1 mg	1.22 (1.09 to 1.37)*
Estradiol >1 mg	1.35 (1.18 to 1.55)*
Combined oral HRT	
Conjugated equine oestrogen ≤0.625 mg, norgestrel	1.53 (1.36 to 1.72)*
Conjugated equine oestrogen >0.625 mg, norgestrel	2.38 (1.99 to 2.85)*
Estradiol ≤1 mg, dydrogesterone	1.12 (0.90 to 1.40)
Estradiol >1 mg, dydrogesterone	1.34 (0.94 to 1.90)
Estradiol ≤1 mg, norethisterone	1.38 (1.23 to 1.56)*
Estradiol >1 mg, norethisterone	1.84 (1.69 to 2.00)*
Transdermal HRT	
Estradiol ≤50 µg	0.94 (0.85 to 1.03)
Estradiol >50 µg	1.05 (0.88 to 1.24)

Yana Vinogradova et al. BMJ. 2019.

HORMONAL THERAPY FOR TRANSGENDER ADULTS

- Confirm the diagnostic criteria of GD
- Evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment
- Measure hormone levels during treatment
- Endocrinologists should educate patients undergoing sex hormone treatment regarding onset and time course of physical changes

QUESTION 5

Patient asks you how long until she can expect starting of breast growth. What is the expectation?

- 1 month
- 6 months
- 1 year
- 2 years

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INDENTICAL TWINS
TRANSGIRL AND BOY – 14 YO

- HTTPS://ABCNEWS.GO.COM/HEALTH/IDENTICAL-TWIN-BOYS-TRANSGENDER-BROTHER-SISTER/STORY?ID=15142268

INDENTICAL TWINS - TRANSGIRL AND BOY – 14 YO

Expected changes MTF hormone therapy

- breast growth (variable)
- decreased erectile function
- decreased testicular size
- increased %fat/muscle mass

Expected changes FTM hormone therapy

- deepened voice
- Clitoral enlargement (variable)
- growth in facial and body hair
- cessation of menses
- decreased %fat/muscle mass

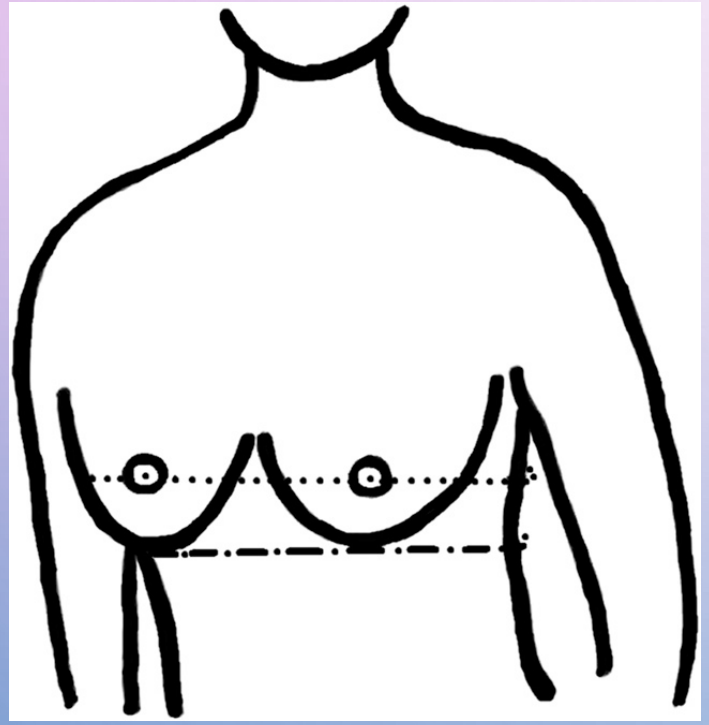
https://abcnews.go.com/Health/identical-twin-boys-transgender-brother-sister/story?id=15142268

FEMINIZING EFFECTS IN TRANSGENDER FEMALES

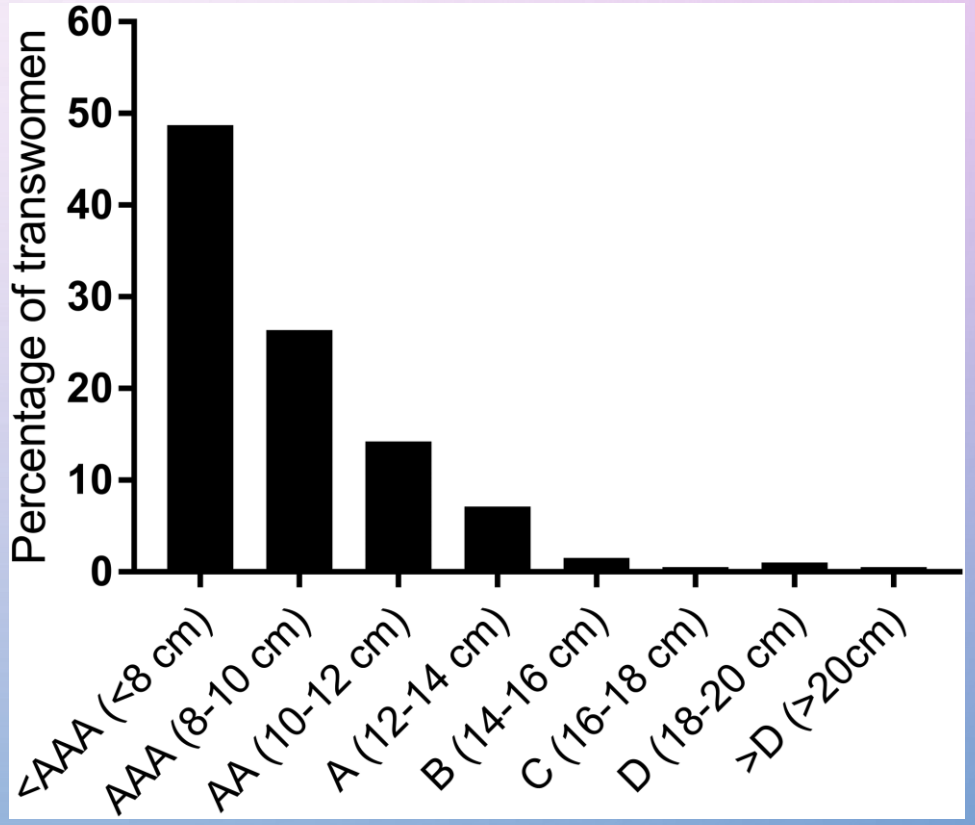
Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	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]

[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.

GAINED BRA CUP SIZES IN 197 TRANSGENDER WOMEN AFTER 1 YEAR OF HORMONAL THERAPY (HT)



Dotted line → fullest part of the breast
Dashed-dotted line → inframammary fold



De Blok CJM et al. JCEM.2018.

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

[a]Prevention and treatment as recommended for biological men.
[b]Menorrhagia requires diagnosis and treatment by a gynecologist.

QUESTION 6

What is the goal for hormonal therapy in this patient?

- Estradiol 200-300 ng/dL and testosterone <100 mg/dL
- Estradiol 200-300 ng/dL and testosterone <50 mg/dL
- Estradiol 100-200 ng/dL and testosterone <100 mg/dL
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- **Estradiol 100-200 ng/dL and testosterone <50 mg/dL**

HORMONE LEVEL GOALS

Laboratory	Transfemale	Transmale (IM)	Transmale (SC)
Estradiol	100–200 pg/mL	<50 pg/mL	<50 pg/mL
Testosterone	<50 ng/dL	400–700 ng/dL	400 ng/dL
Hematocrit	Normal female range	<55%	<55%

LONG-TERM CARE WHILE IN SEX HORMONE THERAPY

REGULAR FOLLOW UP

- SCHEDULE
  - Q3 MONTHS → FIRST YEAR
  - 1-2X/YEAR→ AFTER FIRST YEAR
- WHAT TO MONITOR
  - BP, WEIGHT CHANGES
  - CHANGES ON SEXUAL CHARACTERISTICS
  - CBC, CMP, E2 AND TESTOSTERONE
- CV RISK FACTORS: FASTING LIPID PROFILES, DIABETES SCREENING, OTHER TOOLS
- BMD IF RISK FACTORS FOR OSTEOPOROSIS

OTHER MONITORING

- TRANSFEMALE:
  - PROLACTIN LEVELS YEARLY
  - MAMMOGRAM EVERY 1-2 YEARS
  - PROSTATE DISEASE SCREENING INDIVIDUALIZED
- TRANSMALE:
  - CERVICAL CANCER SCREENING
  - DISCUSS TOTAL HYSTERECTOMY AND OOPHORECTOMY
  - PERIAUREOLAR BREAST EXAMS

COMPLICATIONS

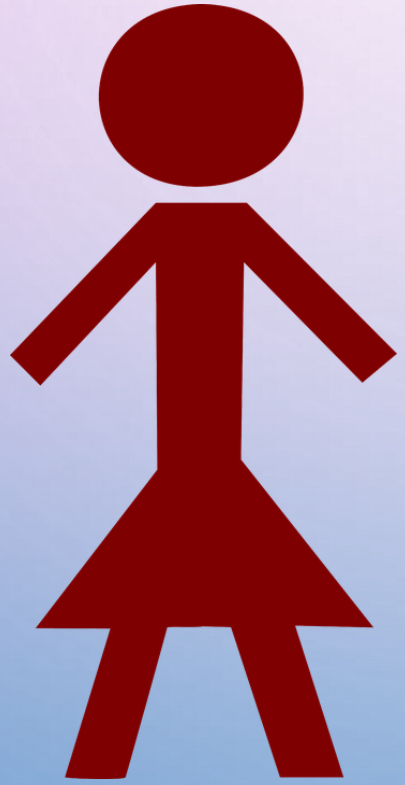
TRANSFEMALES: ESTROGEN

Very high risk of adverse outcomes:

- Thromboembolic disease

Moderate risk of adverse outcomes:

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



TRANS MALES: TESTOSTERONE

Very high risk of adverse outcomes:

- Erythrocytosis (hematocrit > 50%)

Moderate risk of adverse outcomes:

- Severe liver dysfunction (transaminases > 3x ULN)
- Coronary artery disease
- Cerebrovascular disease
- Hypertension
- Breast or uterine cancer

QUESTIONS?

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