Masculinizing and feminizing hormonal care in transgender people

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LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Health care professionals working with trans people have to recognize the diversity of genders, including male, female and gender diverse individuals.

2. If masculinisation is desired, testosterone therapy is recommended with monitoring of serum sex steroid levels and signs of virilisation. If feminisation is desired, estrogens and/or anti-androgen therapy is recommended with monitoring of serum sex steroid levels and signs of feminisation. For both, the principles of gender affirming hormone treatment and their (side-)effects should be known.

DISCLOSURE

Scientific Grants as principal investigator: Ipsen, Bayer Shering, Sandoz
Consulting fee as advisory board member: Ipsen, Novartis
Lecturer fee as speaker: Ferring, Novartis

Co-editor:
International Journal of Transgenderism
Journal of Sexual Medicine

Interim President:
European Professional Association for Transgender Health (EPATH)
Disclosures
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ENIGI

Ghent University Hospital, Dept. of Endocrinology

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INTRODUCTION
Gender affirming endocrine care

Female to male = TRANS MAN

Male to female = TRANS WOMAN

The challenge

Suicide attempt rates

- Belgium: 38.7%
- USA: 45.0%
Prevalence

0.5 – 1.3% for birth-assigned males
0.4- 1.2% for birth-assigned females
Scientific output in 1913 - 2017


Hormones and Mental Health

Agoraphobia - Anxiety - Depression - Somatisation - Paranoia - Aggression

Hormones and Mental health

Psychopathology

Depressive Symptoms

Body Uneasiness

Conclusion 1

• The need for transgender health care is much higher than expected.

• Endocrinologists definitely have a role to play, for those who desire a medical intervention.
Gender affirming therapy

Diagnostic phase
Hormonal phase
Surgery
Hormones continued


Gender affirming therapy

Self-diagnosis

Diagnostic phase*
Hormonal phase
Surgery
Hormones continued

* Informed consent, and decisions about gamete storage

### Endocrine treatment in adults

#### Risks, benefits and limitations

<table>
<thead>
<tr>
<th>Anti-androgens</th>
<th>GnRH analogues</th>
<th>Cyproterone acetate 25-50mg OD</th>
<th>Other progestins?</th>
<th>Spironolactone 200-400mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans women</td>
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#### Estrogens

- Oral estradiol
- Estradiol valerate 4mg daily
- Injectable estradiol
- Transdermal estradiol
- Gel 3mg daily
- Patch 100µg/72h

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### Treatment in adolescent transgender boys and girls

#### Self-diagnosis

- **Diagnostic phase**
  - GnRH analogue

- **Hormonal phase**
  - GnRH analogue + gender affirming hormones
  - Female puberty with 17-beta oestradiol, increasing the dose every 6 months: 5 – 10 – 15 – 20 µg/kg/day
  - Male puberty with testosterone enanthate, increasing the dose every 6 months: 25 – 50 – 75 – 100 mg/m²/2 weeks IM

- **Surgery**
  - Surgery + gender affirming hormones

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### The Netherlands vs. Belgium

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Gender affirming therapy

Self-diagnosis

- Diagnostic phase*
- Hormonal phase
- Surgery
- Hormones continue

Suppression

Substitution

* Informed consent, and decisions about gamete storage

Feminizing treatment in trans women

Anti-androgen and estrogen treatment in trans women

Effects
- Breast growth
- Body hair
- Softening of the skin
- Reduction of muscle mass
- Testicular, prostate size
- Changes in emotional function
- Redistribution of body fat
  (Little effect on facial hair)

Anti-androgen and estrogen treatment in trans women

Effects
- Breast growth
- Body hair
- Softening of the skin
- Reduction of muscle mass
- Testicular size
- Changes in emotional function
- Redistribution of fat

( little effect on facial hair)

Side effects
- Risk for thromboembolism
- Risk of depression
- Risk of osteoporosis
- Changes in sexual desire
- Fertility

Virilizing treatment in trans men

Effects
- Deepening of voice
- Facial and body hair
- Clitoral growth
- Cessation of menses

↑ Muscle mass and strength
- Fat mass
- Sexual desire

Treatment
- Same principles as testosterone treatment in hypogonadal men
- If menses persist: add a progestagen

Testosterone treatment in trans men

Effects
- Breast growth
- Body hair
- Softening of the skin
- Reduction of muscle mass
- Testicular size
- Changes in emotional function
- Redistribution of fat

( little effect on facial hair)
Testosteron treatment in trans men

**Effects**
- Deepening of voice
- Facial and body hair
- Clitoral growth
- Cessation of menses
  - Muscle mass and strength
  - Fat mass
  - Sexual desire

**Side effects**
- Acne
- Frontal and temporal hairline recession
- Fertility

Debate: which testosterone in trans men is preferred?

No differences between intramuscular T-undecanoate, T-enanthate, or transdermal T with regard to anthropometric or biochemical variables.

Debate: sc injection of testosterone?

Clinical effects: BREAST DEVELOPMENT

Debate: Progesterone for trans women- Yes or no?


Breast development
Clinical effects: BODY FAT DISTRIBUTION

ENIGI: effects of hormone treatment

Trans men  | Trans women
---------|---------

Trans men

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<th>Mean change (95% confidence interval)</th>
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ENIGI: effects of hormone treatment (2)

Clinical effects: VOICE

ENIGI: self-perception of voice

Trans men (n = 80) Trans women (n = 103)

MONITORING

Every 3 months in the first year
Every 6-12 months thereafter with a physical exam and labs.

Serum testosterone < 50ng/dl

Estradiol levels should be kept in the physiologic range of about 200pg/ml. (?)
SAFETY: Cardiovascular safety

Hematocrit

- Trans men: +4.9% hematocrit
- 11.5% of trans men hematocrit > 50%
- Trans women: -4.1% hematocrit
- Most changes within the first 3 months


Mid-term morbidity and mortality

Trans women
- venous thrombosis (6-8% incidence with ethinyl estradiol)
- cardio- and cerebrovascular disease (MI and stroke)
- depression
- osteoporosis
- no increased cancer morbidity
- no increased overall + CV mortality

European studies


Mid-term morbidity and mortality

**US study**
- 2842 transfeminine members compared to 48775 cisgender women

**Trans women**
- Higher incidence of venous thrombosis
- Higher incidence of ischemic stroke
- Higher incidence of myocardial infarction (similar to cisgender men)

Getahun et al. Cross-sex hormones and acute cardiovascular events in transgender persons, a cohort study. Annals of Internal Medicine 2018 1-10

Adjusted cumulative incidence curves comparing rates of VTE among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (left) and reference women (right) from KPNC, KPSC, and KPGA, 2006–2016. Adjustment for covariates was made at the population mean values. KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; RD = risk difference; VTE = venous thromboembolism.

* Per 1000 persons.
Cardiovascular risk factors


Cardiovascular endpoints


Systematic review on lipids

29 studies
No increase in CV morbidity

Trans men (n = 1503)
- Triglycerides
  - at 3-6 months (+9 mg/dl)
  - at ≥ 24 months (+21.4)
- LDL-C levels
  - at 12 months (+11.3)
  - ≥ 24 months (+17.8).
- HDL-C levels decreased
  (highest at ≥ 24 months, -8.5).

Trans women (n = 3238)
- Triglycerides were higher at
  ≥ 24 months (+31.9)
- No change in other parameters

Endocrine safety

Prolactin

- 107 trans women
- Mild increase of prolactin (9 to 23 ìg/L)
- After orchiectomy (stop CPA) serum prolactin returned to normal.
Systematic review in bone

**Trans men**
- Baseline measurements: normal
- No significant changes

**Trans women**
- T-score <2.5 in 16% at baseline

Lumbar spine BMD
- At 12 months +0.044 g/cm²
- At 24 months +0.057 g/cm²


13 studies
no fracture data available


**Clinical recommendations**
- Screen for osteoporosis
- If risk factors
- Prevention of bone loss
- Compliance
- Limit anti-androgens alone in time

FIGURE 1. Simplified overview of bone geometry before and during cross-sex hormonal therapy in trans men and women. The lighter color is representative of lower cortical volumetric bone mineral density.

Breast cancer risk?

N = 3,556 (trans women), N = 1,579 (trans men)

Cases of breast-Ca. trans men: 7 and trans women: 3

Incidence 20.0/100,000 patient years

No difference in comparison to an age – (birth) sex-matched general population

### Breast cancer risk?

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects</th>
<th>Cases</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans women</td>
<td>n = 2,307</td>
<td>2</td>
<td>4.1 / 100,000 patient years</td>
</tr>
<tr>
<td>Trans men</td>
<td>n = 795</td>
<td>1</td>
<td>5.9 / 100,000 patient years</td>
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No difference in comparison to age – (birth) sex-matched general population

- Lower incidence than age-matched women, same incidence as age-matched men

- No evidence for increase in breast cancer risk under CHT in trans men or trans women

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**Conclusion 2**

- Gender affirming hormone treatment is easy
- Gender affirming hormone therapy is safe (VTE and CV safety vigilance!)
- It saves lives
Do transgender persons wish to have children?

Trans men: 30 – 55%
Trans women: 30 – 60%

Barriers?

Fertility = “The price to pay” for transition?
## Current fertility preservation options for trans women

<table>
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<tr>
<th>Description</th>
<th>Considerations</th>
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<tr>
<td>Sperm cryopreservation</td>
<td>Cryopreservation of ejaculated sperm through masturbation or vibratory stimulation</td>
</tr>
<tr>
<td>Surgical sperm extraction</td>
<td>Percutaneous aspiration of sperm from testis or epididymis</td>
</tr>
<tr>
<td>Immature testicular tissue cryopreservation</td>
<td>Surgical biopsy of testicular tissue</td>
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### Future use of gametes in trans women

**Sperm cryopreservation and surgical sperm extraction**
- Male partner
- Need of donor oocyte + surrogate mother

**Immature testicular tissue cryopreservation**
- Male partner
- *In vitro maturation* + donor oocyte + surrogate mother

**Future use of gametes in trans women**

**Sperm cryopreservation and surgical sperm extraction**
- Male partner
- Need of donor oocyte + surrogate mother

**Female partner**
- IUI or IVF/ICSI depending on sperm quality followed by embryo transfer in partner

**Immature testicular tissue cryopreservation**
- Male partner
- *In vitro maturation* + donor oocyte + surrogate mother

**Female partner**
- *In vitro maturation* and IVF/ICSI followed by embryo transfer in partner
## Current fertility preservation options for trans men

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<td>Embryo cryopreservation</td>
<td>Controlled ovarian stimulation for oocyte retrieval + fertilization to obtain embryos for cryopreservation</td>
<td>Established method: Controlled ovarian stimulation&lt;br&gt;Partner or donor sperm</td>
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<td>Controlled ovarian stimulation to obtain oocytes for cryopreservation</td>
<td>Established method: Controlled ovarian stimulation&lt;br&gt;Post-pubertal&lt;br&gt;No partner required</td>
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<tr>
<td>Ovarian tissue cryopreservation</td>
<td>Surgical excision of ovarian tissue for cryopreservation</td>
<td>Experimental&lt;br&gt;Prepubertal or post-pubertal&lt;br&gt;No control ovarian stimulation&lt;br&gt;No partner required</td>
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Brain studies
2019 review

Regret

- 1972-2015
- 6793 (4432 birth-assigned male, 2361 birth-assigned female)
- Number of people assessed per year: x 20
- Regret: 0.6% of trans women, 0.3% of trans men
