Gender Diverse Youth: Blockers and Hormones

Jeremi M. Carswell, MD
Boston Children’s Hospital
11/2/19
Disclosures:
Liberal discussion of off-label medications
Roadmap
Fig. 1  Sex assigned at birth of assessed adolescents

Arnoldussen M et al, 2019
GeMS NEW patient Volume by Year

Number of Patients by Year

- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017

Number of Patients:
- 0
- 50
- 100
- 150
- 200
- 250
- 300
- 350
- 400
Fig. 3  Percentage of assessed adolescents diagnosed with a GD diagnosis

Arnoldussen M et al, 2019
Figure 1. Proportion of trans youth age 16-24 years in Ontario experiencing positive health and life conditions, by level of parental support

- Satisfied with life: 72% very supportive, 33% somewhat to not at all supportive
- VG/excellent physical health: 66% very supportive, 31% somewhat to not at all supportive
- VG/excellent mental health: 70% very supportive, 15% somewhat to not at all supportive
- High self esteem: 64% very supportive, 13% somewhat to not at all supportive
- Intent to parent: 58% very supportive, 42% somewhat to not at all supportive
- Adequate housing: 100% very supportive, 45% somewhat to not at all supportive
- Adequate food: 92% very supportive, 82% somewhat to not at all supportive

* = statistically significant difference (p < 0.05)
Figure 2. Proportion of trans youth age 16-24 years in Ontario experiencing negative health and life conditions, by level of parental support

- **Parent(s) very supportive**
  - Depressive symptoms: 23%
  - Considered suicide, past yr: 34%
  - Suicide attempt, past yr*: 4%

- **Parent(s) somewhat to not at all supportive**
  - Depressive symptoms: 75%
  - Considered suicide, past yr: 70%
  - Suicide attempt, past yr*: 57%

* = statistically significant difference (p < 0.05)
It doesn’t need to be this way
How We Can Help

Psychosocial support
- No medical intervention

Irreversible therapies
- Surgery

Reversible therapies
- Blockers, +/- hormones

Partially reversible therapies
- Hormones
A Team Effort
Multi- & Inter-disciplinary Team

Admin Staff

Psychology

Adolescent Medicine

PNP

Social Work

Trainees

Pediatric Endocrine

Friends: Plastic Surgery, Urology, Repro-Endo, Cardiology, Hematology...
What is Unique About Treating Youth?
Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects

Henriette A Delemarre-van de Waal and Peggy T Cohen-Kettenis

(Admsterdam Gender Clinic, Department of Pediatrics and Medical Psychology, Institute for Clinical and Experimental Neuroscience, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands)

(Correspondence should be addressed to H A Delemarre-van de Waal; Email: h.delemarm@vumc.nl)
“The Dutch Model”

1. Prevent the unwanted physical signs of puberty with a GnRH analog

2. Wait a while

3. Induce puberty with hormones congruent with gender identity
Puberty Blockers (aka GnRH analogs)

- Mimic the action of GnRH, diminishing pulses of the GnRH
  - Lupron
  - Supprelin LA
  - Vantas
  - Triptodur (triptorelin)
  - *progestins (MPA, provera)
The Hypothalamic-Pituitary-Gonadal Axis

- **Hypothalamus**
  - Gonadotropin-releasing hormone (GnRH)
- **Pituitary**
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH)
- **Ovary/Testis**
  - Gonads
Profertility (Physiologic)

GnRH (pulsatile)

GnRH
LH

0
Time (hr)
8

Pump

Release of LH and FSH

Gonads

Conn PM and Crowley WF. NEJM 1991
Antifertility
(Pharmacologic)

GnRH agonist (daily)

Agonist phase

Antagonist phase

0

Time (wk)

4

Release of LH and FSH

Conn PM and Crowley WF. NEJM 1991
Puberty vs. Adrenarche
When are blockers appropriate?

- Any sex: Tanner 2 (breast buds, testicular enlargement)
- Assigned males: prevention of the late secondary characteristics (facial hair, angular jaw, broadening of shoulders)
- Assigned females: severe dysmenorrhea after all other options have failed
Implications of Blockers

Benefits
- Prevention of secondary sex characteristics
- Avoiding Surgery
- Passing more easily/entirely
- Reversibility

Risks/consequences
- Prolonged prepubertal stage when peers are in puberty
- Bone Health?
- Brain Maturation?
- Fertility
- Height SDS
Psychosocial Functioning after GnRHa

- **Time 0**: baseline
- **Time 1**: 6 months from baseline (i.e. 6 months of psychological support, both groups)
- **Time 2**: 12 months from baseline (delayed eligible GD after 12 months support or immediately eligible plus 6 months GnRHa)
- **Time 3**: 18 months

Costa R. J Sex Med. 2015
Outcomes

Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

WHAT'S KNOWN ON THIS SUBJECT: Puberty suppression has rapidly become part of the standard clinical management protocols for transgender adolescents. To date, there is only limited evidence for the long-term effectiveness of this approach after gender reassignment (cross-sex hormones and surgery).

WHAT THIS STUDY ADDS: In young adulthood, gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers. The clinical protocol including puberty suppression had provided these formerly gender-dysphoric youth the opportunity to develop into well-functioning young adults.

Authors: Annemou L.C. de Vries, MD, PhD,* Jennifer K. McGuire, PhD, MPH,* Thomas D. Steensma, PhD,* Eva C.F. Wagenaar, MD,* Theo A.H. Doreleijers, MD, PhD,* and Peggy T. Cohen-Kettenis, PhD*

*Center of Expertise on Gender Dysphoria, VU University Medical Center Amsterdam, Netherlands; and Department of Human Development, Washington State University, Pullman, Washington

de Vries et al. Pediatrics 2014
ASSESSMENT

Before Suppression
13.6 y/o

At Initiation of X-sex hormones
16.7 y/o

Gender Affirmation Surgery
20.7 y/o

ASSESSMENT

ADVANCING EXCELLENCE IN TRANSGENDER HEALTH
**Intervention improves global functioning**

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Psychological Functioning of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N^\circ$</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Global functioning (CGAS)</td>
<td>32</td>
</tr>
<tr>
<td>Mtf</td>
<td>15</td>
</tr>
<tr>
<td>FtM</td>
<td>17</td>
</tr>
<tr>
<td>Depression (BDI)</td>
<td>32</td>
</tr>
<tr>
<td>Mtf</td>
<td>12</td>
</tr>
<tr>
<td>FtM</td>
<td>20</td>
</tr>
<tr>
<td>Anger (TPI)</td>
<td>32</td>
</tr>
<tr>
<td>Mtf</td>
<td>12</td>
</tr>
<tr>
<td>FtM</td>
<td>20</td>
</tr>
<tr>
<td>Anxiety (STAI)</td>
<td>32</td>
</tr>
<tr>
<td>Mtf</td>
<td>12</td>
</tr>
<tr>
<td>FtM</td>
<td>20</td>
</tr>
</tbody>
</table>
Findings

- Gender Dysphoria alleviated
  - Subjective, Objective and psychological functioning
    - Measures – body image scale, global, depression, anxiety
  - No regrets expressed

- Conclusion:
  - Well-functioning young adults
  - Protocol of suppression and addition of GAH
  - Multidisciplinary team of MH, Endocrine MDs, Surgeons

- NO assessment after blocker alone
D0=start of GnRHa  C0=start of CSH  C24=24 months after CSH

Klink, D et al. JCEM 2015
Blockers

“It is recommended that any use of pubertal blockers (and subsequent use of sex hormones...) include a discussion about implications for fertility.”
KEEP CALM AND I'M JUST WAITING
How We Can Help

Psychosocial support
- No medical intervention

Reversible therapies
- Blockers, +/- hormones

Partially reversible therapies
- Hormones

Irreversible therapies
- Surgery
Hormones

shutterstock.com • 190188015
Estrogen

- Estrogen:
  - Transdermal (preferred)
  - Oral
    - 17-B Estradiol (estrace)
    - Ethinyl Estradiol (NOOOOOO)
  - Injected

- Timing: replicate puberty, over about 1-2 years
Psychological and CNS
↓ Gender dysphoria
↓ Anxiety
↓ Depression
↓ Perceived stress
↑ Quality of life

Breast
↑ Breast tissue

Skin
↑ Softness
↓ Sebum and acne

Reproductive system
↓ Penile erections
↓ Prostate size
↓ Sperm count and quality

Body composition
↓ Lean mass
↑ Fat mass
↑ Visceral fat

Sexual health
↓ Sexual desire

Hair
↓ Facial and body hair
↓ Male pattern baldness

Voice
No change

Blood pressure
↓ Systolic blood pressure

Blood
↓ Hemoglobin and hematocrit

Lipids and metabolism
↑ LDL cholesterol
↑ Triglycerides
↑ Sex hormone-binding globulin

Hormone concentrations
↓ Testosterone
↓ Luteinising hormone
↓ Follicle-stimulating hormone
↑ Prolactin

T’Sjoen et al. Endocrine Reviews 2019:40;97-117.
Testosterone

- Injected
  - Cypionate – cotton seed
  - Enanthate – sesame
  - Subcutaneous vs. IM

- Transdermal
  - Patch (Androderm)
  - Gel
  - Deodorant

- SubcutaneousImplants

- Timing: replicating puberty but a little faster, 1-2 years
**Psychological and CNS**
- ↓Gender dysphoria
- ↓Anxiety
- ↓Depression
- ↓Perceived stress
- ↑Total grey matter volume
- ↑Cortical thickness in several areas

**Hair**
- ↑Facial and body hair
- ↑Hair density, diameter, and growth rate
- Alopecia

**Breast**
- ↓Breast cancer
- ↓Glandular tissue
- ↑Fibrous connective tissue

**Reproductive system**
Cessation of menstruation and infertility
- ↑Clitoral size
- ↓Vaginal epithelium thickness
- Atrophic endometrium (according to data from some studies)
- Ovarian hyperplasia and polycystic ovaries

**Skin**
- Acne

**Voice**
- ↓Pitch

**Muscle**
- ↑Lean mass
- ↑Cross-sectional area
- ↑Bodyweight
- ↑Grip strength

**Blood pressure**
- ↑Systolic blood pressure

**Blood**
- ↑Hemoglobin and hematocrit

**Lipids and metabolism**
- ↓HDL cholesterol
- ↑Triglycerides
- ↓Sex hormone-binding globulin

**Hormone concentrations**
- ↓Estradiol
- ↓Luteinising hormone
- ↓Follicle-stimulating hormone
- ↓Prolactin
Uncomfortable Truths about Hormone Effect

- Testosterone effects at physiologic doses will overpower those of estrogen
  - i.e. giving testosterone to a woman will produce virilization
  - Lower levels than cis-male physiologic as well (IAAF/IOC rules)
  - Amenorrhea is not a given, nor is contraception

- For a post-pubertal birth-assigned male, estrogen alone is not typically sufficient to induce feminization
  - Use of adjunct therapies
    - Blockers
    - Progestins
Testosterone Trumps Estrogen

(*applies only to hormones, not a social commentary)
Option 1
Option 2
Feminizing, *blocked patient*

1. Prevent masculinization
   - GnRHa
     - Progestins
     - Bicalutamide

2. Feminize
   - Estrogen*
     - *replace over 1-2 years up to normal physiologic levels
     - (Surgery)
Masculinizing, Blocked Patient

Prevent female characteristics
- GnRHa
- Progestins?

Masculinize
- Testosterone
# Estrogen Effects: Timetable

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Growth</td>
<td>3-6 months</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Decreased testicle size</td>
<td>3-6 months</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Redistribution of body fat</td>
<td>3-6 months</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Decreased muscle mass/strength</td>
<td>1-2 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Decreased body hair growth</td>
<td>6-12 months</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>Decreased erections</td>
<td>1-3 months</td>
<td>3-6 months</td>
</tr>
</tbody>
</table>
## T effects: Timetable

<table>
<thead>
<tr>
<th>Effect</th>
<th>Expected onset</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin oiliness/acne</td>
<td>1-6 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Facial/body hair growth</td>
<td>3-6 months</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Scalp hair loss</td>
<td>12 months</td>
<td>Variable</td>
</tr>
<tr>
<td>Increased muscle mass/strength</td>
<td>6-12 months</td>
<td>2-5 years</td>
</tr>
<tr>
<td>Body fat redistribution</td>
<td>3-6 months</td>
<td>2-5 years</td>
</tr>
<tr>
<td>Cessation of menses</td>
<td>3-6 months</td>
<td>n/a</td>
</tr>
<tr>
<td>Clitoral enlargement</td>
<td>3-6 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>3-6 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Deepened voice</td>
<td>3-12 months</td>
<td>1-2 years</td>
</tr>
</tbody>
</table>
Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons
A Cohort Study

Darios Getahun, MD, PhD, MPH; Rebecca Nash, MPH; W. Dana Flanders, MD, MPH, DSc; Tisha C. Baird, MD; Tracy A. Becerra-Culqui, PhD; Lee Cromwell, MS; Enid Hunkeler, MA; Timothy L. Lash, PhD; Andrea Millman, MA; Virginia P. Quinn, PhD; Brandi Robinson, MPH; Douglas Roblin, PhD; Michael J. Silverberg, PhD; Joshua Safer, MD; Jennifer Slovis, MD; Vin Tangpricha, MD, PhD; and Michael Goodman, MD, MPH

**Objective:** To examine the incidence of these events in a cohort of transgender persons.

**Design:** Electronic medical record–based cohort study of transgender members of integrated health care systems who had an index date (first evidence of transgender status) from 2006 through 2014. Ten male and 10 female cisgender enrollees were matched to each transgender participant by year of birth, race/ethnicity, study site, and index date enrollment.

**Setting:** Kaiser Permanente in Georgia and northern and southern California.

**Patients:** 2842 transfemine and 2118 transmasculine members with a mean follow-up of 4.0 and 3.6 years, respectively, matched to 48 686 cisgender men and 48 775 cisgender women.

**Results:** Transfeminine participants had a higher incidence of VTE, with 2- and 8-year risk differences of 4.1 (95% CI, 1.6 to 6.7) and 16.7 (CI, 6.4 to 27.5) per 1000 persons relative to cisgender men and 3.4 (CI, 1.1 to 5.6) and 13.7 (CI, 4.1 to 22.7) relative to cisgender women. The overall analyses for ischemic stroke and myocardial infarction demonstrated similar incidence across groups. More pronounced differences for VTE and ischemic stroke were observed among transfeminine participants who initiated hormone therapy during follow-up. The evidence was insufficient to allow conclusions regarding risk among transmasculine participants.

**Conclusion:** The patterns of increases in VTE and ischemic stroke rates among transfeminine persons are not consistent with those observed in cisgender women. These results may indicate the need for long-term vigilance in identifying vascular side effects of cross-sex estrogen.
Higher rate of VTE and ischemic stroke

Figure 1. 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.
The GeMS Team

- Norman Spack MD

Medical
- Carly Guss MD
- Jessica Kremen MD
- Sarah Pilcher PNP
- Stephanie Roberts MD
- Charu Baskaran, MD
- Kate Millington, MD
- Rebecca Harris, MD, PhD

Mental Health
- Francie Mandel, LICSW
- Ariel Botta, LICSW
- Jennifer Gentile PsyD
- Peter Hunt, PhD
- Kerry McGregor, PsyD
- Amy Tishelman, PhD
- Coleen Williams PsyD

Administrative
- Timothy Ross
- Ellen Mitchell

And friends...
- Richard Yu, MD (urology)
- Serene Srouji, MD (repro/endo)
- Elizabeth Ginsburg, MD (repro/endo)
- Oren Ganor, MD (Plastics)
- Elizabeth Boskey, PhD, MPH, LICSW (Plastics)
- David Diamond MD (urology)
- Michael Kurtz, MD (urology)
- Frances Grimstad, MD
- The entire CfGS