Chase Brexton Health Care
Because everyone's health matters.

Gender Dysphoria in Children and Adolescents: Medical Considerations

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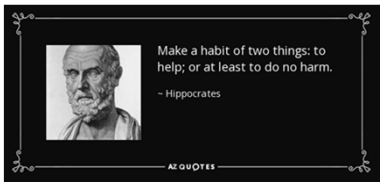
Adolescents

I have no relevant financial relationships with commercial interests
I WILL be discussing off-label uses of medications

Medical Interventions



Doing Nothing Can be Harmful!

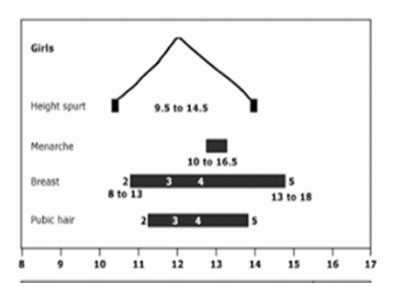
Physical Interventions for Adolescents

- 1. Fully reversible interventions.
  - GnRH agonists "puberty blockers"
  - Spironolactone to decrease testosterone
  - Oral contraceptives or Progestin to suppress menses
- 2. Partially reversible interventions.
  - Hormone therapy
- 3. Irreversible interventions.
  - Surgical procedures.

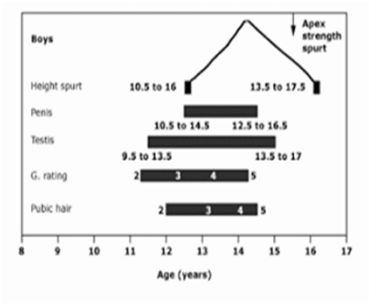
Typical Puberty

- Female puberty - onset (breast bud) age 8 to age 13
  - menarche < 5 years from breast bud
- Male puberty - onset (testicular enlargement) $\geq$ age 9, to onset by age 14
- Pace of puberty
  - Typically 2 years from breast bud to first period
  - Typically 2 years from testicular enlargement to growth spurt, voice changes, facial hair

Female Pubertal Development



Male Pubertal Development



"Side Effects" of Puberty

- Masculinizing changes of puberty
  - Deepening of voice
  - Adam's apple
  - Facial and body hair
  - Skeletal changes of face
- Feminizing changes of puberty
  - Breast growth
  - Change in body shape- hips/thighs
  - Menstrual cycles (reversible)

The Dutch Protocol

- GnRH agonists at age 12, cross sex hormone treatment at 16.
- The first 70 Dutch candidates treated with GnRH analogs between 2000 and 2008 showed improved psychological functioning.
- None opted to discontinue pubertal suppression and all eventually began cross-sex hormone treatment.
- More recently, the Amsterdam group found that adolescents with GID who underwent pubertal suppression had improved behavioral, emotional, and depressive symptoms with psychometric testing.

Psychological Outcome after Puberty Suppression and Gender Reassignment

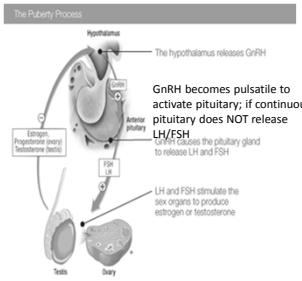
- 55 young transgender adults were assessed at baseline prior to puberty blockers, at introduction of cross sex hormone therapy, and at least 1 year after gender reassignment surgery
- After gender reassignment gender dysphoria steadily improved.
- Well-being was similar to or better than same-age young adults from general population.
- Improvements in psychological functioning were positively correlated with post-surgical subjective well-being
- "A clinical protocol of a multi-disciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults.

DeVries, A. et.al. "Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment" Pediatrics (2014) 134(4).

GnRH agonists

- Leuprolide(IM injection) or Histrelin (implant) used successfully for central precocious puberty
- Not FDA approved for puberty suppression in transgender children.
- Has been used for decades for central precocious puberty, and is used for treatment of endometriosis, prostate cancer, and infertility in adults
- Block central puberty but do not stop adrenarche- body odor, acne, or pubic hair

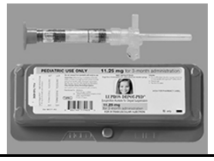
GnRH Agonists



Puberty Blocker Regimens

- GnRH agonists
  - Leurpolide Acetate IM 7.5 mg, 11.25 mg, or 15 mg monthly, 11.25, 22.5 mg or 30 mg q3 months, based on weight and efficacy
  - Histrelin implant 50 mg subcutaneous (yearly, but possibly longer)
  - Nafarelin acetate intranasal
- Alternative methods
  - Medroxyprogesterone po (up to 40 mg/day) or 150 mg IM q 3 months
  - Spironolactone 100-300 mg/day to decrease androgen action
  - Finasteride 2.5-5 mg/day for blocking testosterone conversion to 5 –alpha DHT

Rosenthal, Stephen, "Approach to the Patient: Transgender Youth: Endocrine Considerations", JCEM 2014



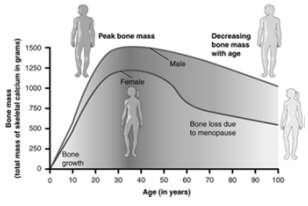
Benefits of Puberty Blockers

- Delays or avoids development of undesired secondary sexual characteristics (breasts and periods, deeper voice, facial hair, growth spurt, genital changes)
- Allows the opportunity to explore gender without the anxiety of natal pubertal development
- Can avoid the need for future surgeries
- Associated with decreased depression and anxiety, though not body dysphoria
- Does not stop growth or cognitive development
- Can act as a diagnostic procedure- if gender dysphoria worsens at puberty and is relieved by puberty blockers, possible predictive value

Risks of Puberty Blockers

- Lack of accumulated bone density during treatment
- Slower growth
- Surge in hormones for one month after first shot/implant
- Sterile abscess
- Leg pains
- Headaches
- Weight gain
- Risks of anesthesia if surgically implanted, and difficulty in removal (particularly if used for more than one year)
- Hot flashes for pubertally mature individuals
- May lag behind peers with pubertal development

Effects on Bone Mass



Cost of Puberty Blockers

- Monthly Pediatric Leuprolide- $1000-$2100
- 3 Month Pediatric Leuprolide (30 mg)- $6000
- 3 Month Leuprolide (22.5 mg) - $3000
- Pediatric Histrelin implant- $20,000-30,000
- Histrelin implant- $6,000-12,000

Insurance Coverage-
Legal issues of insurance coverage/exclusions may depend on state.

Puberty Blockers for Older Adolescents

- The role of puberty blockers for pubertally mature adolescents is less established
- Puberty blockers can stop menses without the use of female hormones (continuous oral contraceptives or progesterone)
- Puberty blockers can prevent further development in both sexes (further voice and facial hair, facial bone structures changes, body shape changes), but does NOT reverse changes that have already occurred.
- If pubertally mature, then hot flashes and low libido may result

Timing of Puberty Blockers

- WPATH, Endocrine Society, - puberty suppression at Tanner stage 2-3, cross sex hormone treatment at age 16, or earlier with parental consent, surgery after age 18 and more than 1 year of living in affirmed gender
- Dutch Protocol- puberty suppression at age 12, cross sex hormone therapy at 16
- Some programs in the US start cross sex hormones at age 12

Monitoring During Puberty Blocking

- Growth and weight gain
- LH, FSH, testosterone/estradiol
- Bone age
- Bone density
- Calcium, phos, alk phos, Vitamin D 25 OH
- +/- LFT, Creatinine, Glucose, insulin, HbA1c, Lipids

Cross-sex hormone therapy

- What age to start
  - Peer concordance vs. time to mature
- Benefits in appearance, psychological
- Concerns about consent, irreversibility, fertility

Feminizing Hormone Therapy

- Goals of therapy: to reduce male physical characteristics and feminize one's body
  - Increase breast size
  - Change fat distribution to hips/buttocks/thighs
  - Decrease muscle mass and upper body strength
  - Decrease facial and body hair growth
  - Softer skin
  - Slow/stop scalp hair loss

Feminizing Therapy

- The hormonal treatment often affects sexual function
  - Decrease libido
  - Decrease erections and ejaculate volume
  - Smaller, softer testes (25-50% reduction)
  - Sperm number and fertility may be reduced, but not necessarily

Feminizing Therapy

- Feminizing therapy does NOT
  - Affect voice pitch or speech patterns
  - Decrease the size of the Adam's apple
  - Stop facial hair growth
  - Stop body hair growth

Timing of Feminizing Effects

Effect	Onset	Maximum
Redistribution of body fat	3-6 months	2-3 years
Decrease in muscle mass and strength	3-6 months	1-2 years
Softening of skin/decreased oiliness	3-6 months	Unknown
Decreased libido	1-3 months	3-6 months
Decreased Spontaneous erections	1-3 months	3-6 months
Male Sexual dysfunction	Variable	Variable
Breast growth	3-6 months	2-3 years
Decreased testicular volume	3-6 months	2-3 years
Decreased sperm production	Unknown	>3 years
Decreased terminal hair growth	6-12 months	>3 years
Scalp Hair	No regrowth	n/a

Known Risks of Feminizing Therapy

Risk of Estrogen	Degree of Risk	Comments
Thromboembolic events- blood clots	Ethinyl estradiol had a 6-8% incidence, other types had no elevated risk. 5% incidence in those with risk factors (smoking, immobilization, hypercoagulable state)	Newer estradiol, such as skin patches had no increased risk even in women genetically prone to blood clots. MI rate for transwomen equal to cismen.
Cholesterol	Triglycerides increased by 30 points over 5 years	Other studies showed decrease in LDL, or no change
Prolactinoma (pituitary tumor)	6 case reports	Prolactin levels may be elevated on estrogen without a tumor
Liver, creatinine, H/H, uric acid	Increase in uric acid	No other changes
Mortaility- rate of death	Increased mortality in transwomen	NOT due to hormone therapy
Cancer	10 cases of breast cancer, lower than rates for ciswomen	No increase in mortality due to cancer
Bone health	Osteopenia in transwomen, esp if on androgen blockers prior to estrogen	No increased fracture risk
Sexual dysfunction	1/3-2/3 of transwomen had decrease in libido	One study similar level in pre-menopausal ciswomen

Known Risks of Feminizing Therapy

Risks of Spironolactone	Degree of Risk	Comments
Dehydration		Recommend increased fluids
Hyperkalemia	Low in those with healthy kidneys and normal kidney function	May need to be on a low-potassium diet for some
Prostate Screening Antigen	PSA level may be lower	Cannot rely on test to evaluate for prostate cancer

Estrogen Regimens

- Transdermal estradiol patch- 0.1 mg to 0.4 mg twice weekly
  - May start at 0.025 or 0.05 mg twice weekly with younger people
- Oral estradiol 0.5 mg – 6 mg daily, may be taken sublingually
- Injections
  - Estradiol Valerate 5-20 mg q 2 weeks (some sources say up to 40 mg q2 weeks)
  - Estradiol Cypionate 2-10 mg q week
- Doses are for pre-orchiectomy, may be lowered postoperatively

Anti-Androgen Regimens

- Goal of Anti-androgen is to decrease testosterone production and block androgens from binding to androgen receptor
- Spironolactone
  - Start at 50 mg and titrate upwards
  - 200 mg average
  - 300 mg maximum

Masculinizing Hormone Therapy

- Goals of Therapy to reduce female physical characteristics and masculinize one's body
- Effects of Testosterone
  - Increased body hair
  - Lowers the voice pitch
  - Induce facial hair growth
  - Clitoral growth/vaginal dryness
  - Increased upper body strength and musculature, redistribution of fat
  - May induce hair loss on scalp, increase acne
  - Increase Libido
  - Decrease/stop menses

Masculinizing Therapy

- Masculinizing therapy does NOT
  - Decrease breast size, though some atrophy does occur
  - Alter voice patterns
  - Typically produce enough clitoral growth sufficient for penetrative sex

Timing of Masculinizing Effects

Effects	Onset	Maximum
Acne/skin oiliness	1-6 months	1-2 years
Facial/body hair growth	6-12 months	4-5 years
Scalp Hair loss	6-12 months	
Increased muscle mass/strength	6-12 months	2-5 years
Fat redistribution	1-6 months	2-5 years
Cessation of menses	2-6 months	
Clitoral enlargement	3-6 months	1-2 years
Vaginal atrophy	3-6 months	1-2 years
Deepening of voice	6-12 months	1-2 years

Known Risks of Testosterone Therapy

Side Effect	Degree of Risk	Comments
Polycythemia- too many red blood cells	Higher risk if testosterone above target range	Monitor CBC, phlebotomy as treatment
Lipid changes	Increased TG by 31 mg/dL, LDL increased, HDL lower	No evidence of increased CV mortality
Increased intraabdominal fat	Increased risk of DM	Increased fasting glucose, some insulin resistance at baseline (possible PCOS)
Vaginal atrophy	Varies	Increases risk of contracting STI
Bone health	Lower BMD after oopherectomy	Risk of fracture not studied, pre-surgical testosterone maintained bone mass
Breast, ovarian, uterine cancer	4 cases of breast cancer, ovarian cortex and stroma thickened, but only few case reports of cancer, uterine atrophy, less likely hyperplasia	Risk comparable to natal males, less risk than natal females
Emotional changes	Increased aggression, increased libido	Decreased depression and anxiety

Testosterone Regimens

- Topical patch- 5-10 mg q24 hours
- Topical gel- 5-10 g daily
  - WARNING- gel can transfer to close contacts easily
- Injectable- Testosterone cypionate or Testosterone enanthate
  - Initial dose 25-40 mg weekly, or 50-80 mg every 2 weeks
  - Titrate up to clinical effect and testosterone levels within normal range for natal males
  - Typical dose 50-100 mg Q week or 100-200 mg Q 2 weeks
- Subcutaneous testosterone- Jo Olson published on use of subcutaneous testosterone- can be used safely, doses needed are half of intramuscular and has less variability in levels than intramuscular
  - Can use 25-50mg subcutaneously weekly
- Testosterone pellets
- Increase dose to mimic pubertal stages

Risks of Non-Prescribed Medications and Treatments

- Hormones obtained from the internet or friends may be of dubious quality and unknown doses
- Injectable hormones have risks of shared vials or shared needles
- There are higher risks of certain types of estrogen
- Silicone injections can cause infections, be disfiguring, or trigger a life-threatening reaction in the body

Medical options for non-binary individuals

- GnRH agognists can lower hormones- but not indefinitely
- Low dose testosterone
- Estradiol used without male hormone blocker
- Intrauterine Device or implanted progesterone to stop periods
- Surgery without hormones

Fertility

- There are options to preserve fertility
  - Must be physically late in puberty
    - Sperm production occurs, on average, at age 13-14, with Tanner III-IV testes and II-III pubic hair
    - Egg maturation occurs, on average at age 12-13, with Tanner IV breasts and pubic hair
  - In order to harvest eggs, must take medications, invasive, expensive, and unclear feasibility
  - Sperm preservation relatively less expensive and simpler
  - If puberty blockers are used, then one cannot just collect sperm or eggs because they will be immature

Fertility

Blockers, no significant pubertal development

- Testicular or ovarian biopsy to see if there has been sperm/egg development
- No current options for fertility preservation
- However, there have been advances of cryopreservation of prepubertal ovary with later successful fertility (used as part of cancer protocols)

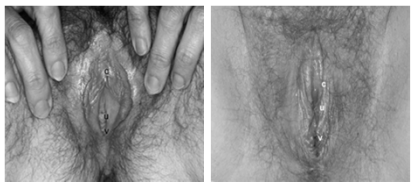
Blockers after pubertal development, or no blockers, and have been on sex hormone therapy

- If development has already occurred, there may be options for fertility preservation, even after hormone therapy
- Transmen have had pregnancies (intentional or not) after being on testosterone for years
- Transwomen have had sperm production after being on estrogen for years
- There is no guarantee of fertility or infertility after hormone therapy

Surgical Options for Trans Youth

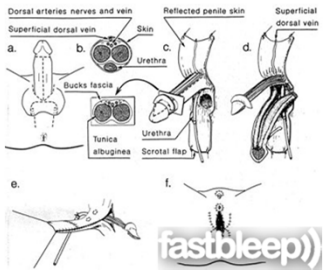
- There are people who choose not to have surgery or cannot have surgery
- Top surgery (double incision or periareolar/keyhole) is performed by some surgeons for affirmed males under 18 years
- Genital reconstruction is typically reserved for those 18 years and above
  - Additional surgeries for transmen are removal of uterus and ovaries, removal of cervix and vagina
  - Additional surgeries for transwomen are removal of testes and scrotum, removal of penis
- Other surgeries, such as facial feminization, tracheal shave, or breast augmentation, are sometimes performed
- With early use of puberty blockers, many of these surgeries can be avoided
- However, there will be less penile skin for vaginal construction
- Surgeries have not been covered in the past, however, an increasing number of insurance plans are covering surgeries if medically necessary

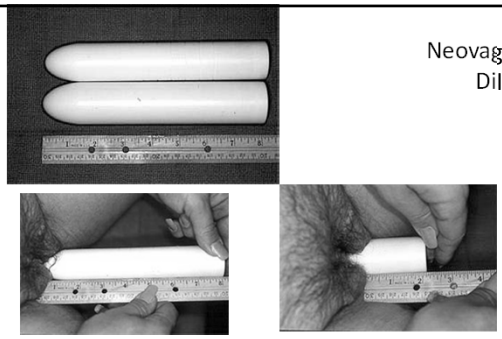
Vaginoplasty compared to genetic female



Slides courtesy of Eva Hersch, MD

Vaginoplasty: Penile skin inversion technique





Neovaginal Dilation

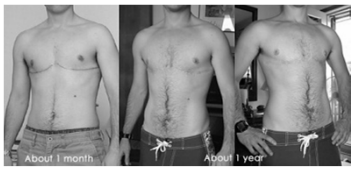
Slides courtesy of Eva Hersch, MD

Vaginoplasty: colon graft technique

Similar to scrotal skin grafts, but vagina is constructed from rectosigmoid colon tissue.

- Advantage: vagina is deep and self-lubricated.
- Disadvantages:
  - invasive bowel surgery
  - excessive chronic vaginal drainage

Masculinizing Chest Surgery



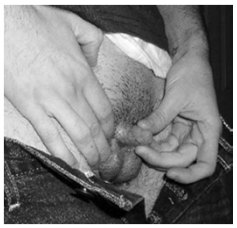
Slides courtesy of Eva Hersch, MD

Metaoidioplasty

- Goals:
  - Ability to urinate while standing
  - Preservation of sensation to clitoris
  - Removal of vaginal cavity
  - Creation of a scrotal sac
- Approx duration of surgery: 3-4 hours
- Procedure: Clitoris release to form mini-phallus, create neourethra from mucosa of labia minora and vagina, create neoscrotum with labia majora, insert testicular implants

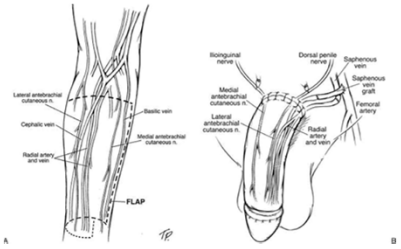
Slides courtesy of Eva Hersch, MD

Metaoidoplasty result

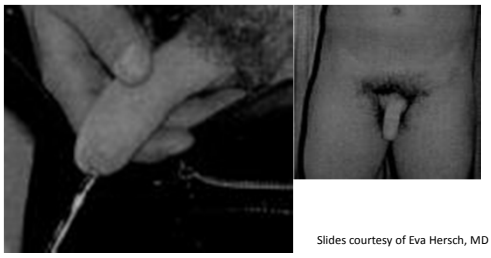


Slides courtesy of Eva Hersch, MD

Phalloplasty



Phalloplasty, demonstrating urethroplasty



Slides courtesy of Eva Hersch, MD

Guidelines

- World Professional Association for Transgender Health (WPATH) Standard of Care, Seventh Version, 2012
- Primary Care Protocol for Transgender Patient Care, 2011- UCSF Center for Transgender Excellence
- The Endocrine Society Clinical Practice Guidelines- Endocrine Treatment of Transsexual Persons, 2009
- Protocols for Hormonal Gender Reassignment- Tom Waddell Center, 2006
- Guidelines for Transgender Care, Trans Care Project, 2006, Vancouver, British Columbia