The Fertility Counseling Challenges for Transgender Youth and Families
Proceedings of the Working Group Session on Fertility Preservation for Individuals with Gender and Sex Diversity

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Risk of Infertility
FP Options
Technical requirements
Ethical concerns
Barriers to Care
Challenges

Scientific Unknowns

Psychosocial considerations

Youth Knowledge and Maturity

Attitudes of Youth & Parents
Basic Reproduction
Fertility Potential
Early Development

<table>
<thead>
<tr>
<th>Prenatal</th>
<th>Birth</th>
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<tbody>
<tr>
<td><strong>Oogenesis</strong></td>
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<tr>
<td>[Diagram of Mitosis]</td>
<td>Arrow connecting Oogonium to Primary oocytes</td>
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<td>Oogonia divide mitotically and produce primary oocytes.</td>
<td>Three months after conception, the ovaries contain two million oocytes, arrested in prophase I.</td>
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<tr>
<td><strong>Spermatogenesis</strong></td>
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<tr>
<td>[Diagram linking Spermatogonium to Spermatogon]</td>
<td>Transition is in your future.</td>
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</tbody>
</table>

Transition is in your future.
Timing of Potential Intervention

- **Tanner 2**
  - 8-14 years
  - GnRH Analogs

- **Adolescence**
  - 13+ years
  - Gender Affirming Hormones

- **Adulthood 18+ years**
  - Genital Surgery
Which Treatments Affect Fertility?

- **Tanner 2**  
  8-15 years  
  - GnRH Analogs

- **Adolescence**  
  13+years  
  - Gender Affirming Hormones

- **Adulthood**  
  18+ years  
  - Orchietectomy
  - Oophorectomy
GnRH analogs

GnRHa: Prevent Gamete Maturation
Fertility?

Tanner 2
8-15 years

GnRH Analogs

Pause Gamete Maturation

Adolescence 13+ years

Gender Affirming Hormones

What happens if gender affirming hormones are started with no gamete maturation? What is the future fertility potential?
• Started GnRHa @ Tanner 2 (Age 14 years)
• Oocyte cryopreservation attempted @ Age 16 years
  • Remained on GnRHa
  • FSH & HCG given (monitoring via estradiol level, no transvaginal u/s)
  • 5 oocytes retrieved, 4 preserved
• Side effects
  • Distressing vaginal bleeding & breast development (regressed after 3 months)
  • Depressed mood and brief suicidal thoughts, resolved
• Testosterone started

• Successful oocyte harvesting, but guarded prognosis due to # of oocytes
Gender-Affirming Hormones & Fertility

Puberty

Adolescence 13+ years

Gender Affirming Hormones
For Transgender Women...

Treatment strategies:
- Cypionate acetate (50–100 mg/d)
- or Spironolactone (100–200 mg/d)
- or GnRH agonists (3.75 mg s.c.)
- and estrogens (oral, transdermal, i.m.)

??? Short Term vs Long Term Effects ???
Some with severe involution of spermatogenesis & Leydig cells

Others maintained spermatogenesis & normal Leydig cells

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**Table 1** Publications examining the influence of cross-sex hormone therapy on testicular morphology in gender dysphoria patients

<table>
<thead>
<tr>
<th>Year</th>
<th>First author</th>
<th>Country</th>
<th>Patient number</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rodriguez-Rigau et al.</td>
<td>Houston, USA</td>
<td>n = 1</td>
<td>Ethinylestradiol estradiol of 0.5–1 mg daily for 18 months</td>
<td>Germinal cells were absent, except very occasional spermatogonia, seminiferous tubules were reduced in diameter, heavy hyalinization and fibrosis. Atrophy of interstitial area with the absence of recognizable Leydig cells.</td>
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<td>2</td>
<td>Lu et al.</td>
<td>Houston, USA</td>
<td>n = 4</td>
<td>Long term treatment with ethinylestradiol (1–2 mg) daily</td>
<td>The estrogen-treated testicular tissue contained only Sertoli cells and very few spermatogonia within the seminiferous tubules. Inconsistent results: Reduced spermatogenesis and reduced numbers of Leydig cells to complete spermatogenesis with normal Leydig cell abundance. 3 cases of normal spermatogenic activity with normal Leydig cells and 7 cases of total absence of spermatogenic activity with reduced Leydig cells.</td>
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<tr>
<td>3</td>
<td>Payer et al.</td>
<td>Galveston, USA</td>
<td>n = 6</td>
<td>Steroid hormones ranging from 1.25 to 7 years</td>
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<tr>
<td>4</td>
<td>Thiagaraj et al.</td>
<td>Singapore</td>
<td>n = 10</td>
<td>Estrogen therapy (0.05–0.2 mg daily) for 6–13 years. Treatment stopped 2 weeks before SRS</td>
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<td>5</td>
<td>Venizelos et al.</td>
<td>London, UK</td>
<td>n = 5</td>
<td>Estrogen treatment for periods ranging from 18 months till 5.5 years</td>
<td>Leydig cell population was reduced in all patients. Tubular hyalinization was present in all patients. Spermatogenic levels varied. Atrophy of the seminiferous tubules was observed in all cases; its degree, and a marked decrease in Leydig cells, correlated with low plasma gonadotropin levels.</td>
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<td>6</td>
<td>Sapino et al.</td>
<td>Turin, Italy</td>
<td>n = 5</td>
<td>40–50 mg/week of polysteradiol phosphate treatment for varying periods. Withdrawal 10 days before SRS</td>
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<td>7</td>
<td>Schuize et al.</td>
<td>Hamburg, Germany</td>
<td>n = 11</td>
<td>1–12 years of treatment with various amounts of estrogens, estradiol, or ethinylestradiol</td>
<td>Narrow seminiferous cords surrounded by an extensively thickened lamina propria. They contain Sertoli cells and spermatogonia exclusively. There is no evidence of typical Leydig cells. Increase of interstitial tissue, decrease in number and in volume of Leydig cells and spermatogenic arrest.</td>
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<td>8</td>
<td>Kismen et al.</td>
<td>Amsterdam, The Netherlands</td>
<td>n = 8</td>
<td>18 months with a combination of 100 g ethinylestradiol and 100 mg CPA daily</td>
<td>The low dose had no negative effect on sperm motility? and density. High dose reduced motility after a few days and density after 2 weeks. Dramatic decrease of estrogen receptor beta transcripts. Histology revealed a highly heterogeneous picture with 24% patients with normal spermatogenesis irrespective of the treatment strategy. Only patients that did not discontinue hormonal treatment showed feminized blood levels on the day of SRS and the lowest ITT levels.</td>
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<td>9</td>
<td>Lübbert et al.</td>
<td>Berlin, Germany</td>
<td>n = 1</td>
<td>20 ug and 60 ug of ethinylestradiol</td>
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<td>10</td>
<td>Aschim et al.</td>
<td>Oslo, Norway</td>
<td>n = 3</td>
<td>100 ug ethinylestradiol for at least 1 year Anti-androgens (10–100 mg) combined with different dosages of estrogens or only estrogens or a combination of Spironolactone and estrogens. Multicenter study: Patients either discontinued treatment 6 weeks (clinic A) or 2 weeks (clinic B) prior to SRS or not at all (clinic C).</td>
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<td>11</td>
<td>Schneider et al.</td>
<td>Münster, Germany</td>
<td>n = 108</td>
<td>Anti-androgens (10–100 mg) combined with different dosages of estrogens or only estrogens or a combination of Spironolactone and estrogens. Multicenter study: Patients either discontinued treatment 6 weeks (clinic A) or 2 weeks (clinic B) prior to SRS or not at all (clinic C).</td>
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For Transgender Men...

**Testosterone**

- Adeleye et al: 13 Transgender men
  - 6 before HRT and 7 after HRT
  - Mean length of HRT 46 months
  - Transgender men who used HRT had lower peak estradiol (1175 pg/mL vs. 2713 pg/mL) and oocytes retrieved (12 vs. 25.5)
  - No difference in other factors
  - 3 successful pregnancies from those with HRT

- Leung et al:
  - 26 Transgender patients (2/3 after HRT)
  - Mean length of HRT 44 months
  - Mean oocyte retrieval was higher in the transgender cohort and estradiol levels were similar
  - 16 banked oocytes
  - 7 achieved pregnancy

Effects of prolonged anovulatory state? Testosterone exposure? Often reversible

Fertility Preservation Options
Post-Pubertal FP Options

Sperm or Embryo Banking

Oocyte or Embryo Banking

Armaund G et al. Hum Reprod 2017
Peri-Pubertal FP Options

• Testicular or ovarian tissue cryopreservation
  • Experimental
  • Testicular protocols at UCSF and Pittsburgh (and others?)
  • Ovarian protocol at Pittsburgh (and others?)

• Forgo GnRHa to allow in vivo germ cell maturation
  • Worsening dysphoria, self harm, permanent 2° sex characteristics

• Remain on GnRHa with hormone stimulation
  • Experimental
  • Development of secondary sex characteristics, dysphoria, depression
Psychosocial Considerations
Desire for Parenthood/Fertility in Adults

• Many desire parenthood (biological, adoption, sperm bank, fostering)
• Believe fertility preservation should be offered although desire to pursue varies
• Many have regret about not having fertility options
Desire for Parenthood/Fertility in Youth

- Future parenthood desires vary
- Family values around biological parenthood
- Gender dysphoria
- Financial considerations (high costs)
- Fertility Information: lack of awareness of FP options, procedures
- Invasiveness of the available procedures and the potential psychological impact of the FP process.
Factors to consider

• Gametes do not match gender identity
• Procedural Complexities
  – Trigger gender dysphoria
  – Exams and Body dysphoria
  – Hormonal stimulation with hormones that do not match gender identity
  – Procedures like transvaginal ultrasound
• Coping Strategies
  – Focus on reasons for undergoing procedures
  – Support from family and friends
  – Cognitive approaches for body dysphoria
  – Using non-gendered names for body parts
2 of 72 adolescents (MtF) counseled within medical visit pursued FP

13/105 adolescents counseled within medical visit did formal FP consultation
5/13 preserved (4 sperm, 1 oocyte)

66 adolescents, 52/66 counseled within medical visit
11/52 formal FP consultation, 3/11 attempted preservation, 2/3 preserved
35 Transgirls

Reasons for no FP: 17% did not want children, 13% wanted to adopt, body/process 17%, idea of being “father” 4%

Ultimately 9/12 preserved

Reasons FP unsuccessful: 1 unable to ejaculate, 1 azoospermia, 1 oligospermia and poor quality
I understand how it works, I know what I think.

I want to....

Needed:
Standardized counseling protocols and patient decision aids
Northwestern’s campus when it isn’t 9 degrees!