REPRODUCTION, FERTILITY, AND FAMILY PLANNING

Elizabeth Constance, MD

Director, Fertility Preservation Program and LGBTQ+ Health Services

Heartland Center for Reproductive Medicine

Assistant Professor, Department of OB/GYN

University of Nebraska Medical Center

Heartland Center for Reproductive Medicine

GENDER CARE IN 2024 THE HEARTLAND

DISCLOSURES

- Discussion of off-label uses for medications as part of fertility treatment

LEARNING OUTCOMES

1. Discuss the current state of knowledge of the effect of gender-affirming hormone therapy on current and future reproductive capacity

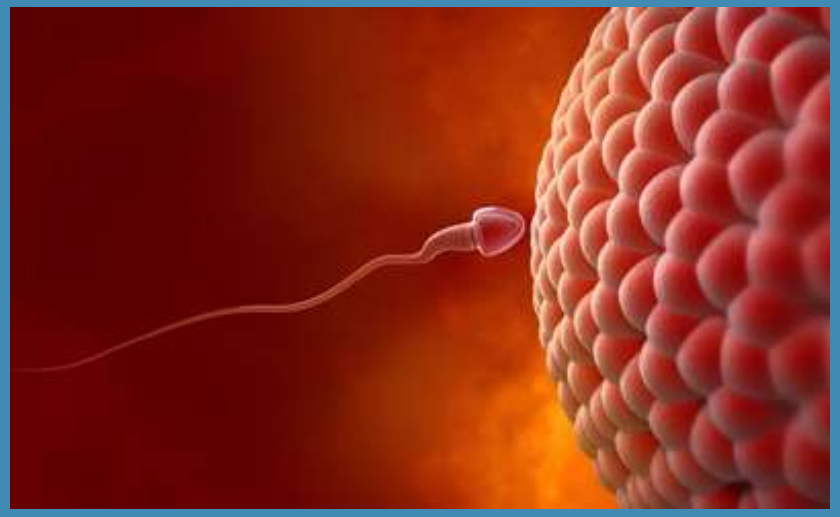
2. Explore options for fertility preservation before initiation of gender-affirming hormone therapy

3. Review fertility treatment and preservation strategies after initiation of gender-affirming hormone therapy

CASE

- Jason is a 23 yo transman (AFAB) who presents to your clinic with his fiancée Kate (cisgender woman) to discuss fertility preservation prior to starting Testosterone
- They plan to have children in 7-8 years using Jason's eggs, donor sperm, and Kate carrying the pregnancy. They want a big family.
- You walk them through the process, including costs, and they tell you they would need to use all of the money they have saved for their wedding
- They want to know if they need to do that, or if it's ok to wait until they actually want to have kids and have saved money again

REPRODUCTION IN GENDER DIVERSE INDIVIDUALS



EFFECT OF GENDER AFFIRMING TX ON FERTILITY

- The effect of long-term gender-affirming hormone therapy on future reproductive capacity is largely unknown
  - Limited human studies are observational in nature, mostly assess short-term therapy, and have mixed results
- Even less is known about fertility in individuals who had puberty halted with GnRH agonists (puberty blockers) prior to starting hormone therapy
- Many gender affirming surgeries remove the gonads and are therefore sterilizing

PUBMED SEARCH 11/2/24

- "cancer and fertility" = 21,014 results
- "transgender and fertility" = 410 results

Heartland Center
for Reproductive Medicine

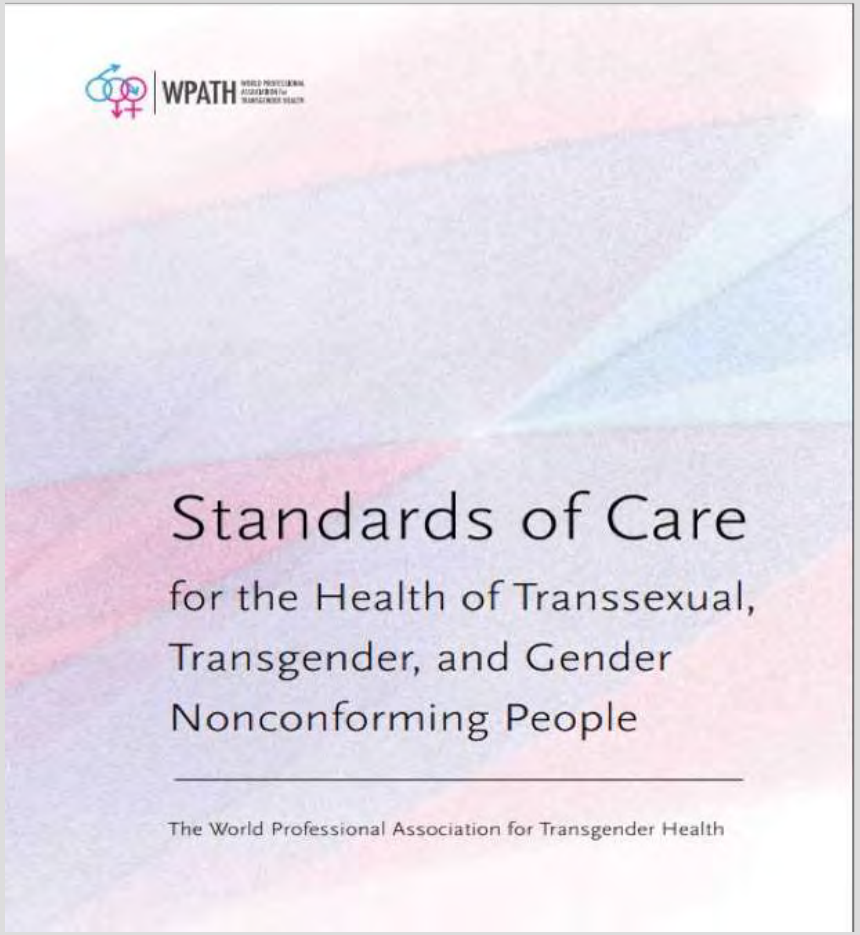
MEDICAL SOCIETY GUIDELINES

ASRM	Endocrine Society
• "Providers should **offer fertility preservation** options to individuals **before gender transition**" • "…ensure that transgender patients who seek fertility services are informed about…the **lack of data** about long-term outcomes"	• "All individuals seeking gender-affirming medical treatment should receive information and **counsel on options for fertility preservation prior to initiating** puberty suppression in adolescents and prior to treating with hormonal therapy in both adolescents and adults"

Heartland Center
for Reproductive Medicine

WPATH GUIDELINES

”Health care professionals…should **discuss reproductive options** with patients **prior to initiation** of these medical treatments for gender dysphoria”



Heartland Center for Reproductive Medicine

PSYCHOSOCIAL DATA

- ~50% of transgender people express the desire to have children
- ~40% of transgender men would consider gamete cryopreservation
- Transgender men with children score better on mental health scales and transgender women with children have a lower suicide risk
- 24-36% of transgender adolescents desire biologic parenthood
  - >25% "did not know"

De Roo C, et al. *Int Rev Psychiatry* 2015; Wierckx K et al. *Human Reprod* 2012;
Hamada et al. *Andologia* 2014;
Chen D, et al. *J Adolesc Health* 2018;
Strang JF, et al. *J Adolesc Health* 2018

UTILIZATION

- There seems to be low utilization of fertility preservation in TGNB persons undergoing medical or surgical transition
- Studies in transgender youth: 2-5% pursue fertility preservation despite counseling (all assigned male at birth)
- Barriers:
  - COST!!!!
  - Knowledge/Access
  - Dysphoria related to treatments/procedures

OPTIONS FOR GENETIC OFFSPRING

TRANSGENDER MEN	TRANSGENDER WOMEN

• Partner with sperm
  • Willing/able to carry pregnancy → intercourse/IUI
  • Not willing/able to carry pregnancy → IVF with gestational carrier
	• Partner with ovaries/uterus:
	  • Partner willing/able to carry pregnancy → intercourse/IUI
	  • Partner not willing/able to carry pregnancy → IVF with gestational carrier

• No partner with sperm:
  • Willing/able to carry pregnancy → Donor insemination
  • Not willing/able to carry pregnancy → IVF to fertilize own eggs (donor sperm) and have partner or gestational carrier carry pregnancy
	• No partner with ovaries/uterus:
	  • Egg donation with gestational carrier

• Fertility preservation only:
  • Oocyte cryopreservation (post-pubertal)
  • Ovarian tissue cryopreservation (pre- or post-pubertal)
	• Fertility preservation only
	  • Sperm banking (post-pubertal)
	  • Testicular tissue cryopreservation (pre-pubertal)

OPTIONS FOR GENETIC OFFSPRING

TRANSGENDER MEN	TRANSGENDER WOMEN

• Partner with sperm
  • Willing/able to carry pregnancy → intercourse/IUI
  • Not willing/able to carry pregnancy → IVF with gestational carrier
	• Partner with ovaries/uterus:
	  • Partner willing/able to carry pregnancy → intercourse/IUI
	  • Partner not willing/able to carry pregnancy → IVF with gestational carrier

• No partner with sperm:
  • Willing/able to carry pregnancy → Donor insemination
  • Not willing/able to carry pregnancy → IVF to fertilize own eggs (donor sperm) and have partner or gestational carrier carry pregnancy
	• No partner with ovaries/uterus:
	  • Egg donation with gestational carrier

• Fertility preservation only:
  • Oocyte cryopreservation (post-pubertal)
  • Ovarian tissue cryopreservation (pre- or post-pubertal)
	• Fertility preservation only
	  • Sperm banking (post-pubertal)
	  • Testicular tissue cryopreservation (pre-pubertal)

OPTIONS FOR GENETIC OFFSPRING

TRANSGENDER MEN	TRANSGENDER WOMEN

• Partner with sperm
  • Willing/able to carry pregnancy → intercourse/IUI
  • Not willing/able to carry pregnancy → IVF with gestational carrier
	• Partner with ovaries/uterus:
	  • Partner willing/able to carry pregnancy → intercourse/IUI
	  • Partner not willing/able to carry pregnancy → IVF with gestational carrier

• No partner with sperm:
  • Willing/able to carry pregnancy → Donor insemination
  • Not willing/able to carry pregnancy → IVF to fertilize own eggs (donor sperm) and have partner or gestational carrier carry pregnancy
	• No partner with ovaries/uterus:
	  • Egg donation with gestational carrier

• Fertility preservation only:
  • Oocyte cryopreservation (post-pubertal)
  • Ovarian tissue cryopreservation (pre- or post-pubertal)
	• Fertility preservation only
	  • Sperm banking (post-pubertal)
	  • Testicular tissue cryopreservation (pre-pubertal)

OPTIONS FOR GENETIC OFFSPRING

TRANSGENDER MEN	TRANSGENDER WOMEN

• Partner with sperm
  • Willing/able to carry pregnancy → intercourse/IUI
  • Not willing/able to carry pregnancy → IVF with gestational carrier
	• Partner with ovaries/uterus:
	  • Partner willing/able to carry pregnancy → intercourse/IUI
	  • Partner not willing/able to carry pregnancy → IVF with gestational carrier

• No partner with sperm:
  • Willing/able to carry pregnancy → Donor insemination
  • Not willing/able to carry pregnancy → IVF to fertilize own eggs (donor sperm) and have partner or gestational carrier carry pregnancy
	• No partner with ovaries/uterus:
	  • Egg donation with gestational carrier

• Fertility preservation only:
  • Oocyte cryopreservation (post-pubertal)
  • Ovarian tissue cryopreservation (pre- or post-pubertal)
	• Fertility preservation only
	  • Sperm banking (post-pubertal)
	  • Testicular tissue cryopreservation (pre-pubertal)

OPTIONS FOR GENETIC OFFSPRING

TRANSGENDER MEN	TRANSGENDER WOMEN

• Partner with sperm
  • Willing/able to carry pregnancy → intercourse/IUI
  • Not willing/able to carry pregnancy → IVF with gestational carrier
	• Partner with ovaries/uterus:
	  • Partner willing/able to carry pregnancy → intercourse/IUI
	  • Partner not willing/able to carry pregnancy → IVF with gestational carrier

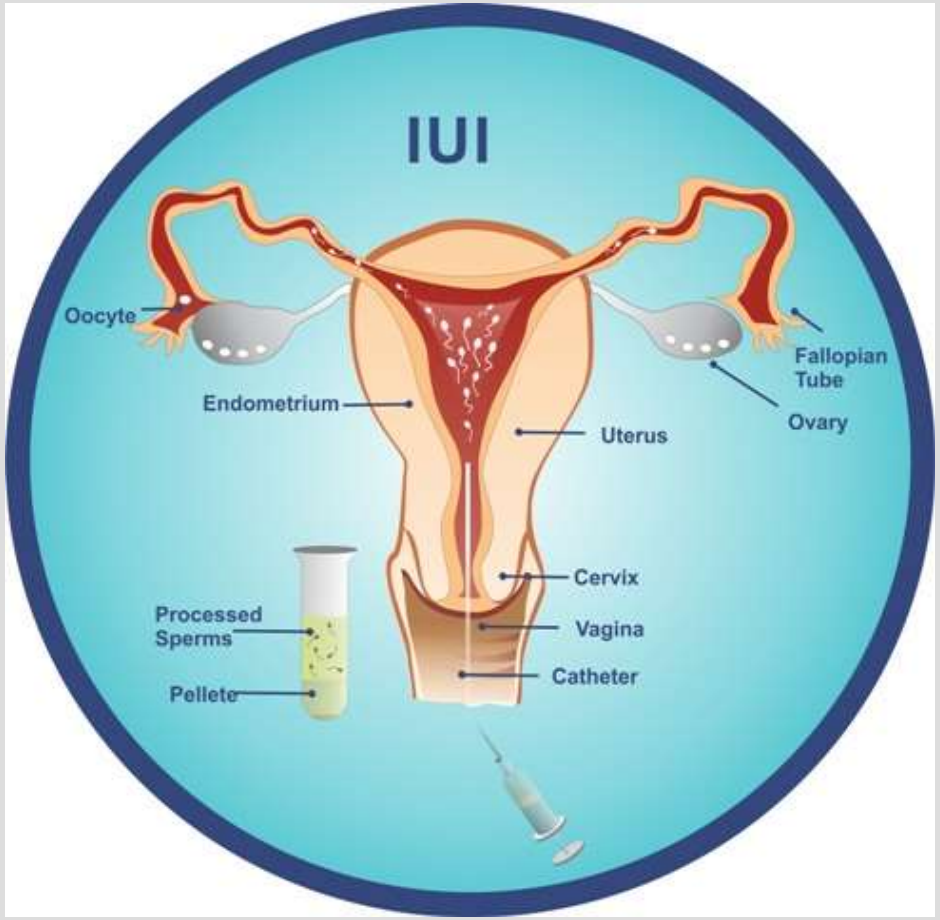
• No partner with sperm:
  • Willing/able to carry pregnancy → Donor insemination
  • Not willing/able to carry pregnancy → IVF to fertilize own eggs (donor sperm) and have partner or gestational carrier carry pregnancy
	• No partner with ovaries/uterus:
	  • Egg donation with gestational carrier

• Fertility preservation only:
  • Oocyte cryopreservation (post-pubertal)
  • Ovarian tissue cryopreservation (pre- or post-pubertal)
	• Fertility preservation only
	  • Sperm banking (post-pubertal)
	  • Testicular tissue cryopreservation (pre-pubertal)

OVARIAN HORMONE THERAPIES

- Stimulate egg development and ovulation
  - Used if not having regular menstrual periods
  - Goal 1-2 eggs
- Stimulate development of multiple eggs at one time
  - Can help overcome reduced egg quality by increasing number of eggs released
  - Goal 2-4 eggs (depending on age)
  - Increased risk of multiples
- Can be oral or injectable
- Used in conjunction with IUI or Intercourse

INTRAUTERINE INSEMINATION (IUI)



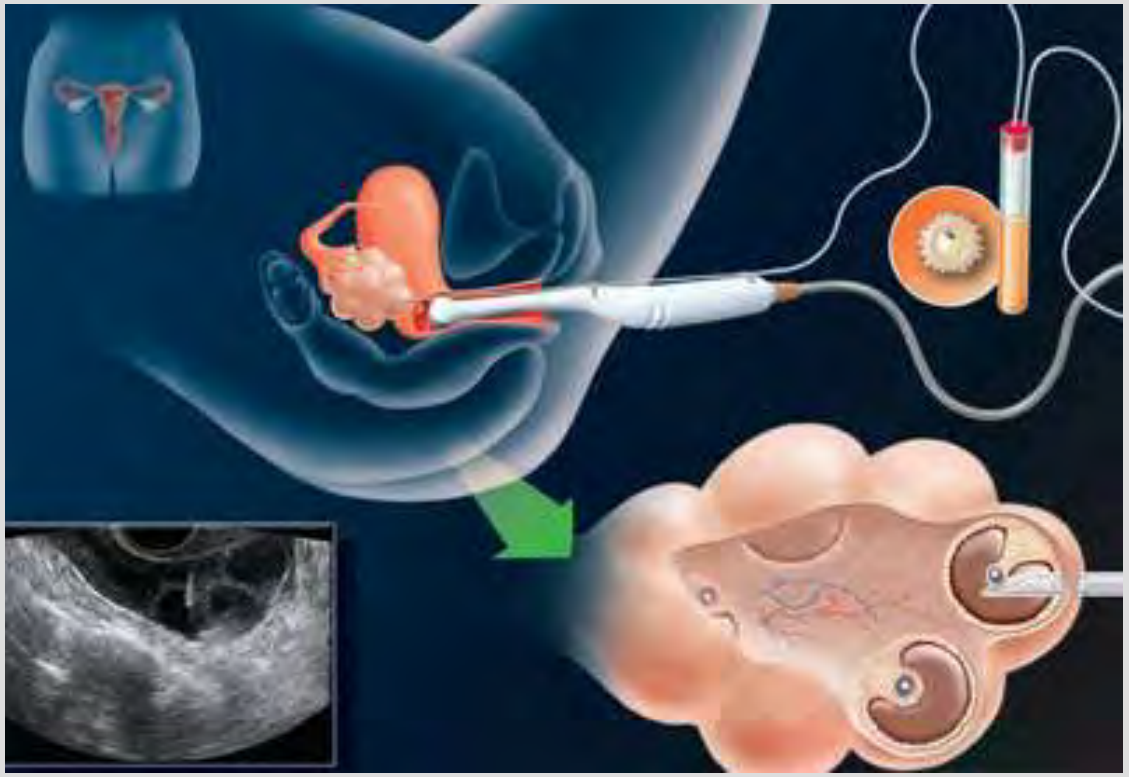
Heartland Center for Reproductive Medicine

IVF AND EGG/EMBRYO FREEZING

- Injectable medications for 10-14 days to stimulate ovaries
  - Overlap with letrozole to reduce estradiol levels
- Medication to prevent premature ovulation
- US monitoring Q2-4 days
- HCG triggers ovulation ~36 hours before egg retrieval
- Genetic testing of embryos (PGT) optional

EGG RETRIEVAL

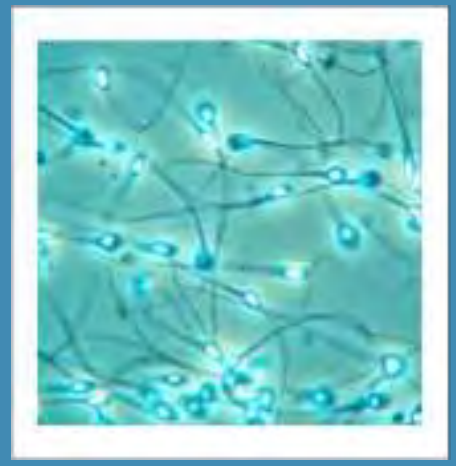
- Retrieval done under conscious sedation with vaginal ultrasound and needle guide
- Know immediately # of eggs
- Find out how many eggs successfully fertilized the following day
- 5-7 days to blastocyst



THIRD PARTY REPRODUCTION

- Donor Eggs
- Donor Embryos
- Donor Sperm
- Gestational Carrier
- Adoption

FERTILITY CONSIDERATIONS IN TRANSFEMININE PATIENTS



HISTOLOGIC DATA

- Estradiol exposure leads to
  - Smaller seminiferous tubules
  - Abnormal appearance of Sertoli and Leydig cells
  - Fatty degeneration of connective tissue
  - Impaired spermatogenesis (maturation arrest)
    - Regardless of anti-androgen use
    - Stage of maturation arrest and azoospermia incidence differed among studies

Heartland Center for Reproductive Medicine

Levy M et al. *Sci Rep* 2017; Matoso A et al. *Hum Pathol* 2018
Kent MA et al. *Urology* 2018

EFFECT OF ESTRADIOL ON SEMEN ANALYSIS

- Studies examining semen parameters both on estradiol and after discontinuation
- Patients on estradiol – substantially worsened parameters, but sperm still present
- Extremely variable histology
- Level of gonadotropin suppression did not necessarily reflect degree of spermatogenesis
- Bottom line: Fertility Preservation is possible although may not get same level of results

Schneider et al. *J Sex Med* 2015; Adeleye et al. *Fertil Steril* 2018.

TRANSGENDER WOMEN NOT ON ESTRADIOL

- Increased incidence abnormal semen parameters
  - Count
  - Motility
  - Morphology

- Pathophysiology unknown

Heartland Center for Reproductive Medicine

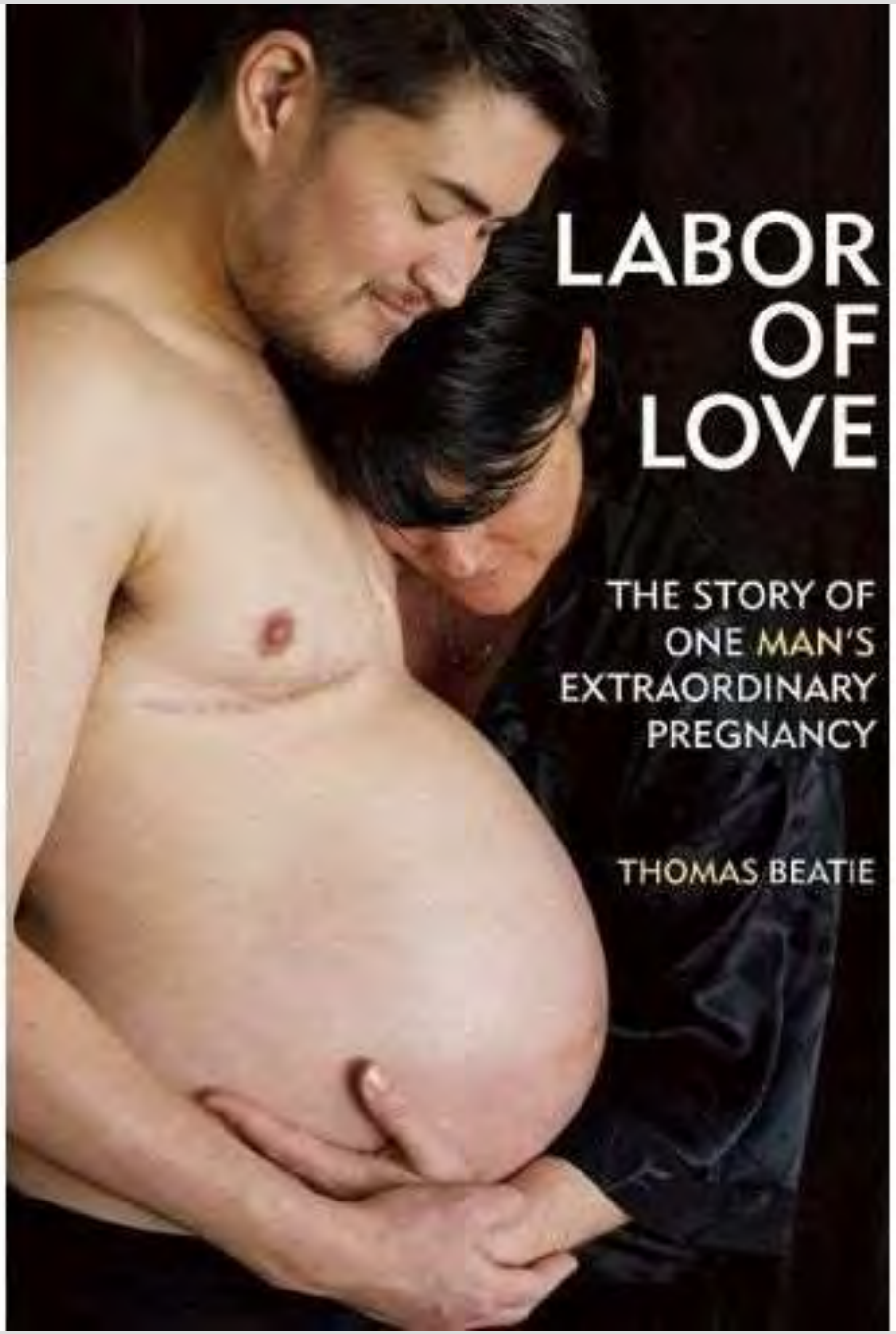
Hamada A et al. *Andrologia* 2015
Li K et al. *Andrology* 2018
Rodriguez-Wallberg K, *Andrology,* 2021

FERTILITY PRESERVATION OPTIONS

- Sperm cryopreservation
  - Can do trial semen analysis in patients on hormone therapy – if azoospermic, try again after at least 3 months off hormone therapy
- Isolation of sperm at time of gender-affirming surgery
- Testicular tissue cryopreservation
  - NO DATA
  - Not currently available in Nebraska
    - Denver (CU) and Kansas City (KU) = closest options

FERTILITY CONSIDERATIONS IN TRANSMASCULINE PATIENTS

POPULAR PRESS



Study on Pregnancy in Transgender Men

- Cross-sectional survey of 41 trans men who had a live birth, mean age 28 yo
- 84% of subjects on T before pregnancy used own eggs
- 32% conceived on T
- No difference in perinatal complications in those previously on T vs not

Table 2. Findings Among Those Who Used Testosterone Before Pregnancy of Report (n=25)

Characteristic	Value
Age (y) when testosterone was initiated	25 (17–35)
Length of testosterone use before pregnancy (y)	
Less than 1	10 (40)
1–2	6 (24)
3–10	4 (16)
More than 10	5 (20)
Stopped taking testosterone to become pregnant	17 (68)
Duration between stopping testosterone and resumption of menses (mo)	
No menses before pregnancy	5 (20)
Less than 1	2 (8)
1	6 (24)
2	7 (28)
3	4 (16)
4–6	1 (4)
Resumed or initiated testosterone after pregnancy*	20 (48)

Data are median (range) or n (%).
* Of total respondents in the study (N=41).

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/con

Original research article

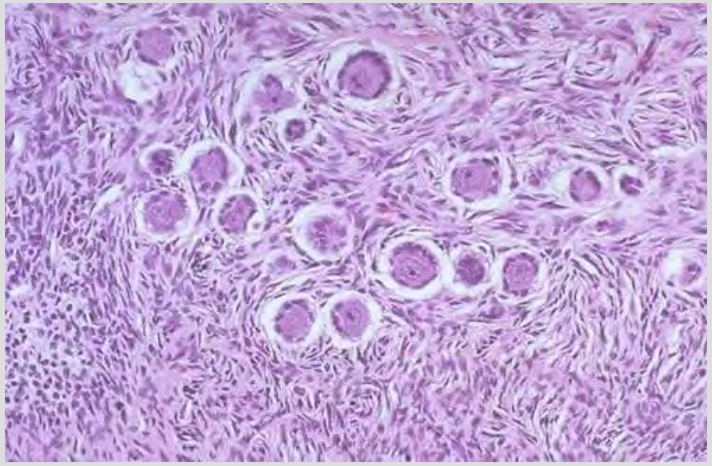
Family planning and contraception use in transgender men☆,☆☆

Alexis Light [a,*], Lin-Fan Wang [b], Alexander Zeymo [c], Veronica Gomez-Lobo [a,d]

- 197 transgender men
- 60 pregnancies among 32 respondents
  - 10 after stopping T, 1 while on T irregularly, Most had never taken T
  - Those who had never taken T were nearly 3x more likely to have been pregnant than those who had taken T (36% vs 13.8)
- 51% reported that their healthcare providers had not asked about their fertility desires

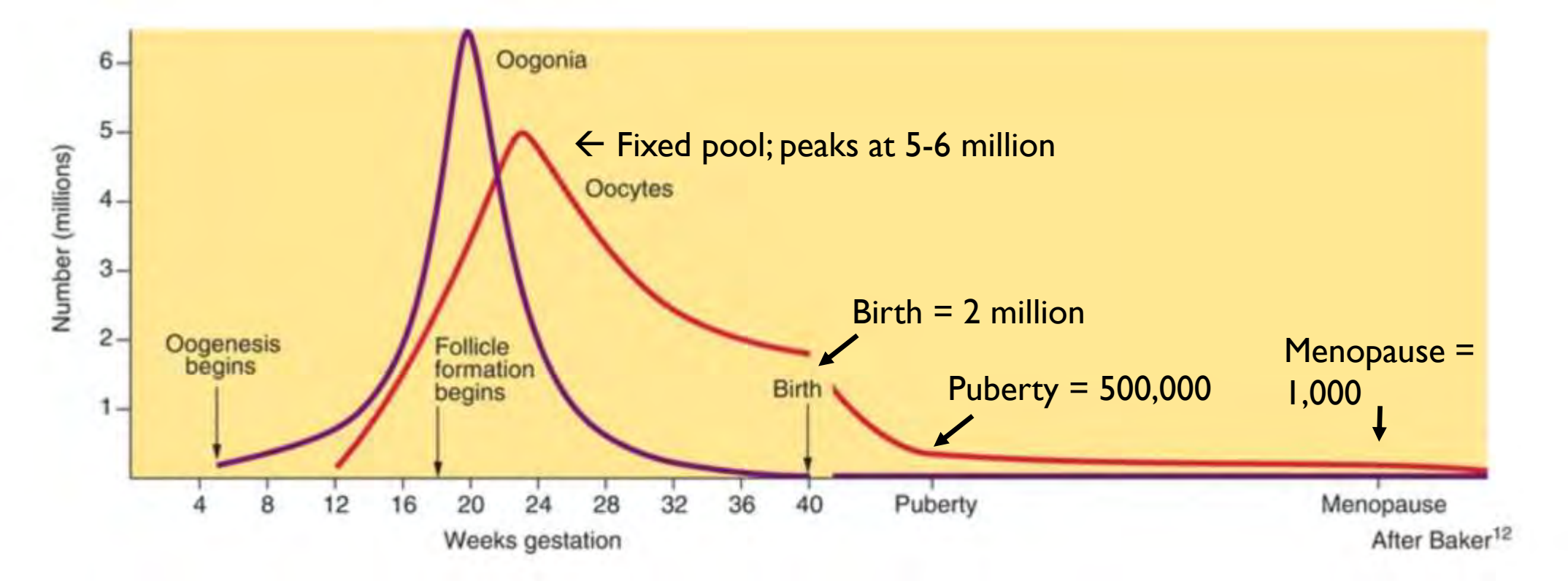
EFFECTS OF TESTOSTERONE ON THE OVARY

- Studies performed at the time of gender-affirming oophorectomy
- Some studies show polycystic ovarian morphology while others show no difference
- Small case series, short T exposure (mean 12-37 months)



Futterweit et al., 1986
Spinder, et al., 1989
Pache et al. 1991
Van den Broeke et al., 2001
Ikeda et al. 2013
Loverro et al. 2016
De Roo et al., 2017

OVARIAN RESERVE (EGG NUMBER)



Modified from: Speroff. Clinical Gynecologic Endocrinology and Infertility. 9th edition

EFFECTS OF TESTOSTERONE ON OVARIAN RESERVE

Caanen et al:

- Measured AMH in 22 trans men (mean 22.4 yo)
- Participants also on GnRHa and AI
- Significant suppression of AMH after 16 weeks vs baseline
  - 4.4 vs 1.4 ng/ml (<0.001)

Tack et al:

- 38 transgender adolescents
- All participants on an androgenic progestin, then added T
- No change in AMH at baseline, 6 months, or 12 months (increased)

Heartland Center for Reproductive Medicine

Caanen MR, et al. *Fertil Steril* 2015
Tack LJW et al. *Biol Sex Differ* 2016

OVARIAN STIMULATION: SPECIAL CONSIDERATIONS

- Cessation of Testosterone – likely to increase dysphoria
  - Some think T should be stopped ~3 months
  - Others think T should be stopped just before
  - Could you maintain T during stimulation???
- Aromatase inhibitors can be used to minimize Estradiol elevations; Progesin IUD can be left in place
- Vaginal exams can be very distressing and T treatment may lead to vaginal atrophy
  - Can do trans-abdominal or trans-rectal ultrasounds or use pediatric US probes
- FDA lab testing

ASSISTED REPRODUCTIVE TECHNOLOGY (ART) OUTCOMES

- Limited to small case series with promising oocyte and embryo cryopreservation results
- No ability to assess long-term outcomes for patients or offspring

Study	Design	Result
Leung 2019	N=26 transmen (16 with prior T)	Transmen with prior T had **no difference in oocyte number or maturity** but **higher med doses needed for oocyte stimulation**
Adeleye 2019	N=13 transmen (7 with prior T) vs BMI-matched cisgender controls	Transmen with prior T had **fewer total oocytes but no difference in mature oocytes** compared to no prior T
Amir 2020	N=12 transmen (6 with prior T) vs cisgender controls	**No difference in oocyte number or maturity**
Stark 2022	Case Study: 2 transmen undergoing IVF while on active T treatment	**Stimulation on T is feasible**: 30 and 9 mature oocytes retrieved respectively
Moravek 2023	Case Study: 2 transmen undergoing IVF while on active T treatment	**Stimulation on T is feasible with development to blastocyst**: 2 blastocysts and 8 blastocysts respectively

SE REPORTS:
ERTILITY PRESERVATION

- 4 mature oocytes cryopreserved

Rothenberg et. al, *NEJM*, 2019

- 15 yo transmasculine adolescent on puberty blocker since age 12
- Puberty blocker implant removed prior to stimulation
- 12 day stimulation with simultaneous aromatase inhibitor administration
- 22 mature oocytes cryopreserved

Martin et. al, *Fertil Steril*, 2021

OVARIAN TISSUE CRYOPRESERVATION

- No longer considered experimental
- Could be performed at time of gender-affirming oophorectomy
  - Does not require hormonal stimulation
- Provider/patient must be ok with relatively little data on both OTC and the effect of T on the ovaries
- Not currently available in Nebraska
  - Denver (CU) and Kansas City (KU) = closest options

QUALITATIVE EXPERIENCES OF FERTILITY PRESERVATION

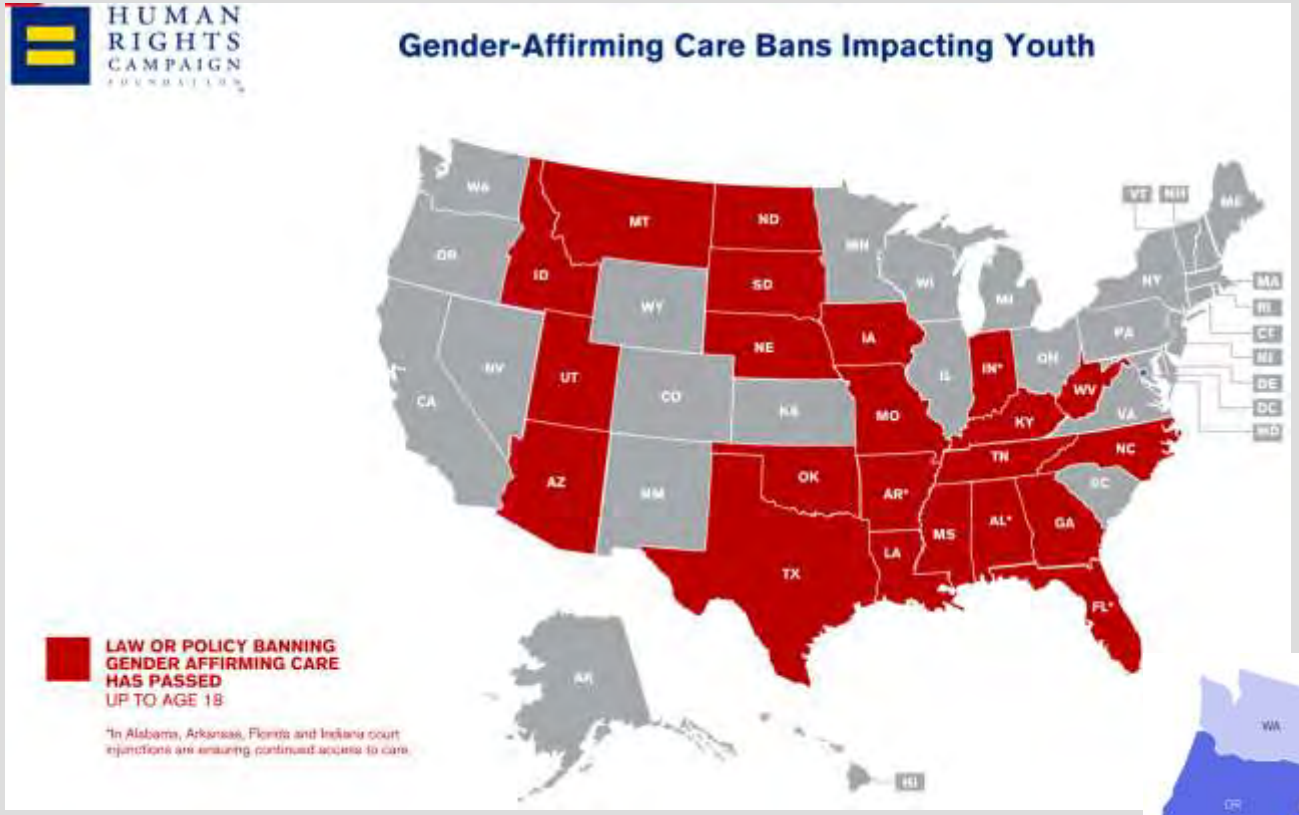
- 15 adult trans men who had completed oocyte cryopreservation
  - 7 had started Testosterone prior
  - Majority found resumption of menses and increased estradiol levels to be psychologically distressing
  - Regret and medical outcomes not assessed
- Trans adolescents report process is emotionally and physically demanding even if
  - Strongly desire fertility presesrvation
  - Had time to mentally prepare
  - Report satisfactory experience

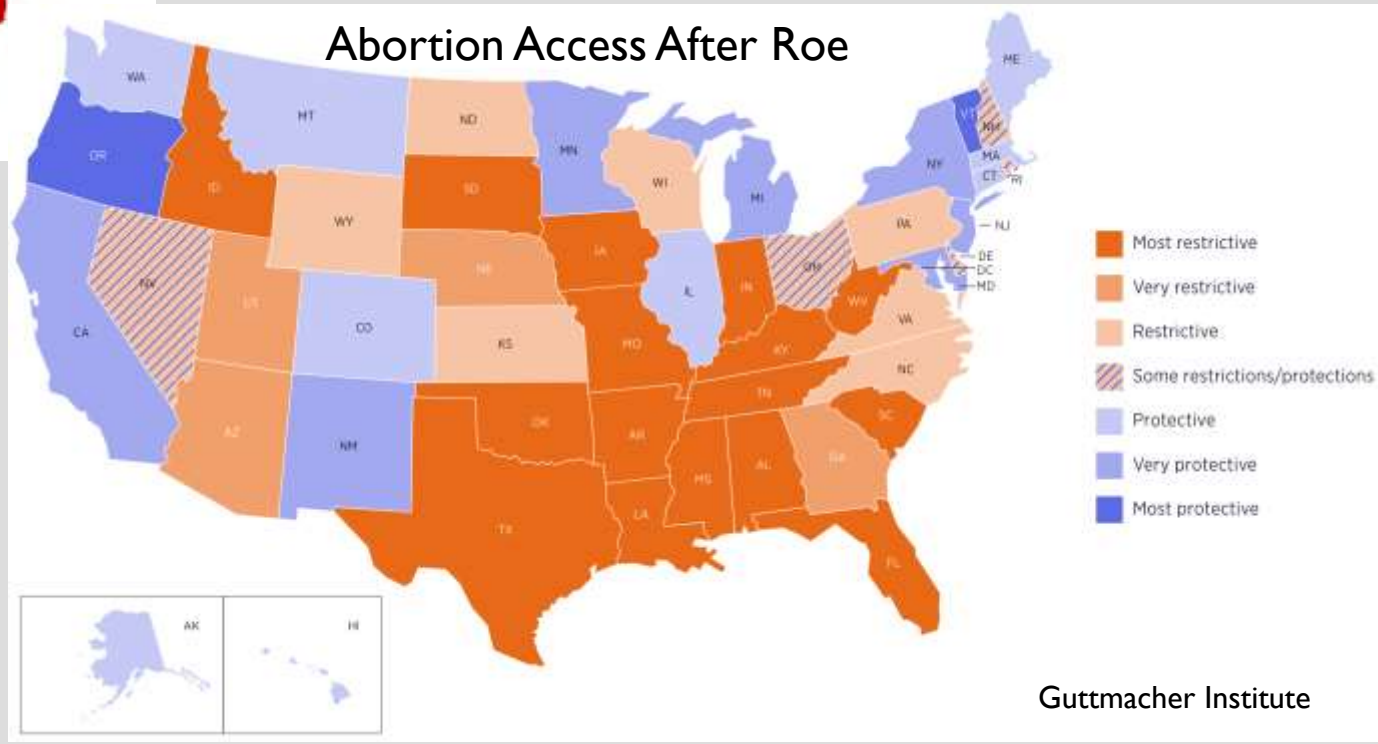
Armuand G, et al. *Hum Reprod* 2017
Chen & Simons. *Clin Pract Pediatr Psychol 2018*

LEGAL CONSIDERATIONS

- Partners have equal legal rights over embryos
- Nebraska: married partners have equal legal rights over unfertilized eggs and sperm too!
- Nebraska: Gestational Carrier goes on the birth certificate as the "mother"
  - Intended parent(s) must go through adoption process even if they are biologically related

Heartland Center
for Reproductive Medicine


HUMAN RIGHTS CAMPAIGN FOUNDATION
Gender-Affirming Care Bans Impacting Youth
LAW OR POLICY BANNING GENDER AFFIRMING CARE HAS PASSED
UP TO AGE 18
*In Alabama, Arkansas, Florida and Indiana court injunctions are ensuring continued access to care.


Abortion Access After Roe
Most restrictive
Very restrictive
Restrictive
Some restrictions/protections
Protective
Very protective
Most protective
Guttmacher Institute

CAMPAIGN FOR A HEALTHY Nebraska

FAQs TV Ads In The News

Donate

THANK YOU!

Email: econstancemd@gmail.com