

Fertility in 2020: Undescended Testis

Kate H. Kraft, MD, FAAP, FACS
September 28, 2019



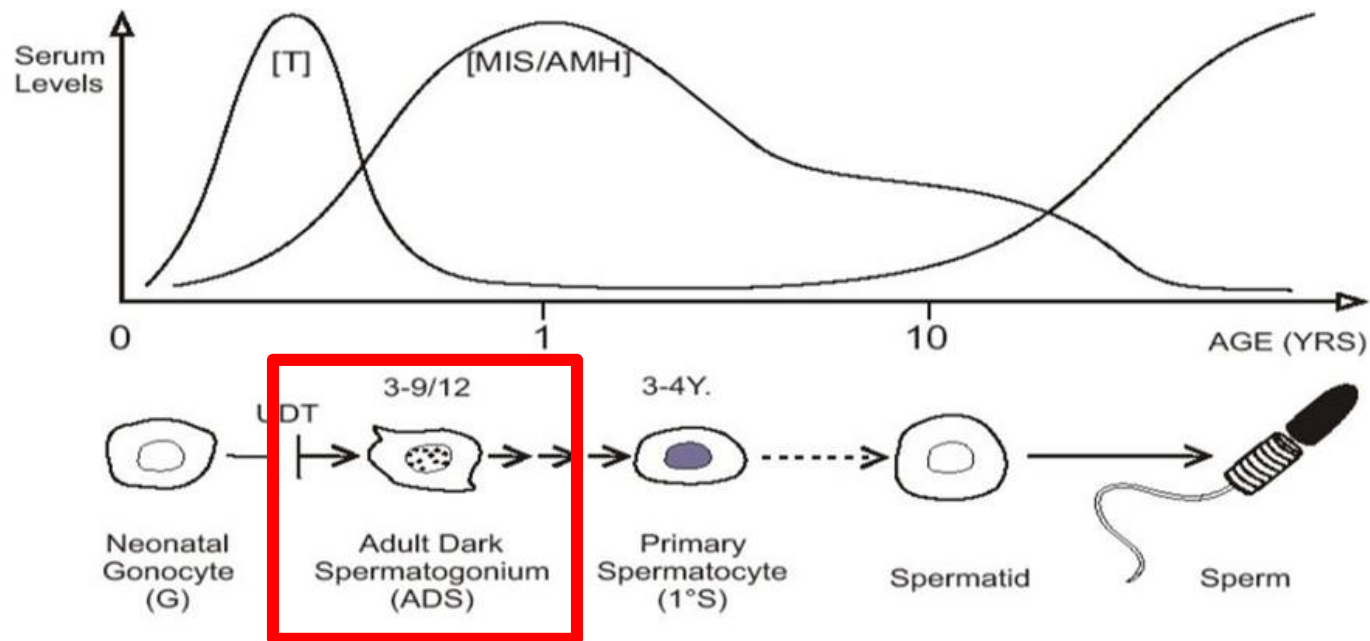
Overview

- AUA Guidelines
- Semen analysis and paternity data
- Hormonal therapy
- Cryopreservation and other future directions



Undescended Testis

- 1-3% full-term male neonates
- ~30% preterm male neonates
- Histopathology – Ad spermatogonia counts



AUA Guidelines – Cryptorchidism (2014)

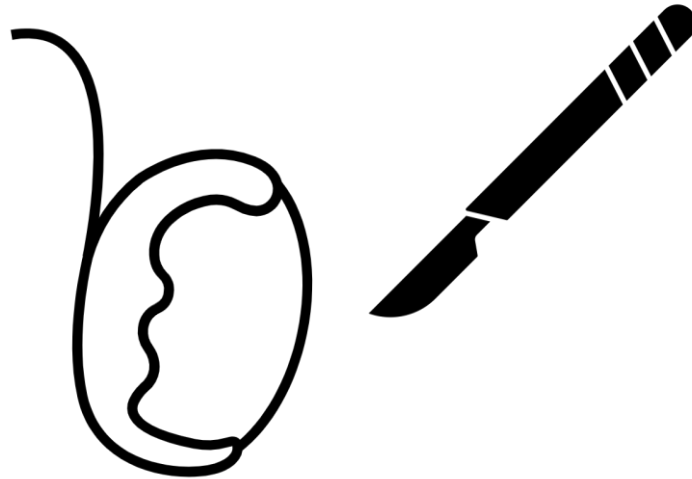
- Diagnose at 6 months
- Orchiopexy within the next year



Kolon TF et al. J Urol 2014; 192: 337.

AUA Guidelines – Cryptorchidism (2014)

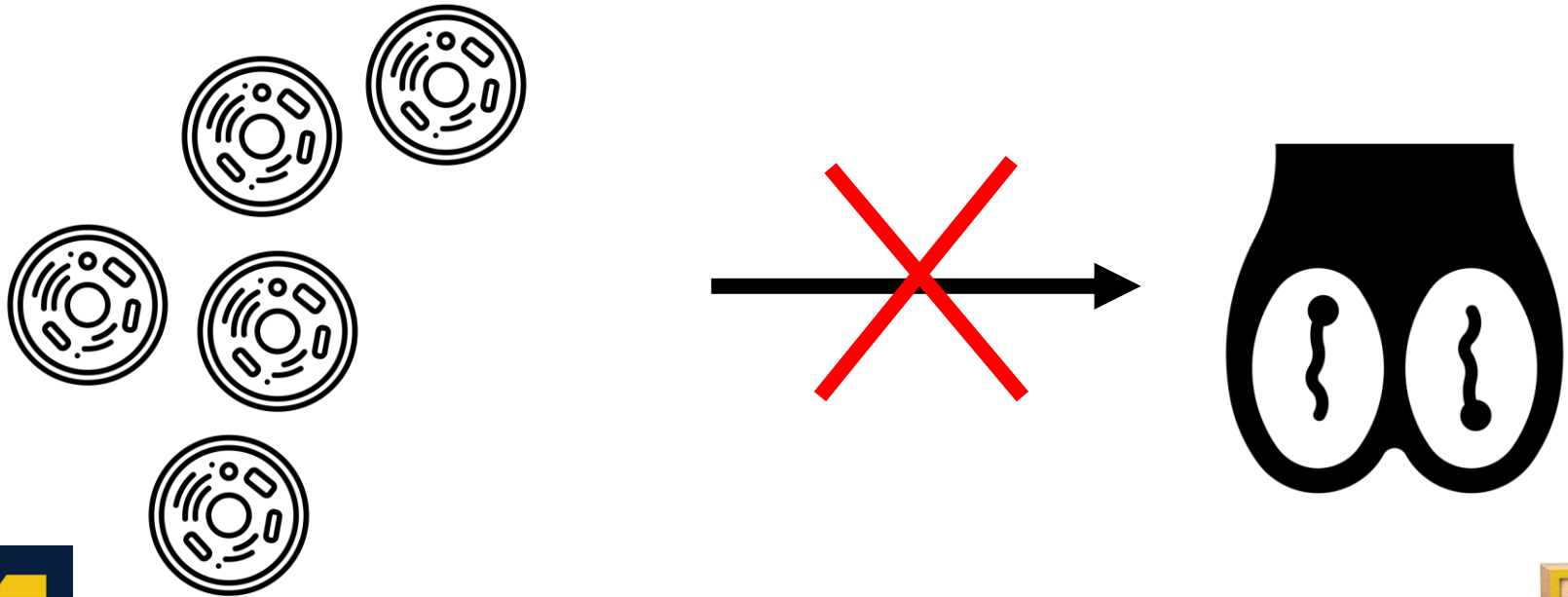
- Orchiopexy within first 18 months → preserve fertility
- 25% cryptorchid boys born with reduced GCs
- After 15-18 mos, some lack GCs
 - No GCs on biopsy increases to ~40% in BUDT at 8-11 years



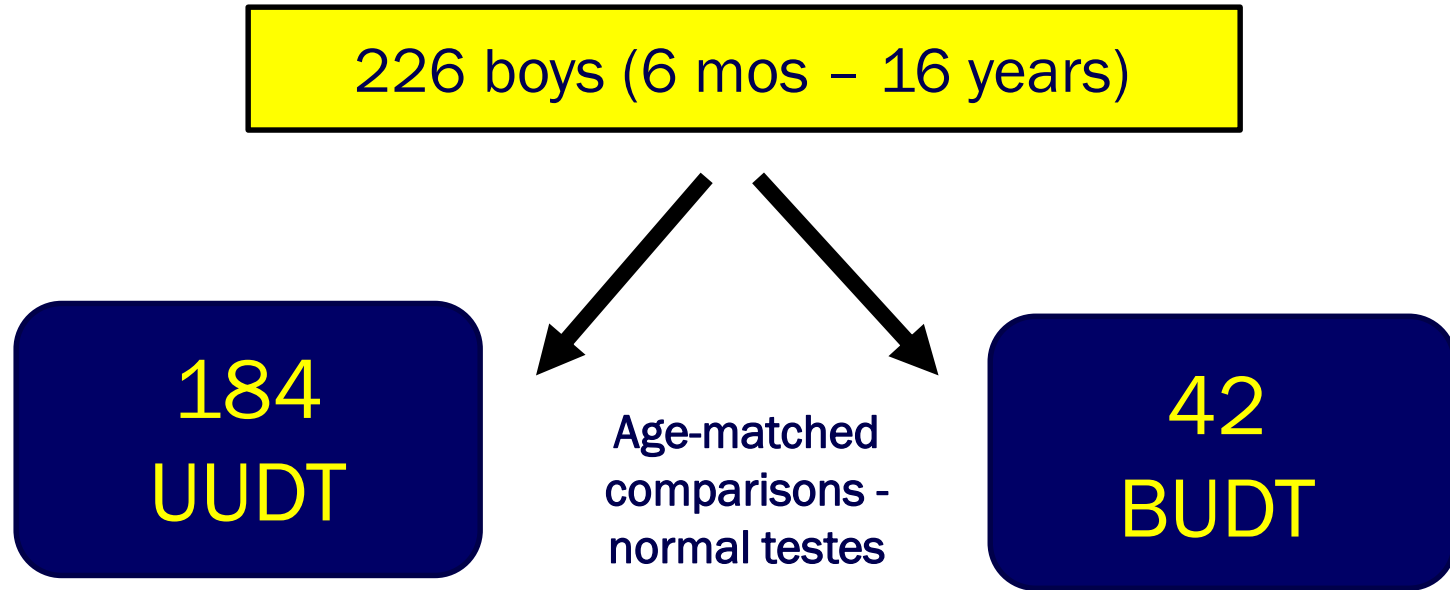
Cortes D et al. J Urol 1995; 154: 1188.
Cortes D et al. Horm Res 2001; 55: 21.

AUA Guidelines – Cryptorchidism (2014)

- # GCs remains low, does not increase with age
- Testes that remain undescended → loss of GCs and Leydig cells
- After 2 years → thermal effects



AUA Guidelines – Cryptorchidism (2014)



- No significant difference in fertility index of patients **<1 year old**
- Fertility index differences statistically significant in all other age groups

AUA Guidelines – Cryptorchidism (2014)

Systematic review

BJS Open

Open Access

Systematic review and meta-analysis comparing outcomes following orchidopexy for cryptorchidism before or after 1 year of age

B. S. R. Allin^{1,3}, E. Dumann², D. Fawkner-Corbett³, C. Kwok³, C. Skerritt⁴, on behalf of the Paediatric Surgery Trainees Research Network

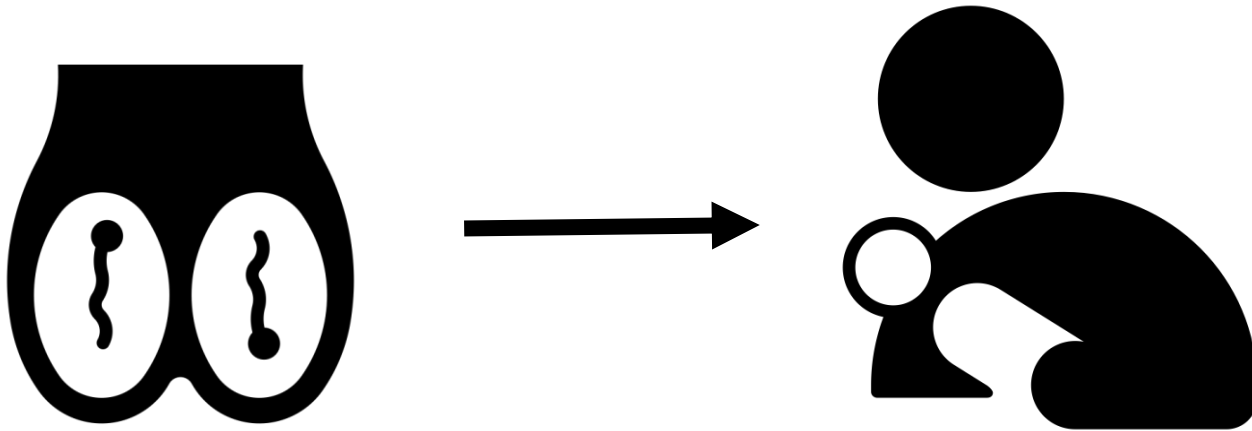
- Systematic reviews/meta-analyses support orchiopexy at 6-12 months for improved fertility

Paternity

- BUDT <<<< UUDT
 - Controls – 94%
 - BUDT – 62%
 - UUDT – 89.5%

Time to pregnancy:

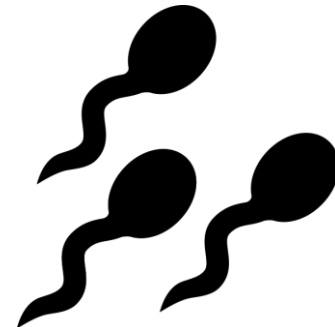
BUDT → 33.9 mos
UUDT/controls → 11.1 mos



Lee PA, et al. Pediatrics 1996; 98: 676.
Lee PA and Coughlin MT. J Urol 2002; 168: 1680.
Lee PA et al. J Urol 2000; 164: 1697.

Semen Analysis

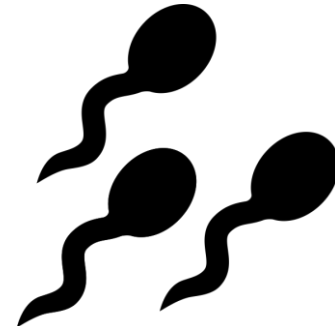
- 91 UUDT, 19 BUDT
- Bilateral testis biopsy in childhood → TGC/T and Ad/T
- SA parameters and hormonal evaluation in adulthood
- Total GC count at orchiopexy is not associated with significant changes in hormones or semen analysis in adulthood (UUDT or BUDT)



Kraft KH et al. J Urol 2012;188: 1429.

Semen Analysis

- In UUDT, low Ad count is associated with lower sperm count and sperm density, but even the lower sperm counts are above WHO standard
- In BUDT, low Ad count at orchiopexy is associated with abnormal FSH and SA results in adulthood
- Testis biopsy at orchidopexy may have limited use in UUDT and may be more clinically useful BUDT



Kraft KH et al. J Urol 2012;188: 1429.

AUA Guidelines – Cryptorchidism (2014)

Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk.
(Clinical Principle)

Assisted Reproductive Technology

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TESTICULAR SPERM EXTRACTION WITH INTRACYTOPLASMIC SPERM INJECTION IS SUCCESSFUL FOR THE TREATMENT OF NONOBSTRUCTIVE AZOOSPERMIA ASSOCIATED WITH CRYPTORCHIDISM

JAY D. RAMAN AND PETER N. SCHLEGEL*

From the James Buchanan Brady Urology Foundation, Department of Urology, Center for Male Reproductive Medicine and Microsurgery, New York Presbyterian Hospital, Weill Medical College of Cornell University (JDR, PNS) and The Population Council, Center for Biomedical Research (PNS), New York, New York



Hormonal Therapy after Orchiopexy

Meta-analysis: 10 studies

UDT +
GnRH



GC/T

UDT – no
hormone



GC/T

>>>

RR 2.86

Hormonal Therapy after Orchiopexy

Selecting Infants With Cryptorchidism and High Risk of Infertility for Optional Adjuvant Hormonal Therapy and Cryopreservation of Germ Cells: Experience From a Pilot Study

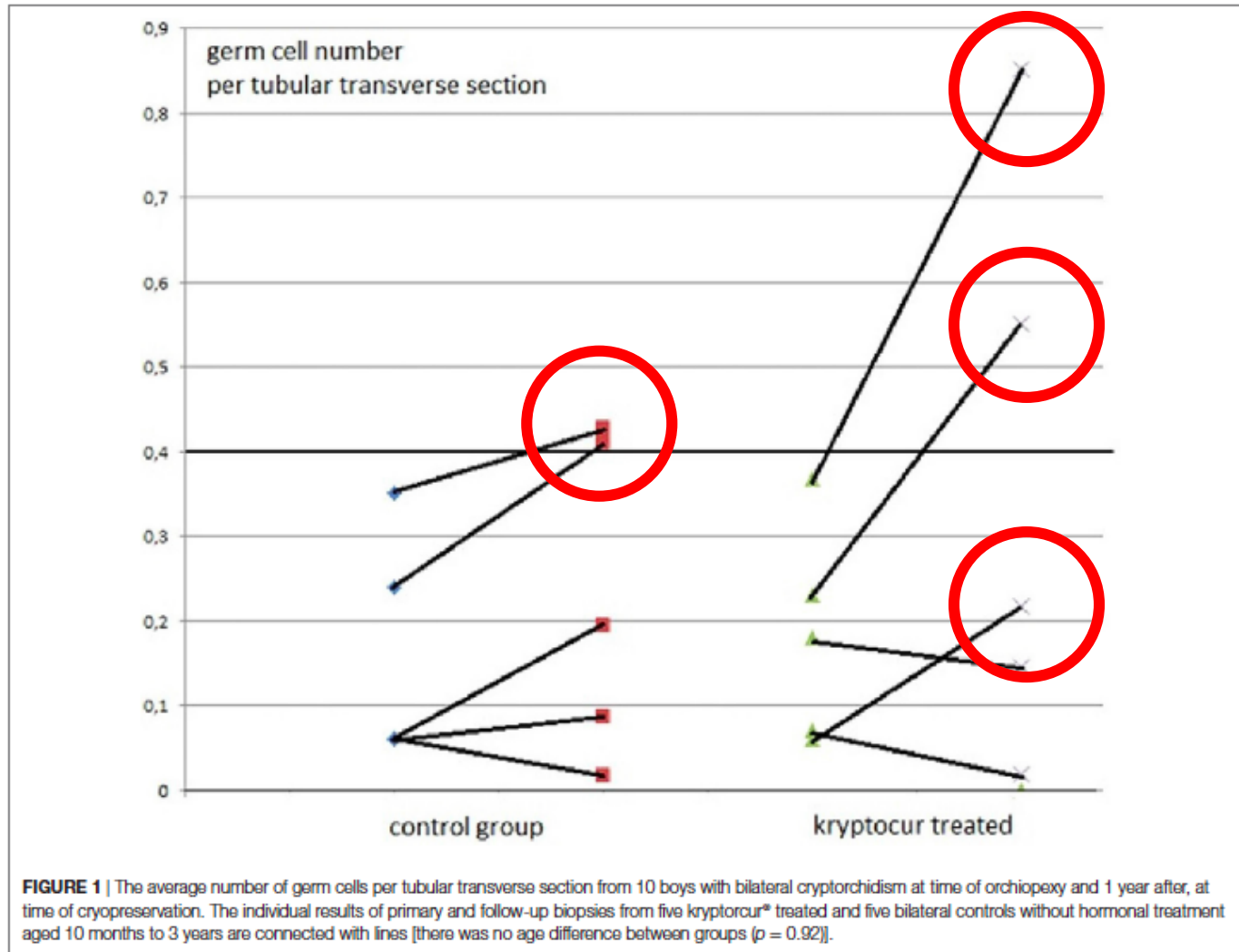


ORIGINAL RESEARCH
published: 05 June 2018
doi: 10.3389/fendo.2018.00299

Jorgen Thorup^{1,2*}, Erik Clasen-Linde³, Lihua Dong⁴, Simone Hildorf¹,
Stine Gry Kristensen⁴, Claus Yding Andersen^{2,4} and Dina Cortes^{2,5*}

- 17 boys with BUDT (7 mos – 3 ½ years)
- Normal FSH, decreased GC/T
- 5 had adjuvant LHRH, compared to controls
- 12 mos after o'pexy → repeat biopsy and cryopreservation

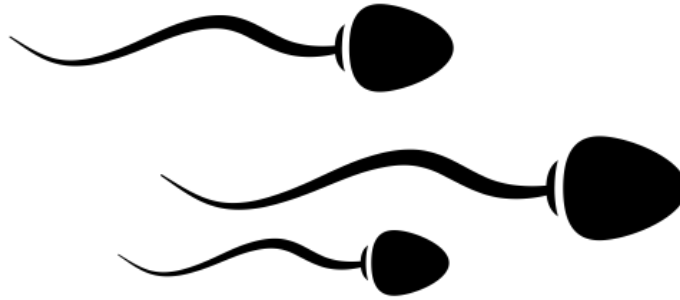
Hormonal Therapy after Orchiopexy



Cryopreservation

When to
freeze?

How many
samples?



Viability of
sperm in
the
future?

SSC Transplantation

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 11303–11307, November 1994
Developmental Biology

Germline transmission of donor haplotype following spermatogonial transplantation

(testis/stem cells/spermatogenesis/transgenic mice/fertility)

RALPH L. BRINSTER* AND MARY R. AVARBOCK

Laboratory of Reproductive Physiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104

Contributed by Ralph L. Brinster, August 18, 1994



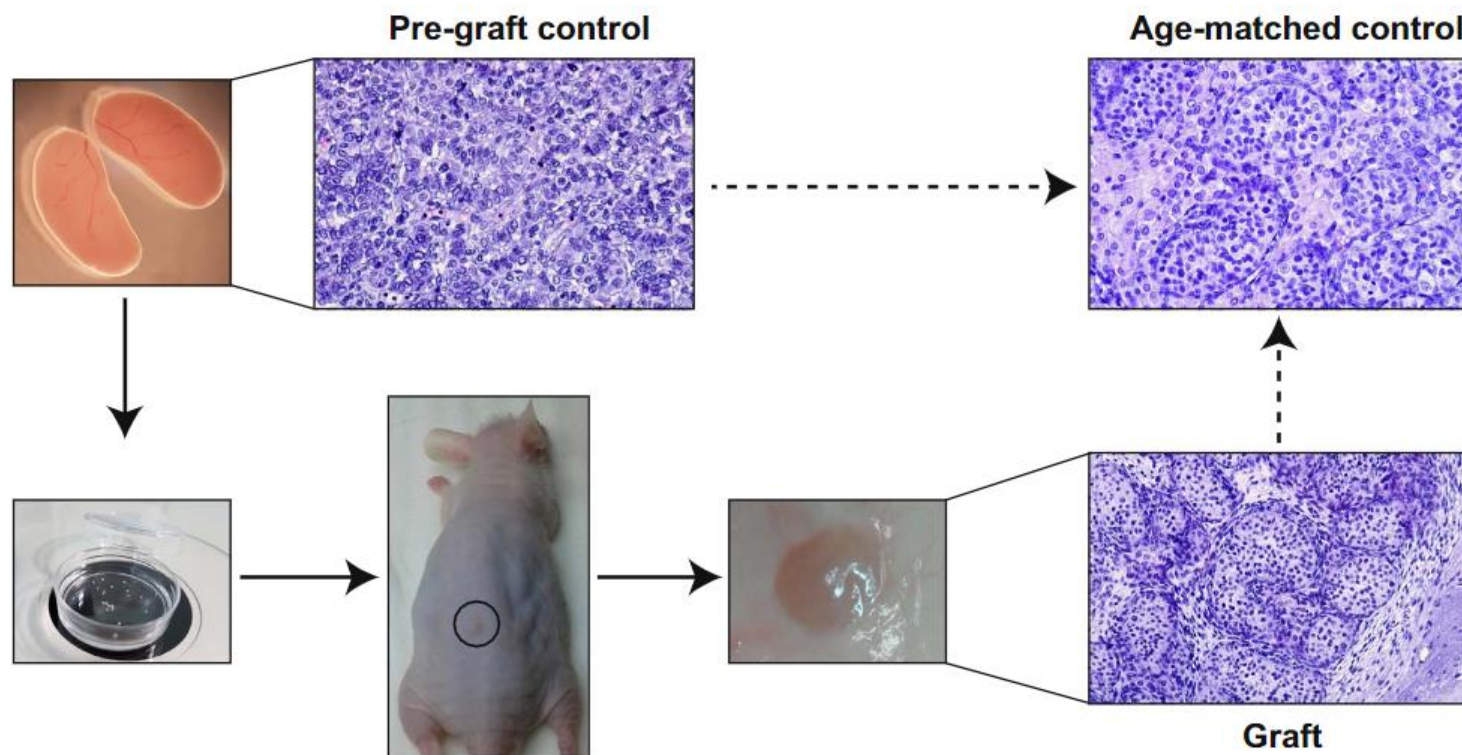


Fig. 1. Human fetal testis (HFT) transplantation as a model of testicular development. First trimester HFT (obtained from elective terminations) are cut into small pieces. A few fragments are fixed as reference histological samples (pre-graft control) to evaluate graft development at baseline (note: no seminiferous cord formation) and the remainder transplanted under the back skin of castrated immunodeficient mice. HFT grafts increase in volume and undergo subsequent development, including seminiferous cord formation

Cryopreservation

Current State	Gaps in Knowledge	Future Work
<ul style="list-style-type: none">• UDT pts at risk for infertility• Feasible procedure• Complications rare• Limited studies using prepubertal tissues	<ul style="list-style-type: none">• Impact of pre-existing pathology• Availability of testicular cryopreservation program• Long-term impact on testis function• Lack of studies using prepubertal tissues	<ul style="list-style-type: none">• Increased access to clinical research programs• Determine optimal transport and storage conditions for prepubertal tissues• Long-term follow up of patients including fertility outcomes

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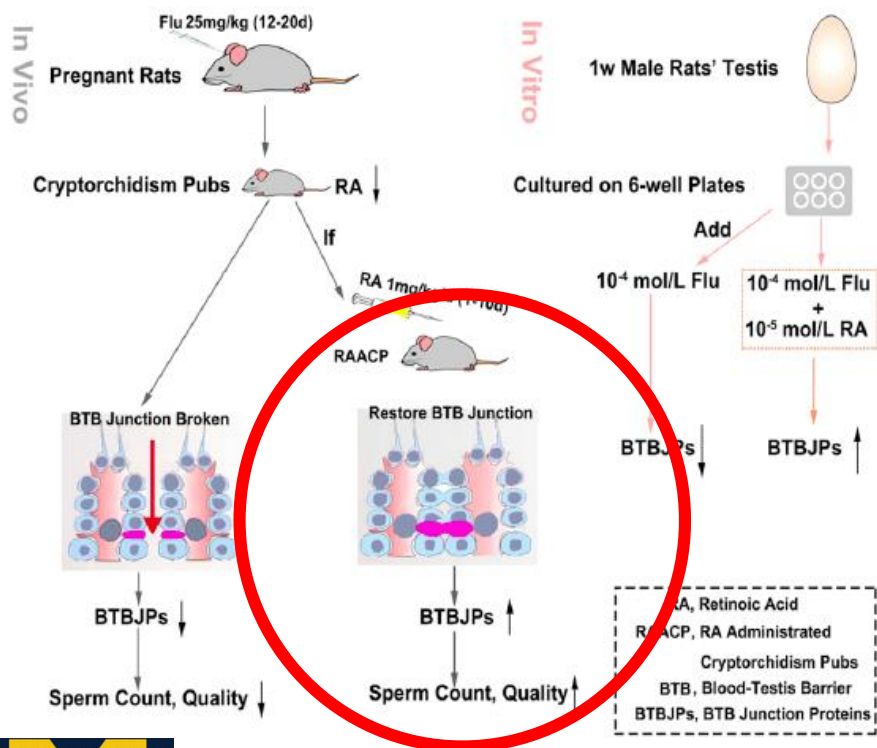
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Retinoic acid: A potential therapeutic agent for cryptorchidism infertility based on investigation of flutamide-induced cryptorchid rats *in vivo* and *in vitro*

Zhou Yu^{a,b,d}, Zhang Deying^{a,b,c,d,*}, Hu Dong^{a,b}, Liu Bo^{a,b,d}, Peng Jinpu^e, Shen Lianju^{a,b,c}, Long Chunlan^{a,b,c}, Yu Yihang^{a,b}, Zhang Yuanyuan^f, Liu Xing^{a,b,c,d}, Tao Xu^g, Timashev Peter^h, Lin Tao^{a,b,c,d}, He Dawei^{a,b,c,d}, Wei Guanghui^{a,b,c,d,*}



- RA concentration lower in cryptorchid rat pups
- Histology approached normal in cryptorchid rats receiving RA

Summary

- Orchiopexy within first 18 months → preserve fertility
- Testes that remain undescended → loss of GCs and Leydig cells
- SA and paternity data are more favorable for UUDT but suggest reduced fertility in BUDT
- ART may need to be considered
- Role for cryopreservation in the future?
- Other therapies (e.g. hormonal tx, retinoic acid) need further investigation