Fertility Preservation in Pediatric and Adolescent Patients

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Objectives

- Describe what is fertility preservation and recognize when it would be needed
- Understand the options available for fertility preservation in both pediatric and adolescent males and females
- Recognize the process of each fertility preservation option
- Know how to contact the fertility preservation team

What is fertility preservation?

- Fertility preservation is the effort to help patients protect their eggs, sperm or reproductive tissue for future use.

Why is fertility preservation important?

- Fertility preservation should be a standard of care for all patients at risk for fertility complications in the future.
- Discussing fertility options can give the patient the chance to make decisions about their future for themselves, and not allow their disease/treatment to decide for them.
- Modern medicine means patients are experiencing a significant increase in overall survival. Fertility preservation is a key component to their comprehensive care when looking at their future and quality of life.

Who needs fertility preservation?

- Any child or adolescent who has been diagnosed with a medical condition that itself or the treatment of could affect their fertility
  - Patients receiving chemotherapy drugs to treat rheumatological disorders or cancer
  - Turner's syndrome
  - Radiation or a bone marrow transplant patients
  - Transgender patients receiving gender affirming hormones or surgery
- The goal is to identify any child at risk for loss of fertility and make sure they are well informed of their options prior to treatment

Background of program

2016 - First ovarian tissue preservation was completed

2017 - GYN APRN hired with goal to grow program

2018 - Self pay pricing was established for ovarian tissue

- First testicular preservation completed

2019 - Cerner order added

- First Turner Syndrome preservation completed

2020 - Started new research project and QI reports

- First Turner Syndrome patient covered by insurance

2021 - FTE for APRN approved and 0.2 nursing FTE in the works

Future goals - philanthropy, nurse navigator, low-risk consults, branching into other disciplines

Historical & Current Volumes

Type	FY17	FY18	FY19	FY20	FY21
Female Fertility					
Ovarian Tissue Preservation	3	2	2	12	15
Oocyte Preservation (Referrals to KU Only)				2	3
Male Fertility					
Testicular Tissue Preservation	0	1	1	3	1
Sperm Preservation – not currently tracked					
Total Consults	16	15	18	50	82

Requirements for a fertility preservation program

- Rapid access
- Interdisciplinary medical team and collaboration
- Laboratory experienced in assisted reproductive technology (ART)
- Counselors (various)
- Medical considerations

High Gonadotoxic Risk - Ovarian

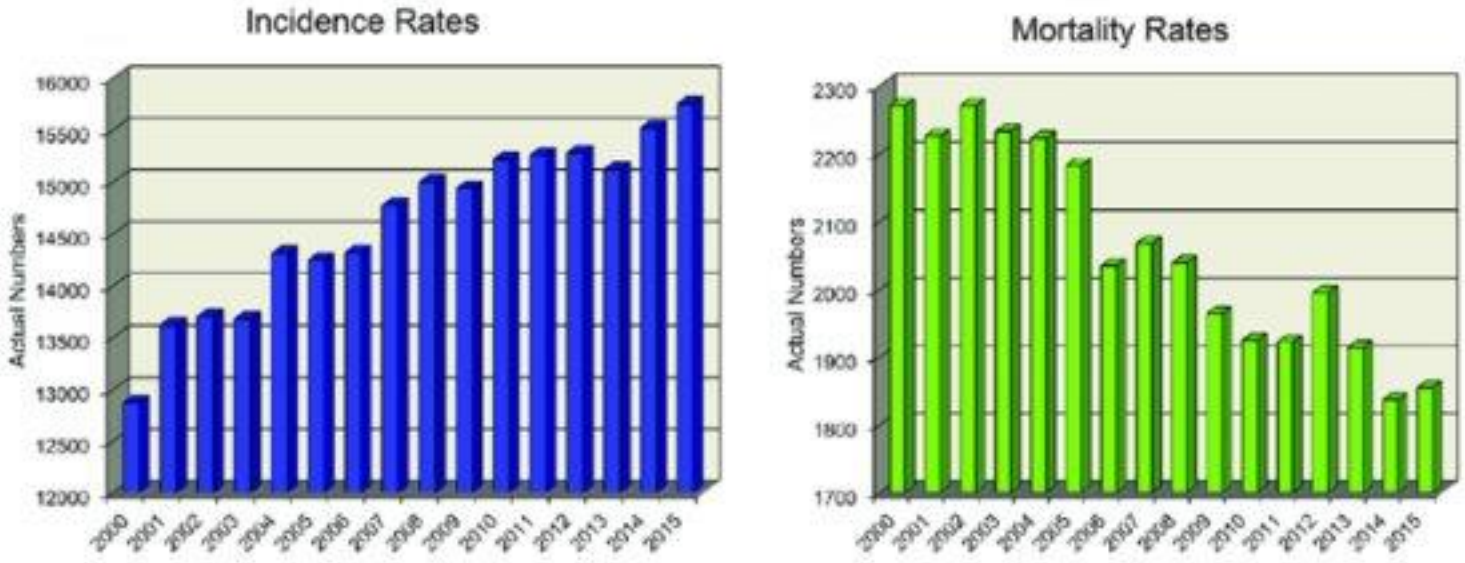
- Alkylating-intensive chemotherapy
  - any treatment regimen containing procarbazine
  - busulfan cumulative dose >600 mg/m2
  - cyclophosphamide equivalent dose (CED) ≥ 8000 mg/m2
  - alkylating chemotherapy conditioning prior to SCT
- Whole abdomen/pelvic irradiation to ovaries
  - ≥15 Gy pre-pubertal, >10 Gy post-pubertal, >6 Gy adult
- Whole abdomen/pelvic irradiation to uterus ≥30 Gy
- Total body irradiation and cranial radiation ≥30 Gy

High Gonadotoxic Risk - Testicular

- Total body irradiation
- Testicular radiation dose >6 Gy prepubertal
- Testicular radiation dose >2.5 Gy in post pubertal
- Alkylating-intensive chemotherapy
  - Any treatment regimen containing procarbazine
  - Alkylating chemotherapy conditioning prior to SCT
  - Cyclophosphamide equivalent dose (CED) > 7,500mg/m2

United States Incidence and Survival

- 1.8 million new cases in 2020
- 11,050 between ages 0 and 14 in 2020
- 5,899 between ages 15 and 19 in 2020
- ~84% SURVIVAL RATE!
- 500,000 childhood cancer survivors estimated by 2020



Childhood Cancer Incidence and Mortality Rates in the United States. Incidence and Mortality rates in childhood cancer in the US between 2000 and 2015, including all types of cancer between the ages of 0-19 years, both male and female patients of all races and ethnicities. The data provided for developing this figure was taken from The United States Cancer Statistics [1999-2015] at the Center for Disease Control and Prevention.

Clinical Health Outcomes Among Adults Treated for Childhood Cancer

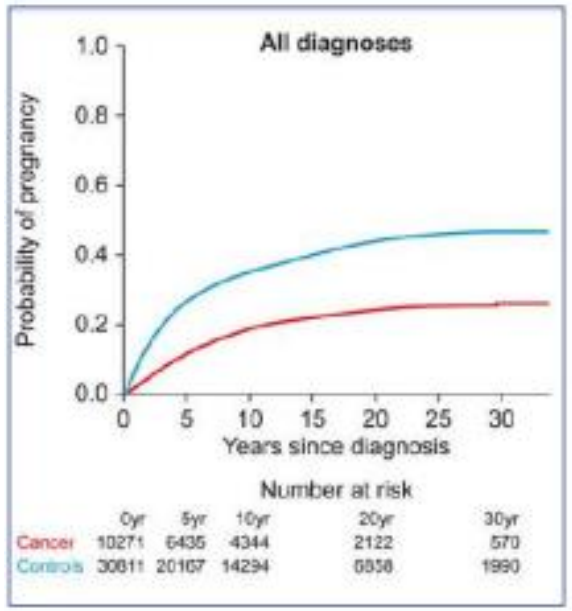
- Health outcomes in 1,713 survivors median age 32 yrs (18-60 yrs)
- Prevalence of primary ovarian failure 12% in at risk females
- Prevalence of male germ cell dysfunction 66%
- Prevalence of Leydig cell failure 12%

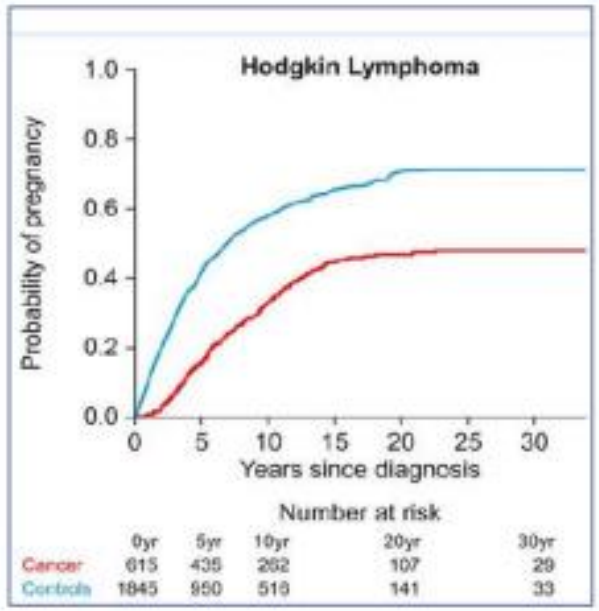
Prevalence of Endocrine/Reproductive Late Effects in At-Risk Populations Following Exposure-Based Screening

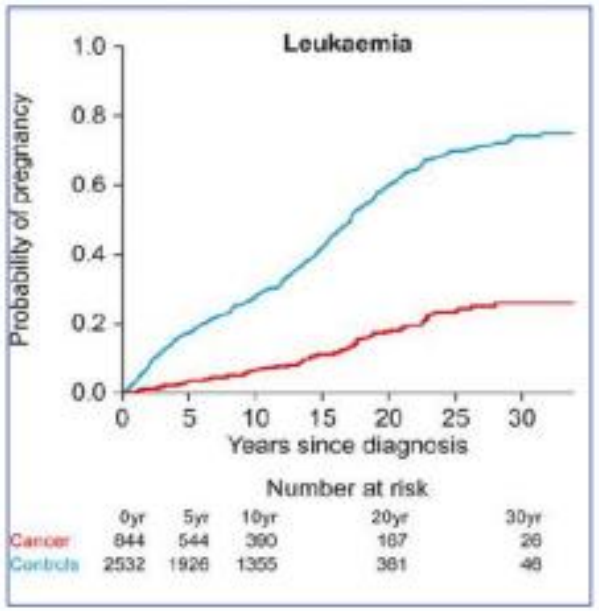
Potential Late Effect	Screening test	Exposure Status	Number at risk	Diagnosis before SJLIFE N	(%)	95% CI	Diagnosis related to SJLIFE N	(%)	95% CI	Diagnosis after SJLIFE N	(%)	95% CI	Overall Prevalence N	(%)	95% CI
Primary ovarian failure	Menstrual history, FSH, Estradiol	Alkylating agents Radiation to female reproductive system	553	44	(8.0)	[5.8-10.5]	20	(3.6)	[2.2-5.5]	1	(0.2)	[0.0-1.0]	65	(11.8)	[9.2-14.7]
Male germ cell dysfunction	Semen sample analysis	Alkylating agents Radiation to male reproductive system	328	9	(2.7)	[1.3-5.1]	209	(63.7)	[58.3-68.9]	0	(0.0)		218	(66.4)	[61.1-71.6]
Leydig cell failure	Morning testosterone, LH	Alkylating agents Radiation to male reproductive system	574	25	(4.4)	[2.8-6.4]	37	(6.4)	[4.6-8.8]	4	(0.7)	[0.2-1.8]	66	(11.5)	[9.0-14.4]

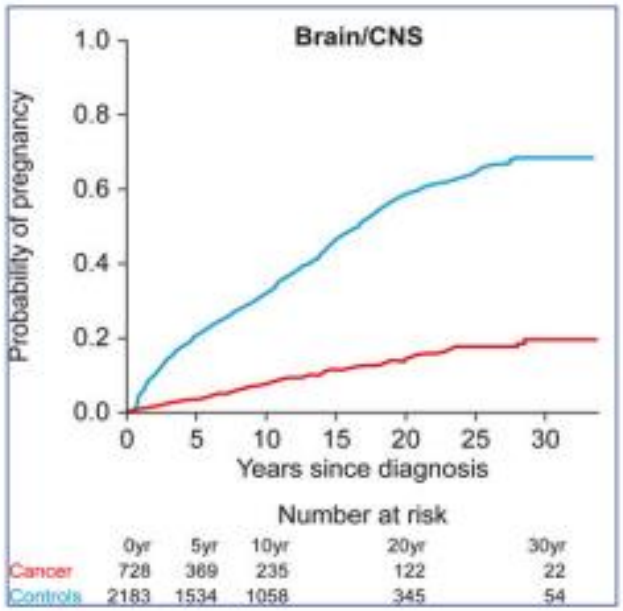
Hudson, et al. (2013)

Impact of cancer on chance of pregnancy









- Young adult survivors ages 18 – 39 years 38% less likely to conceive compared to controls

Anderson, et al. (2018)

Impact on chance of pregnancy cont'd

- Most bone marrow transplant patients will become infertile after treatment.
- Turner syndrome patients
  - 70–80% have no spontaneous pubertal development and 90% experience primary amenorrhea, however the remainder may have a small residual of ovarian follicles at birth or early childhood
- Transgender patients
  - Testosterone therapy effects on transgender men can suppress ovulation and alter ovarian histology, while estrogen therapy in transgender women can lead to impaired spermatogenesis and testicular atrophy

What should we as providers do?

- We should view each patient as unique and work to create a treatment plan individualized for each patient regardless of the patient's age, gender, culture, or socioeconomic status.
- We should assess each patient's risk of infertility based on their proposed treatment plan and/or diagnosis then discuss this with the patient and family.
- Consult the fertility team to meet with the family and the patient to discuss the patient's risk for infertility, as well as available preservation options based on that child's individual needs.

What are the options for preservation?

FEMALES

- **Egg (oocyte) cryo** – only available if post-pubertal
- **Ovarian tissue cryo** – any age
- **Embryo freezing** – must be old enough for egg harvesting and have a partner to donate sperm
- **Ovarian transposition**
- **Ovarian shielding**

MALES

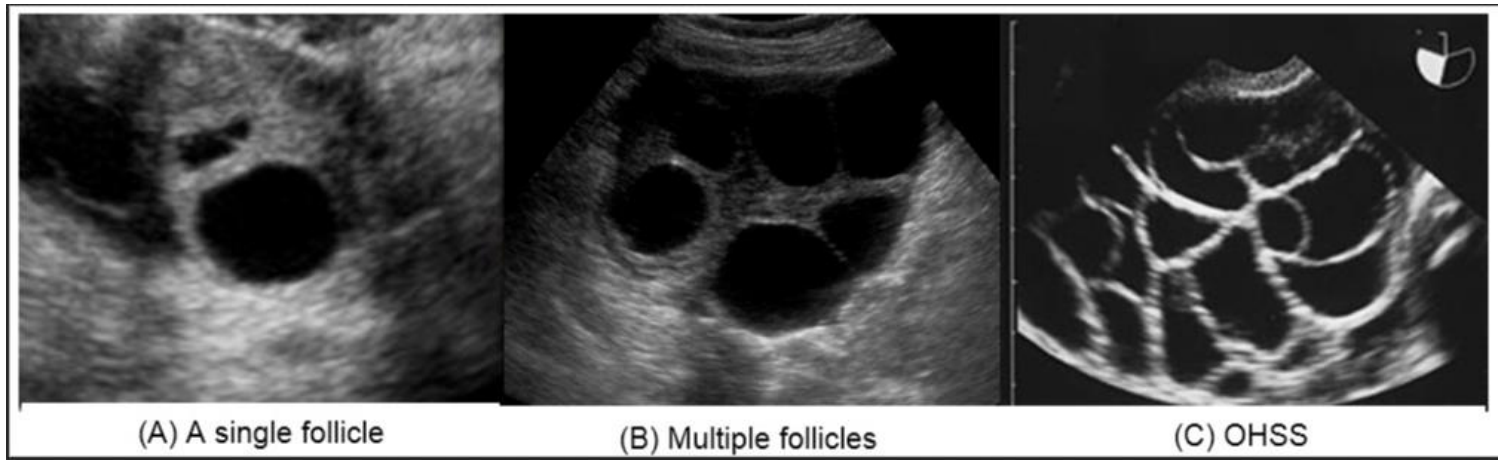
- **Sperm cryopreservation** – only available if post-pubertal
- **Testicular tissue freezing** (can include sperm found in tissue during freezing) – any age (EXPERIEMENTAL)

Oocyte Freezing…Who's a candidate?

- Pubertal females
- At least 2-3 weeks delay before treatment
- Has not received Lupron
- Has not received chemo within the past 6 months
- Able to tolerate daily injections
- Able to tolerate multiple ultrasounds (preferably vaginal)

Oocyte Freezing…What's the process?

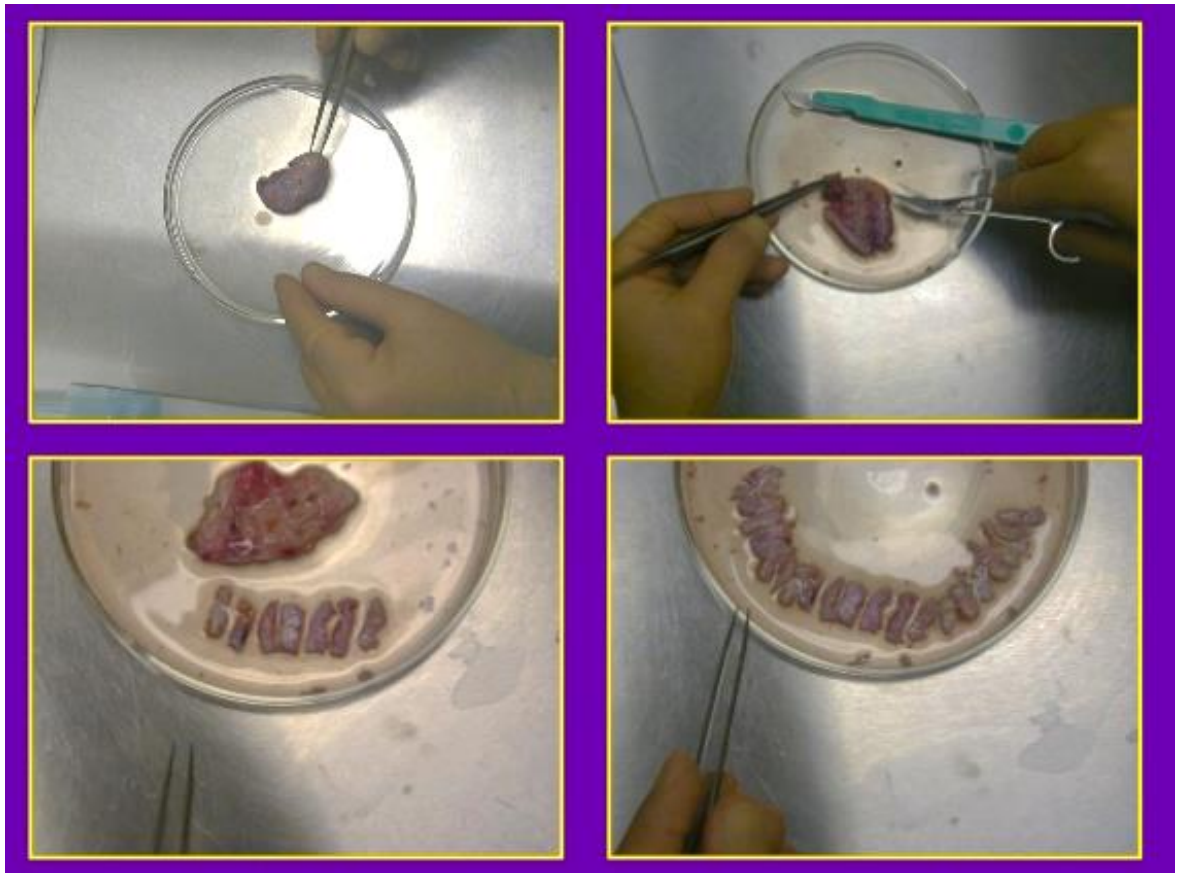
- 10-14 days of stimulation
  - Multiple lab draws
  - Multiple ultrasounds (abdominal vs. vaginal)
- Stimulation may occur at any phase of the cycle
- Surgical procedure for retrieval



Ovarian Tissue Freezing…Who is a candidate?

- Mod/High-High risk of gonadal failure (>40-50%) after cancer treatment
- Absence of previous high gonadotoxic chemotherapy – case by case
- Nonmalignant disorders treated with gonadotoxic therapy
- Individuals with gender and sex diversity
- Genetic predisposition to accelerated follicular loss
- Age > 6 months
- Cleared by anesthesia [ex. Hodgkins, large abdominal masses, etc]

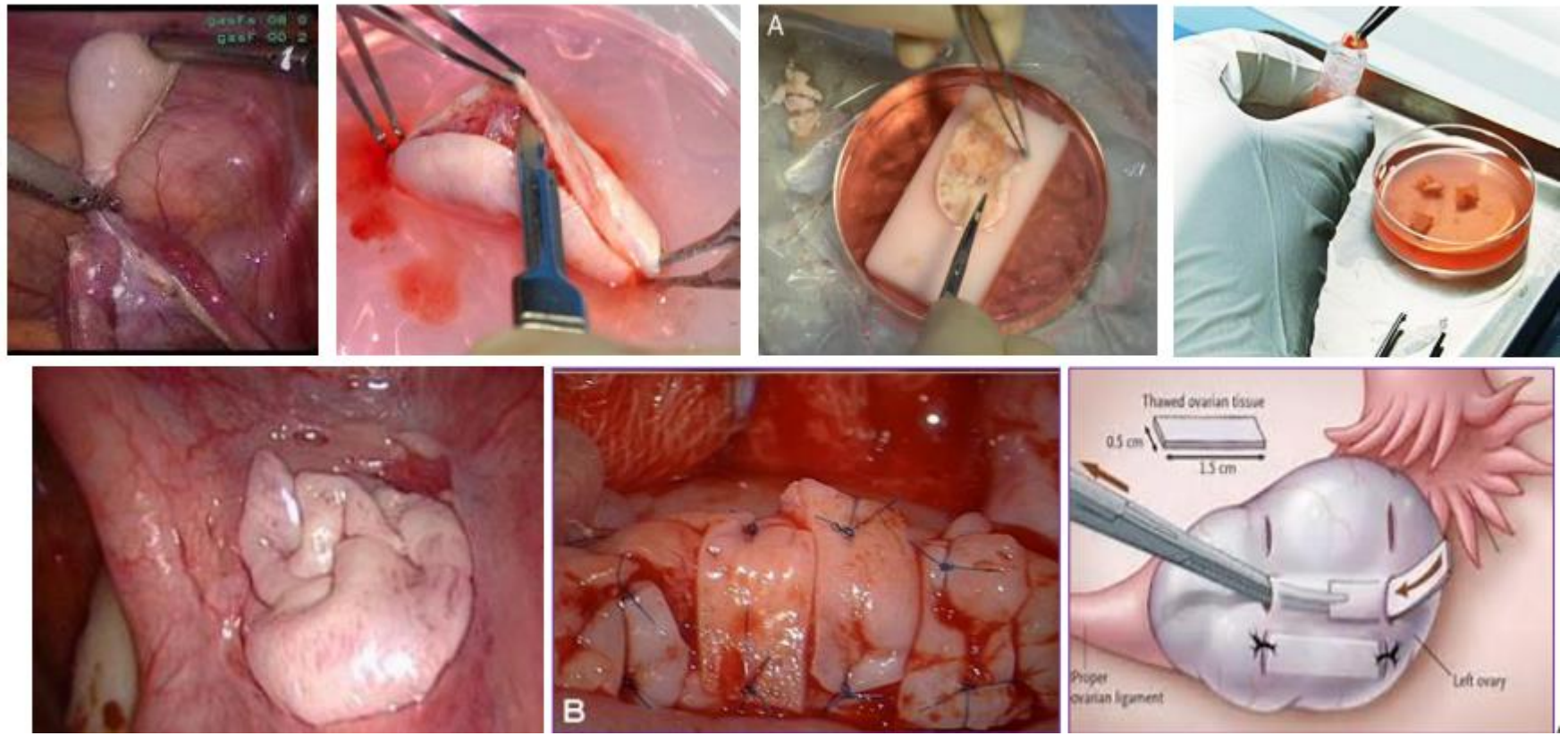
Ovarian Tissue Freezing…What's the process?



- The ovary is cut in half and half again
- Medullary tissue is removed
- Cortex is prepared into strips
- Strips are placed in vials
- Vials are frozen using a controlled freezer

I’m ready to have a baby…now what?

So far, more than 130 live births have been reported after transplantation of cryopreserved ovarian tissue, and almost all patients recovered their ovarian function after tissue reimplantation



Donnez J et al. (2006)

Menstrual Suppression

- Efficacy for protection is frequently debated
- Depo Lupron [leuprolide] – Gonadotropin-releasing hormone (GNRH) agonist
- 11.25 mg IM given every three months, but can do 3.75 mg IM monthly
- If patient is thrombocytopenic, (<10-20,000) consider holding until rising or giving with a transfusion

Menstrual Suppression

- Side effects-
  - Short term: hot flashes, mood changes, headaches, and dryness of mucous membranes.
  - Long term: risk for diminished bone mineral density, therefore calcium supplementation, avoidance of tobacco, and weight bearing exercise as tolerated would be recommended
- Consider add back therapy with norethindrone for prolonged use [> 6 months] or to aid with side effects.

Sperm Freezing…Who is a candidate?

- Males who have gone through spermarche
  - ~Age 12
  - Tanner Stage III
- Moderate to high gonadotoxic risk
  - Due to surgery, chemotherapy, and/or radiation
- Understand method of masturbation

Sperm freezing…What is the process?

- Done at home, sperm banking facility or in the hospital
- If under the age of 18, must have an adult guardian accompany them
- Wash hands, no lotions or lubricants (including saliva)
- Self-stimulation to masturbate into sterile cup
  - No masturbation or ejaculation for 48 hours prior to donating
- Sample needs to be kept at body temperature and taken to facility within 1 hour
- Ideally, do 2-3 sperm collections prior to starting treatment

Semen analysis...

- Sperm count
- Motility
- Morphology

Semen Parameters	Semen Results	Reference Value (WHO 5th Ed.)
Days Abstinence	not provided by patient	
Volume (ml)	1.0	≥1.5ml
Complete Liquefaction	Yes	
Viscosity	Normal	
Color	Normal	
pH	7.2	≥7.2
Sperm Concentration ($x10^6$/ml)	2.87	≥ 15 $x10^6$/ml
Total Motility (%)	46	≥40%
% Rapid Forward Progression	28	
% Slow Progression	10	
% Non-Progressive	8	
% Immotile	54	
Total Motile Sperm ($x10^6$)	1.32	≥40 $x10^6$
Morphology (% Normal)	1	≥4%
Viability (%)	N/A	≥58%
Cryopreservation		
# Vials Cryopreserved	2	
Post-Cryo Motility (%)	21	
Motile/Vial ($x10^5$)	0.17	

Comments: * sperm less than 5 million per ml. * total motile sperm less than 10 million; Severe oligospermia; very low numbers of total motile sperm. * Increased abnormal sperm morphology/ teratozoospermia; amorphous heads and bent necks observed. * Only able to assess 100 sperm for morphology. Cryopreservation: total motile sperm less than 10 million / vial; specimen most suitable for future use with in vitro fertilization techniques. For further evaluation please call 913-588-2229 to schedule a consult with a reproductive specialist.

Testicular tissue freezing…Who is a candidate?

- Pre-pubertal males
- Pubertal males unable to provide specimen by other means
- Moderate to high gonadotoxic risk
  - Due to surgery, chemotherapy, and/or radiation

Removal of testicular tissue

- Can be done via either a unilateral orchidectomy (available only to patients with two testes) or a testicular biopsy – at CMH we do biopsy
- Testicular biopsy performed as unilateral open testicular biopsy
- Frozen as intact tissue pieces – can also be done as cell suspension, but not our current protocol
  - If pubertal, 2 pieces taken to allow for TESE
- Piece of testicular tissue placed in poly-cup and covered with special media [if doing 2 pieces, use separate poly-cups]

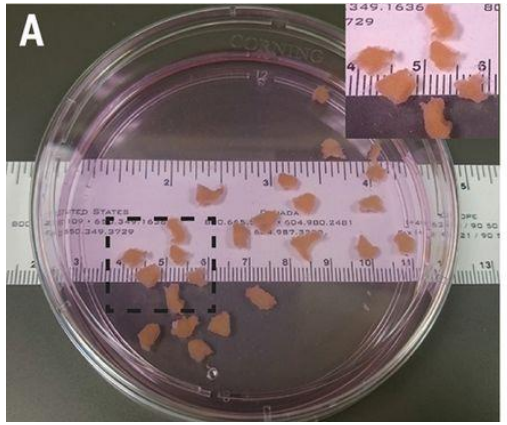
TTC…where are we now?

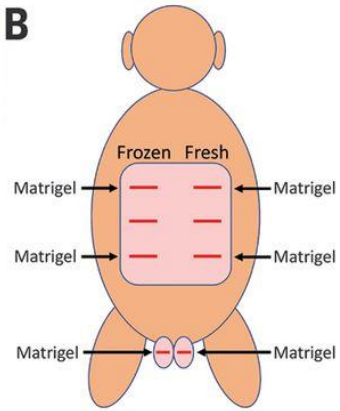
UPMC – large TTC research project

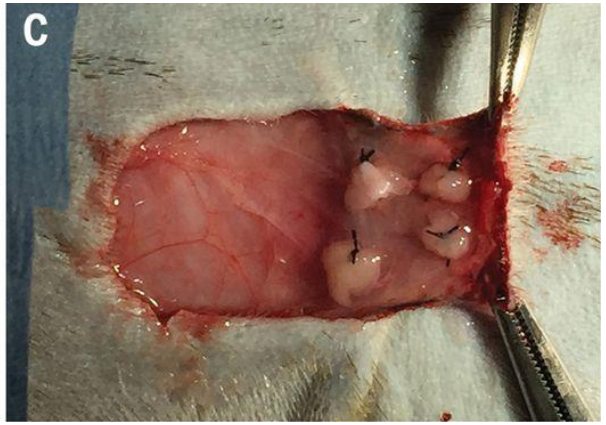
- Biopsy performed
- Sample preserved
- Recipient was castrated and treated with chemo
- Grafts placed
- Testosterone levels rose to normal range
- Sperm collected

Embryo (Oregon Primate Center)

- Egg fertilization: 11/10/17
- Embryo transfer: 11/17/2017
- Pregnancy confirmed: 12/15/17



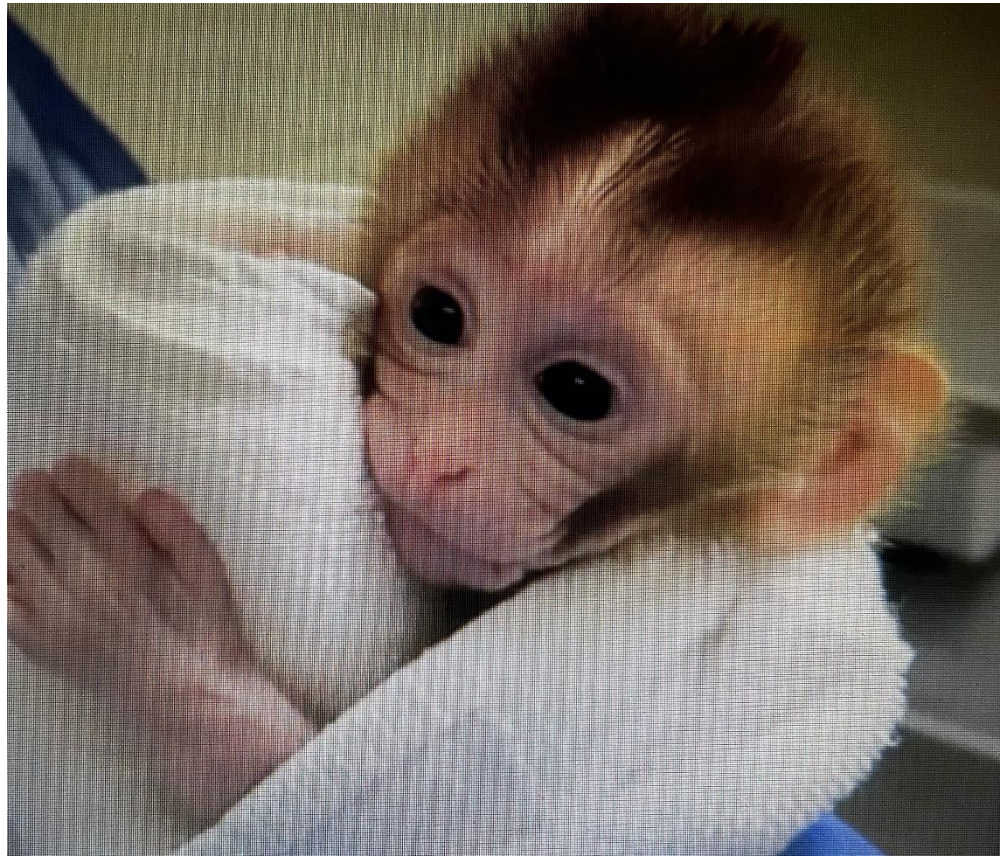




Fayomi *et al*. report proof of principle for preserving fertility of prepubertal primates using testicular tissue frozen before castration. ***SCIENCE.*** 22 MAR 2019 **: 1314-1319**

GRADY – Graft-derived baby

- Born April 16, 2018, via c-section
- First monkey baby born from autologously grafted, frozen and thawed, prepubertal testicular tissue
- Grady is currently healthy and still lives at the Oregon Primate Center



Cost for female options

Ovarian Tissue

- Procedure often covered by insurance
- If not covered, $6750 self-pay price
- All pay $500 out of pocket for processing
- $275/year for storage

Oocyte

- $15,000-20,000
- $400/year
- Assistance Programs
  - Livestrong
  - Verna's Purse
  - Heartbeat

Cost for male options

Sperm

- Sperm cryo - $300
- Semen analysis - $150
- Storage - $275-$450/year

Testicular Tissue

- Procedure often covered by insurance
- Self-pay
  - Combo - $965
  - Biopsy only - $1580
- Tissue processing - $500
- Storage - $275/year

How to contact our team

- Place a consult
  - Cerner order
  - Email fertility@cmh.edu

- Team Members:
  - Oncology Physician: Joy Fulbright
  - Gynecology APRN: Tennille Hilyard
  - Oncology APRNs: Ashley Flynn, Nancy Terwilliger and Wendy Hein
  - Social Work: Amanda Trout
  - Surgeons:
    - Testicular – Alonso Carrasco, Paul Bowlin, John Gatti and Joel Koenig
    - Ovarian – Julie Strickland, Anne-Marie Priebe and Ashli Lawson

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