



Comprehensive Fertility Care and Preservation for Patients Receiving Fertility Altering Interventions

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Medical Director | Comprehensive Fertility Preservation Program

@tketterl X

Learning Objectives

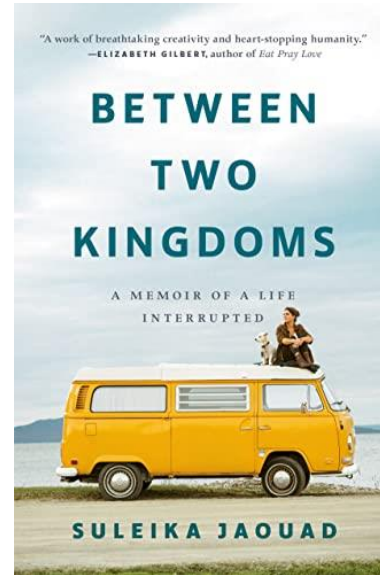
- Review ovarian anatomy/oogenesis and testicular anatomy/spermatogenesis
- Review tools to help quantify risk of gonadal failure and infertility
- Understand fertility preservation options before for individuals with ovaries.
- Understand risk, diagnosis and management of premature ovarian insufficiency after iatrogenic injury.
- Understand preservation options before and after cancer directed therapy for individuals with testicles.

Why Fertility Preservation?

“There on the list of side effects... I saw something that upset me more than any of the bad news I’d received so far: the cancer treatment that would save my life would also most likely leave me infertile.”

“As much as I appreciated their support, the absence of communication on something so important felt like a breach of trust early on in our patient-doctor relationship.”

- Suleika Jaouad





thecancerpatient



For those of us that have infertility due to cancer treatment or diagnosis, how are we really feeling today?



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thecancerpatient This goes out to all the cancer fam that want to have kids but can't because of infertility after diagnosis/treatment. I know Hallmark holidays, like Mother's Day, can sometimes add salt to the wound of mourning the loss of your fertility. This post is your safe place for today. Feel free to share how you feel about this day or even to vent how much it sucks that cancer took this away from you ❤️

For everyone else, please avoid giving advice or offering your success stories. We are happy for those that were able to have kids after cancer, but let's hold space for those of us who did not have the same experience. Just listen and offer your



christineraab.yogischbynature 5w

Very sad. I want to be a Mother all my life and cancer took it away 🥹💔



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acaperla 5w

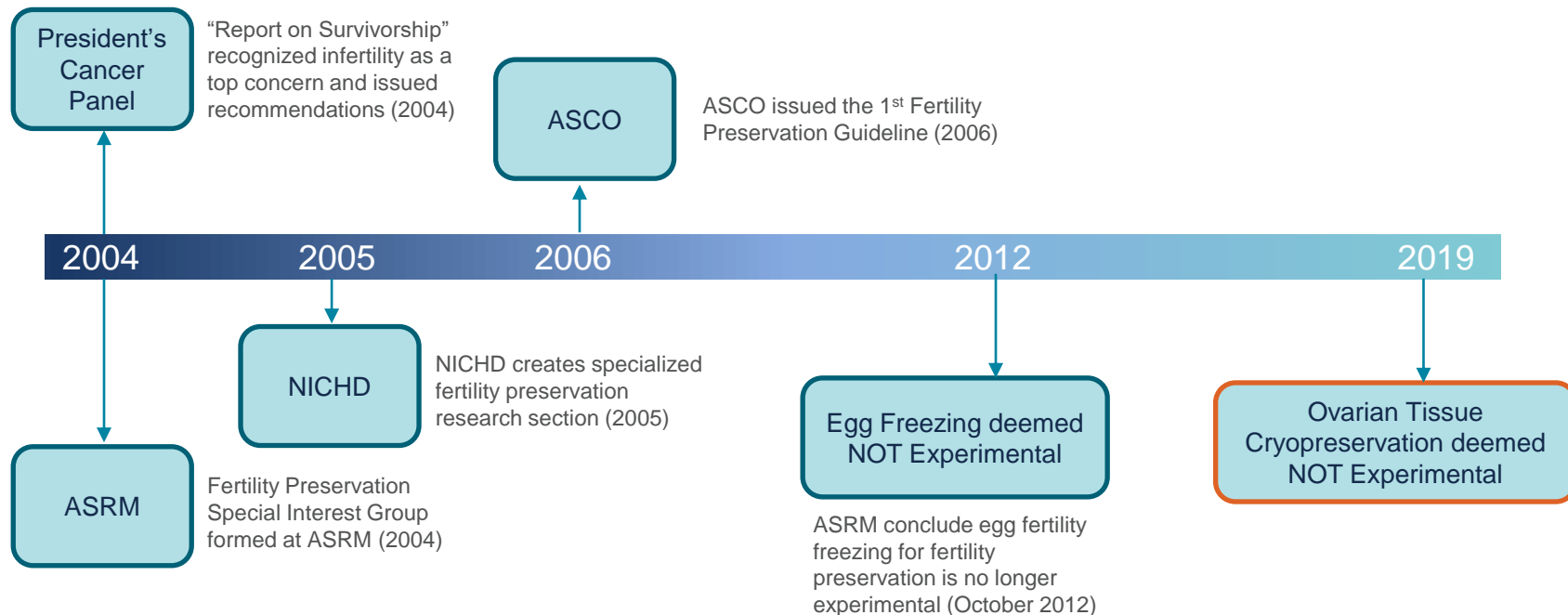
I feel like people TipToe around me on Mother's Day. They include me in gift exchanges and say "but you're a dog mom!" And I totally understand they don't want to exclude me but I wish they didn't feel the need. It sucks i can't have my own children but that's my problem and the mothers around me, I love 'em, they don't need to feel guilty about their success. I'm happy for them. Like I'll figure it out. I'll adopt foster or IVF, but don't have to pretend I'm a mom or that the fact that cancer took that away from me is something everyone else has to compensate for. Happens at work too. People come to the office and say "happy Mother's Day!" Oh you too! I know you Mommin' a lot of cats. Like, stop, I'm not a mom. Thank you but it's ok!



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Oncofertility movement has evolved over the past 20 years.



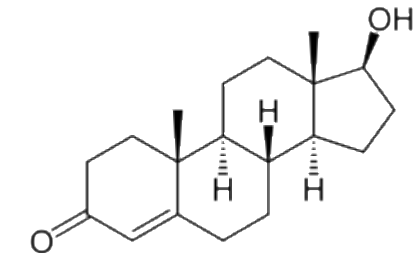
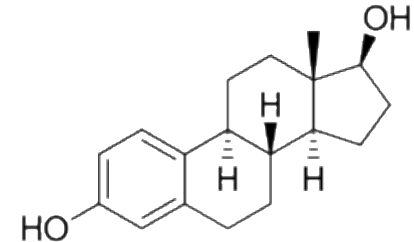
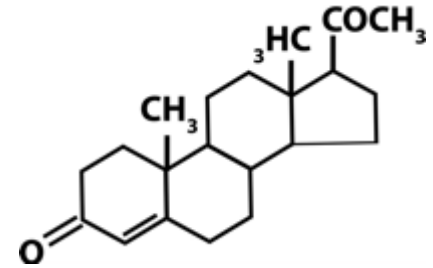
Ovarian and testicular tissue serves a role in both hormone production and reproduction

Ovary

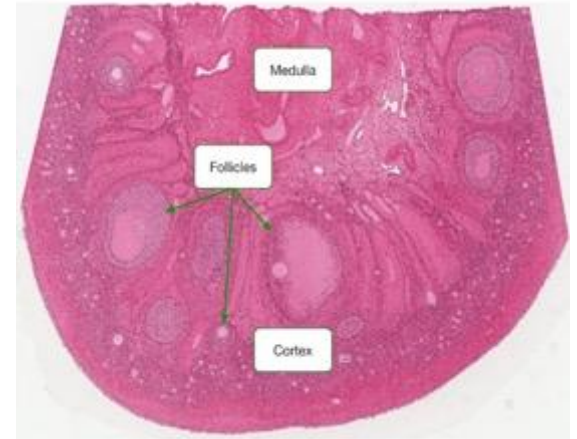
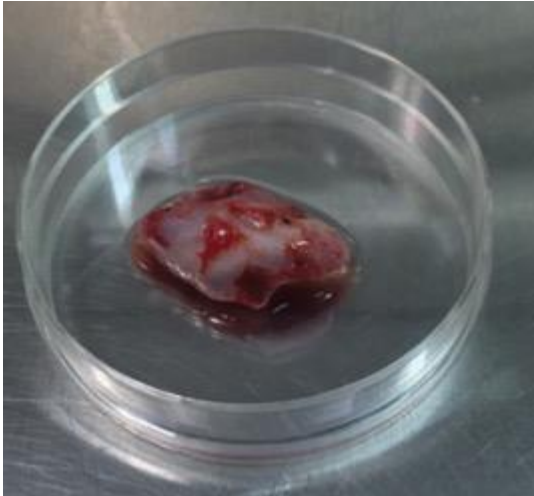
- **Reproduction**
 - Females born with lifetime oocytes
- **Hormones**
 - Progesterone
 - Estrogen (estradiol, estrone, and estriol)

Testes

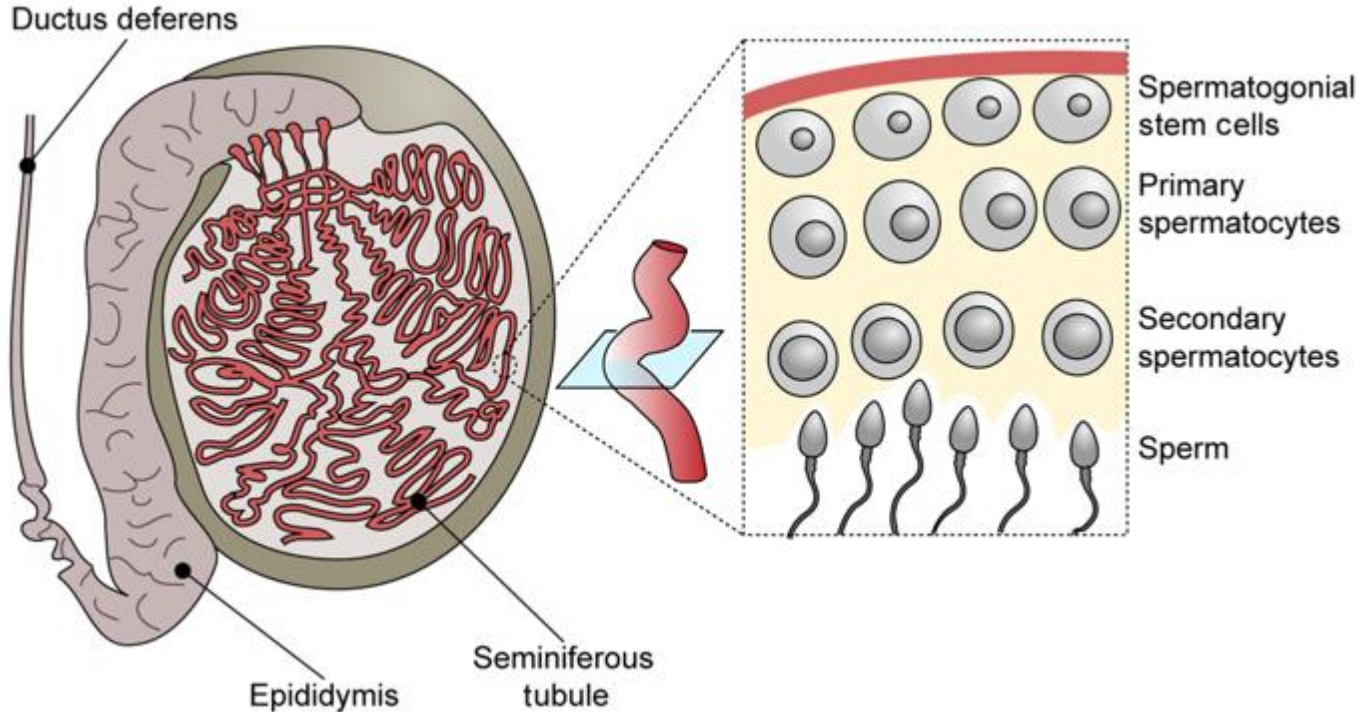
- **Reproduction**
 - Ongoing production of sperm after puberty
- **Hormone**
 - Testosterone



Ovarian Anatomy



Spermatogenesis



Male Tanner Staging

Tanner I

no pubic hair at all (**prepubertal**) (typically age 10 and younger)

Tanner II

small amount of long, downy hair with slight pigmentation at the base of the **penis** and **scrotum** (males)

Tanner III

hair becomes more coarse and curly, and begins to extend laterally (11.5–13)

Tanner IV

adult-like hair quality, extending across **pubis** but sparing medial thighs (13–15)

Tanner V

hair extends to medial surface of the thighs (15+)

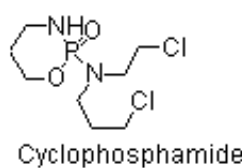
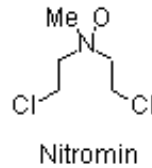
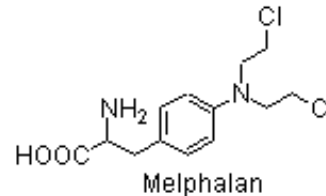
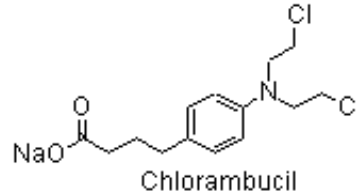


Risk Quantification and Gonadal Failure

Gonadotoxic Therapy



RADIATION



ALKYLATING
CHEMOTHERAPY



CISPATIN &
CARBOPLATIN

+ OTHERS

Cyclophosphamide Equivalent Dose

Cyclophosphamide Equivalent Dose Calculator			
Drug	Dose (mg/m ²)	Multiplier	Equivalent dose (mg/m ²)
Cyclophosphamide		1	0
Ifosfamide		0.244	0
Procarbazine		0.857	0
Chlorambucil		14.286	0
BCNU		15	0
CCNU		16	0
Melphalan		40	0
Thio-TEPA		50	0
Nitrogen Mustard		100	0
Busulfan		8.823	0

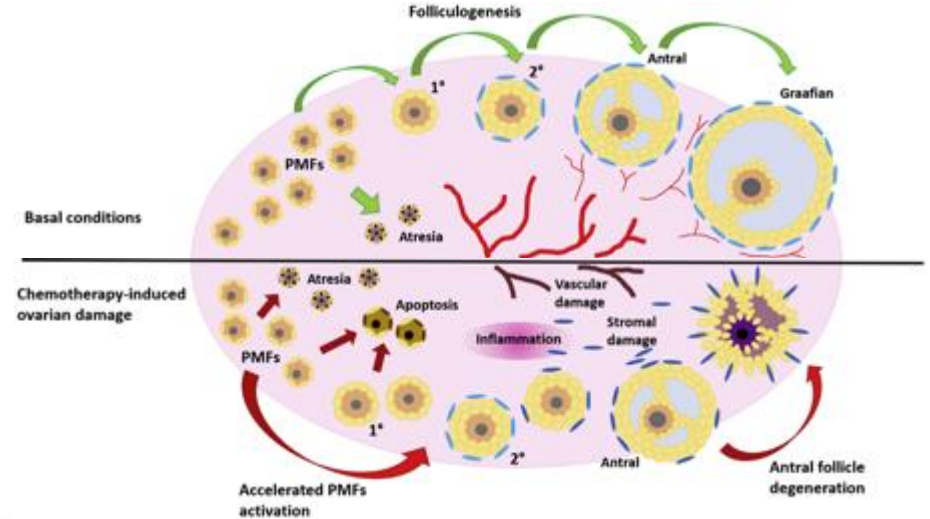
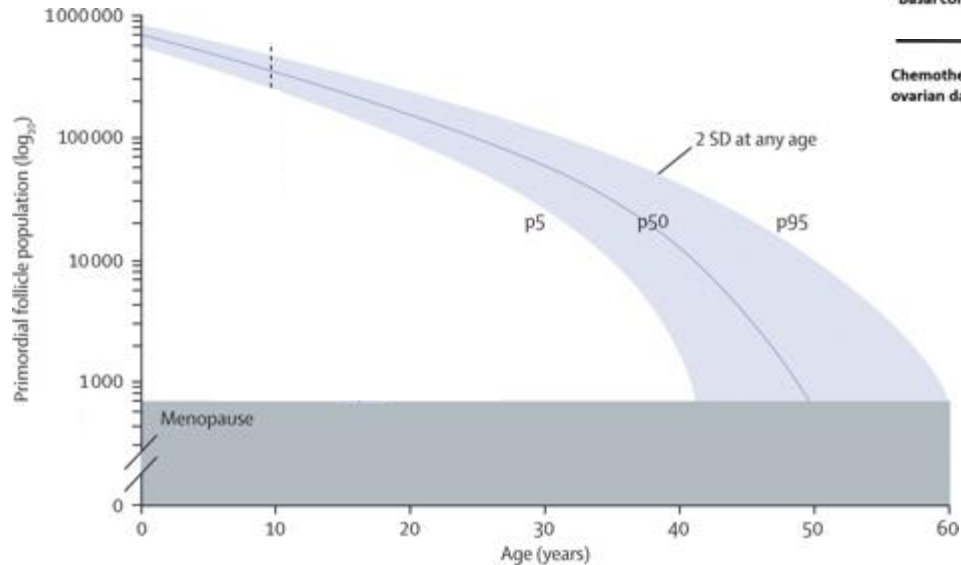
Total CED	0
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The Oncofertility Consortium

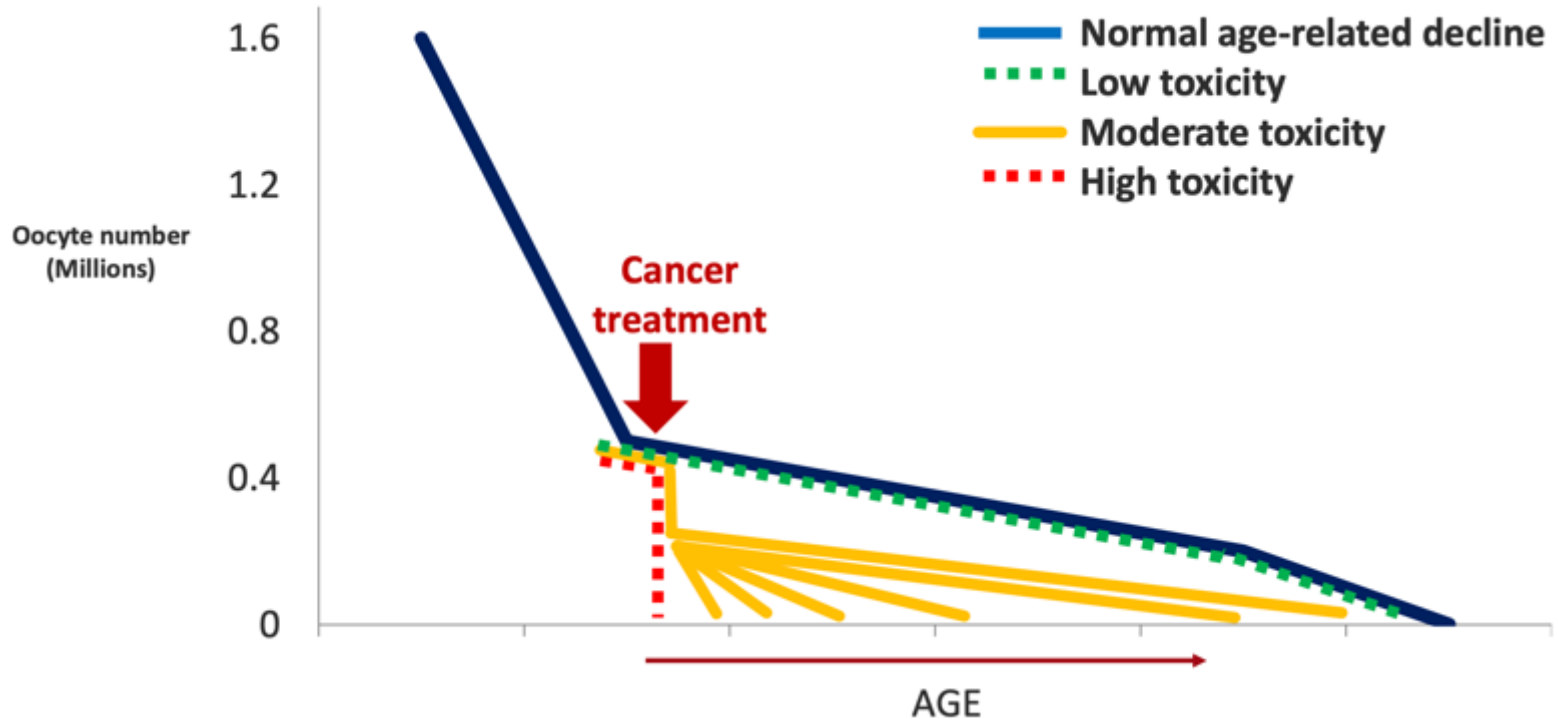


<https://oncofertility.msu.edu>

Cancer directed therapy can impact the primordial follicle population leading to earlier age of menopause.

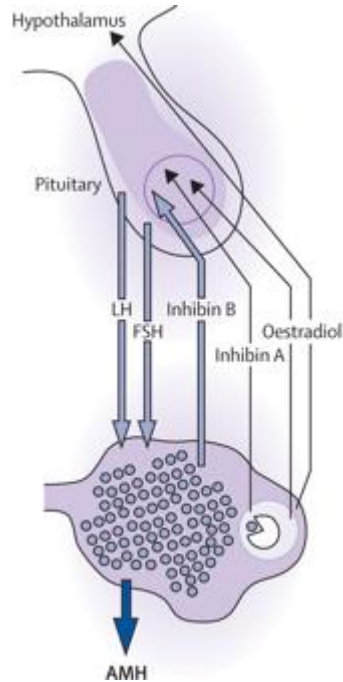


Infertility and Ovaries: Risk Principles

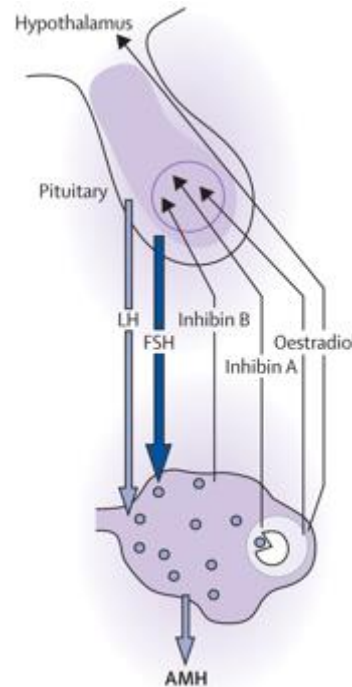


Premature Ovarian Insufficiency (POI)

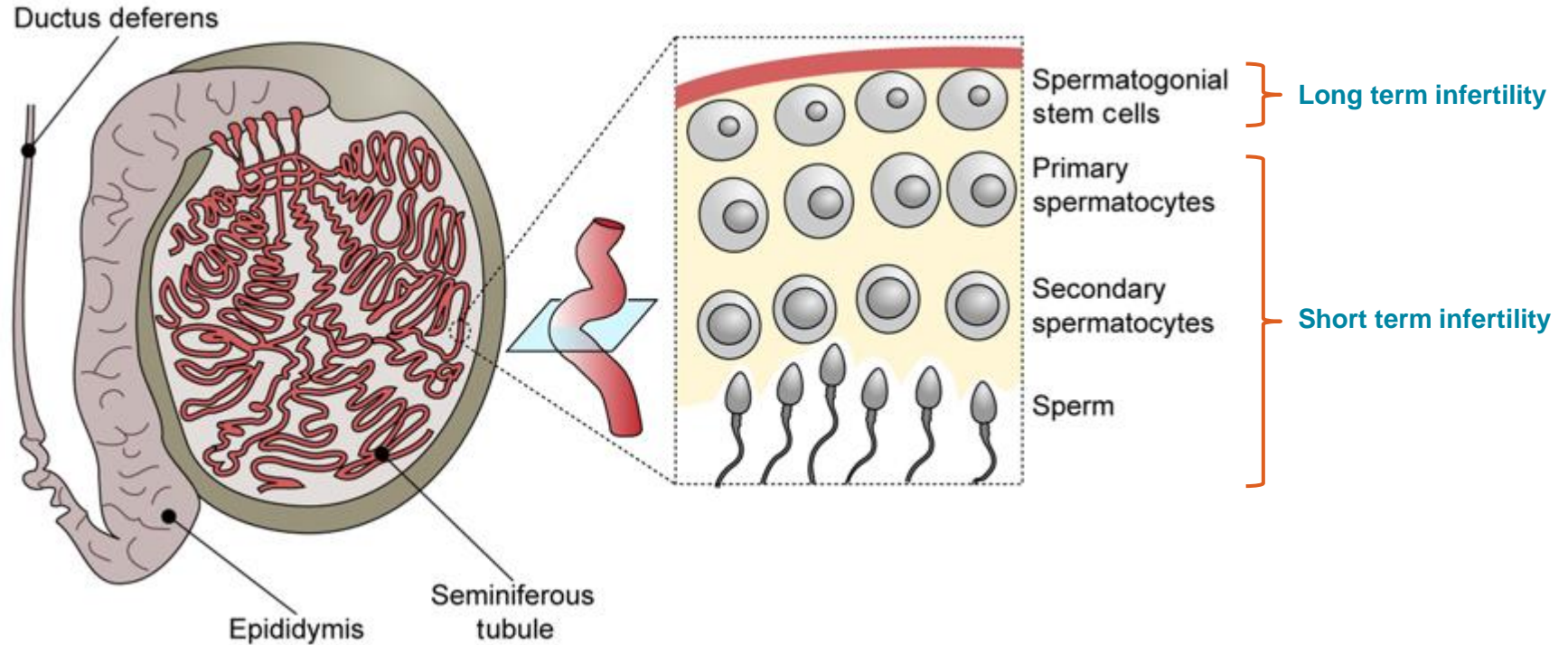
Healthy Ovarian Reserve



Decreased Ovarian Reserve



Spermatogenesis



Pediatric & AYA Gonadal Insufficiency and Infertility Risk Stratification

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Standardizing Risk Assessment for Treatment-Related Gonadal Insufficiency and Infertility in Childhood Adolescent and Young Adult Cancer: The Pediatric Initiative Network Risk Stratification System

Lillian R. Meacham, MD,¹ Karen Burns, MD, MS,^{2,3} Kyle E. Orwig, PhD,⁴ and Jennifer Levine, MD, MSW⁵

Ovarian Risk Stratification

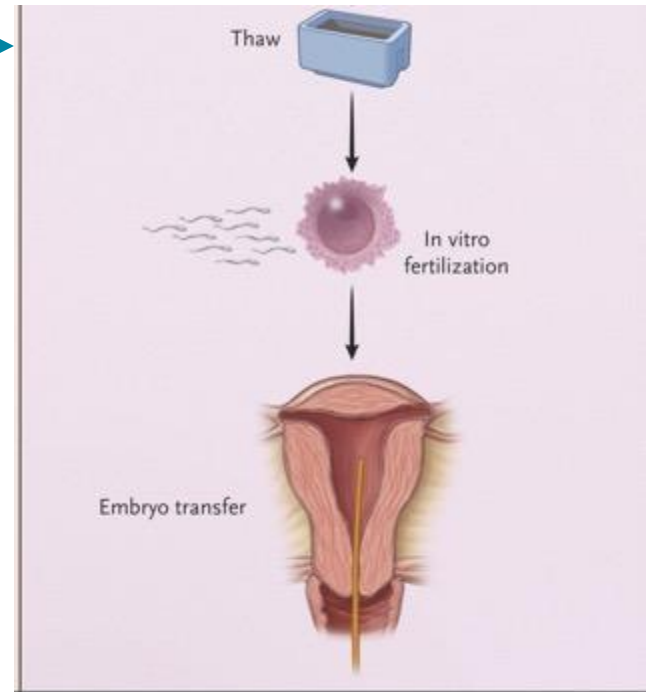
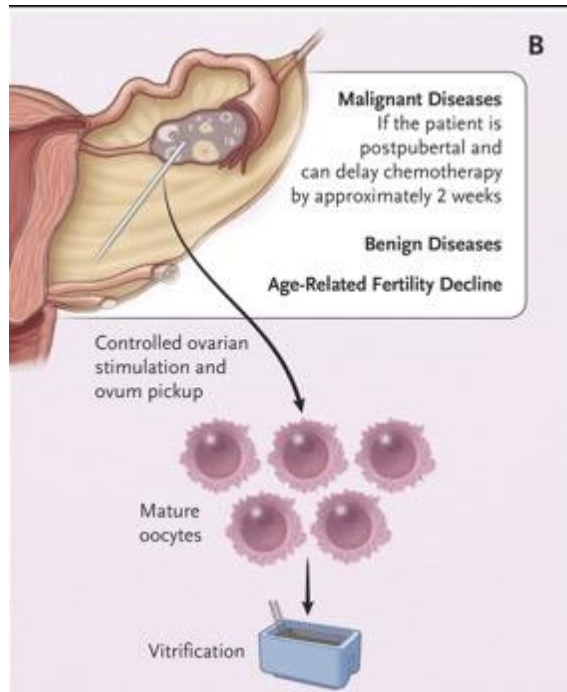
			Minimally Increased Risk	Significantly Increased risk	High level of Increased risk
Alkylators CED* gm/m2	Prepubertal		CED < 8	8-12	> 12
	Pubertal		CED < 4	4-8	>8
Heavy Metal			Cisplatin Carboplatin		
Hematopoietic Stem Cell Transplant					Alkylator +/-Total body irradiation Myeloablative and Reduced intensity regimens
Radiation exposure	Ovary	Prepubertal		< 15 Gy	≥ 15 Gy
		Pubertal		< 10 Gy	≥ 10 Gy
	Hypothalamus		22-29.9	> 30-39.9 Gy	> 40 Gy

Testicular Risk Stratification

		Minimally Increased Risk	Significantly Increased risk	High level of Increased risk
Alkylators CED* gm/m2		CED < 4		CED ≥ 4
Hematopoietic Stem Cell Transplant				Alkylator +/-Total body irradiation Myeloablative and Reduced intensity regimens
Heavy Metal mg/m2		Cisplatin Carboplatin	Cisplatin > 500	
Radiation Exposure	Testicular	0.2-0.6Gy	0.7-3.9 Gy	≥ 4.0 Gy
	Hypothalamus	26-29.99	> 30-39.9 Gy	> 40 Gy
Surgery			RPLND^	

Fertility Preservation in Individuals with Ovaries

Oocyte Cryopreservation



December 2019 ASRM Statement

ASRM PAGES



Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

Patients preparing to undergo gonadotoxic medical therapy, radiation therapy, or gonadectomy should be provided with prompt counseling regarding available options for fertility preservation for iatrogenic infertility. Fertility preservation can best be provided by comprehensive programs designed and equipped to confront the unique challenges facing these patients. This document replaces the document with a similar name, last published in 2013. [Fertil Steril® 2019;112:1022–33. ©2019 by American Society for Reproductive Medicine.]

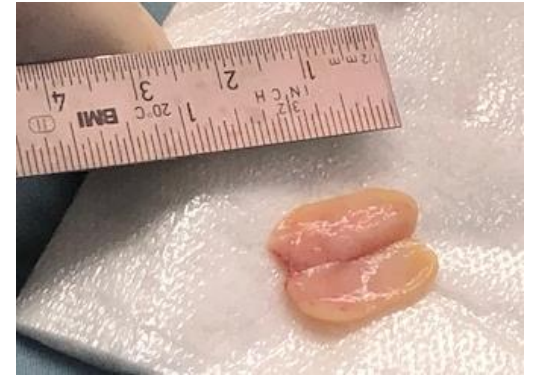
Operative Photos at the time of Ovarian Tissue Cryopreservation



L oophorectomy at time of larger abdominal tumor resection

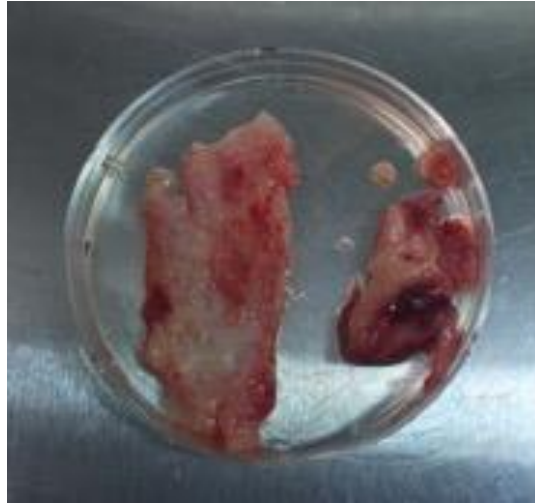


Laparoscopic view of R ovary, removed as a separate procedure (with line placement)



Ovary bisected and put into media

Ovarian Tissue Cryopreservation



Ovarian Tissue Autotransplantation

Transplantation to the ovary



Transplantation to a peritoneal pocket

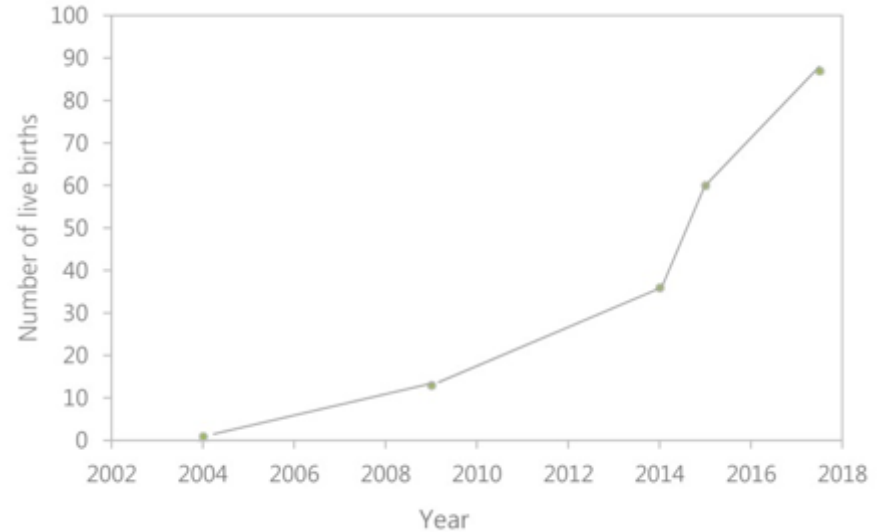


Uses of Cryopreserved Ovarian Tissue

- Auto-Transplantation
 - Subcortical of remaining ovary*
 - Ovarian Bed*
 - Peritoneal Window*
 - Forearm

* Live births in literature

- *In Vitro* Maturation
 - Still Experimental



At least 185 live births have been reported worldwide after transplantation of cryopreserved ovarian tissue, including a combination of both IVF and spontaneous conceptions.

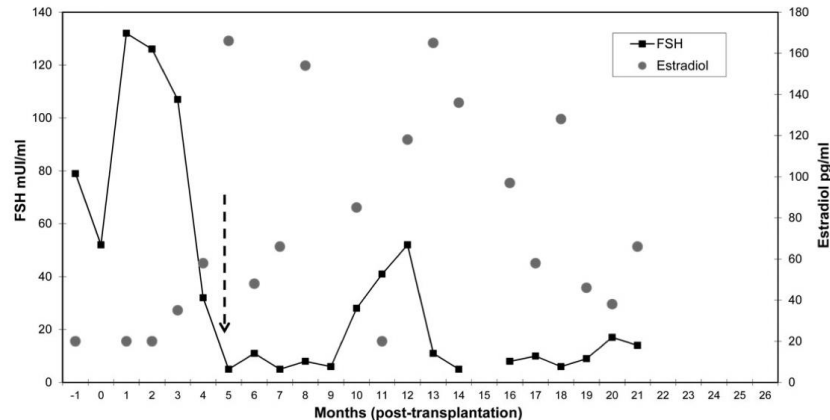
Case 1 - Sickle Cell Anemia

Diagnosis – Age 5 yrs

Pubertal changes – Age 10yrs (breast development)

HSCT/OTC - Age 14yrs (no prior menarche)

Menarche induction – Age 15.5yrs



Ovarian Tissue Transplant - 25 yrs

- POI confirmed prior to transplant
- 6 tissue segment grafted in the peritoneal bursa, and five were grafted subcutaneously

At 5-21 months post autograft

- FSH/LH return to pre-menopausal range
- Regular menstration
- Follicles seen on ultrasound
- AMH undetectable
- Spontaneous pregnancy with healthy baby boy in 2014.

Case 2 - Acute Lymphoblastic Leukemia

Diagnosis – Age 14 years

High Risk protocol/TBI/HSCT - Age 14 years

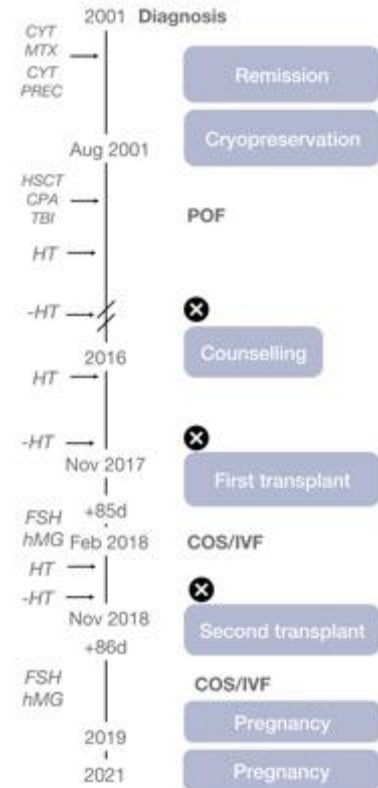
OTC post-chemotherapy/remission status.

Permanent Ovarian Failure

1st Ovarian Tissue Transplant – Age 29 years

2nd Ovarian Tissue Transplant. - Age 30 years

- Pregnancy established through IVF. Nov 2019 healthy baby boy at 35+5 weeks
- Pregnancy established by natural conception. Progressing into week 35 at time of publication.



Fertility Preservation after Chemotherapy in Patients with Ovaries

Oocyte Cryopreservation

- Approximately 4-5 months after chemotherapy.
- Patients who do not collect prior to therapy are encouraged to do so after therapy due to premature ovarian insufficiency.
- Absolute neutrophil count > 750.

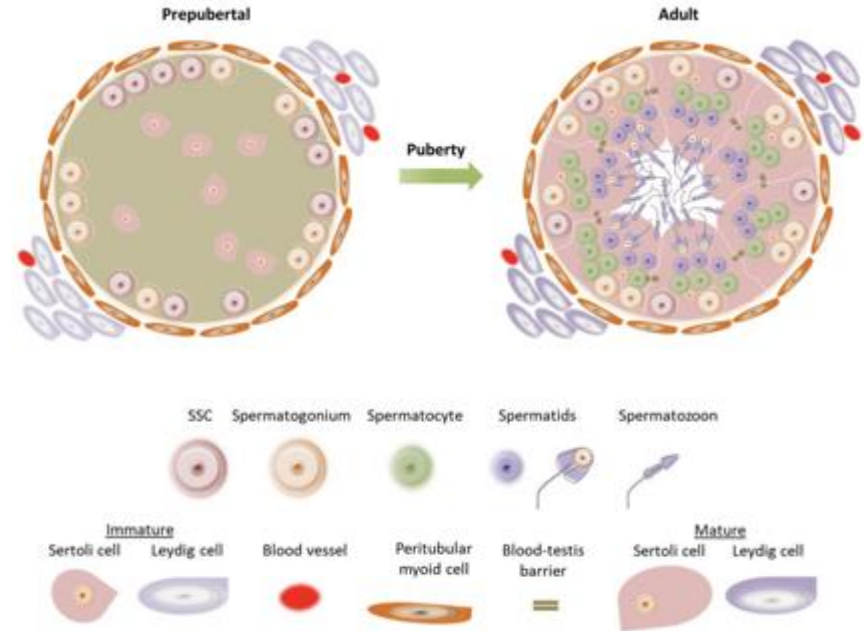
Ovarian Tissue Cryopreservation

- Ovarian follicles are thought to be protected from chemotherapy therefore can be collected any time after non-high risk therapy exposure

Fertility Preservation in Individuals with Testicles

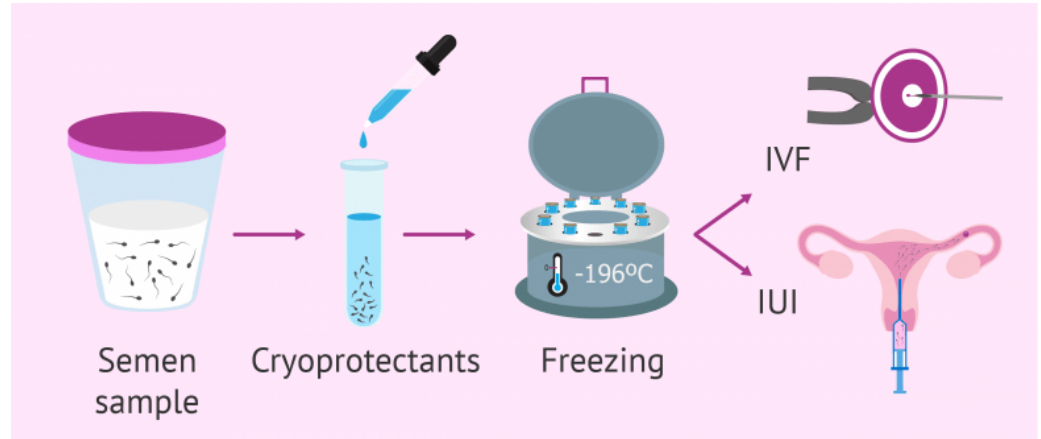
Infertility Risk in Patients with Testicles: Principles

- Long term outcomes: mostly binary (fertile vs not fertile)
- Risks do not vary greatly with age
- Temporary azoospermia is of variable length.



Sperm cryopreservation

- Must be Tanner Stage 3
- Masturbated previously
- No lubricants or saliva
- Sperm must be collected prior to any chemotherapy



Testicular Tissue Cryopreservation

ONLY AVAILABLE ON CLINICAL TRIAL

- Eligibility Criteria
 - “High level of increased risk” of infertility
 - MRD negative prior to procedure (patients with leukemia)
 - Previous chemo exposure: CED <4
- Process
 - Wedge resection of a portion of a single testicle
 - Processing and cryopreservation of tissue at UPMC
- Cost
 - Procedure: billed to insurance
 - Processing and freezing: FREE (covered by study)
 - Long term storage: \$100-350 per year



ASCO 2018 – Male Fertility Preservation

Post Chemotherapy:

- Men should be advised of a potentially higher risk of genetic damage in sperm collected after initiation of therapy.
- It is **strongly recommended that sperm be collected before initiation of treatment** because the **quality of the sample** and **sperm DNA integrity may be compromised after a single treatment**.
- Intracytoplasmic sperm injection allows the future use of a very limited amount of sperm.

Comprehensive Fertility Preservation at Seattle Children's Hospital

OVARIES

Prepubertal

- Ovarian tissue cryopreservation

Pubertal

- Ovarian tissue cryopreservation
- Oocyte/Embryo cryopreservation

TESTICLES

Prepubertal

- Testicular Tissue Cryopreservation (Experimental - Protocol at SCH)

Pubertal

- Sperm Cryopreservation
- Testicular Sperm Extraction (TSE)
- Testicular Tissue Cryopreservation (Experimental - Protocol at SCH)

Comprehensive evaluation and evaluation of all patients facilitated by Oncofertility team including oncology, general surgery, urology, adolescent gynecology and reproductive endocrinology.

Summary

- New female fertility methods such as OTC are available.
- Male fertility preservation methods are limited and should be offered prior to gonadotoxic chemotherapy
- Meachum et al, JAYAO 2020 sets first categories to allow standardization across sites and studies
- Increased clarity about definition of risk and implications for recommendations is critical
- Fertility preservation is important to patients and plays an important role in coping.

Contact with any questions

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