



THE UNIVERSITY OF TEXAS  
**MDAnderson**  
~~Cancer~~ Center  
Making Cancer History®

# Survivorship Considerations: Oncofertility

Young Onset Colorectal Cancer Conference  
May 20, 2023

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**Glad you are here today!**  
**No conflicts of interest**



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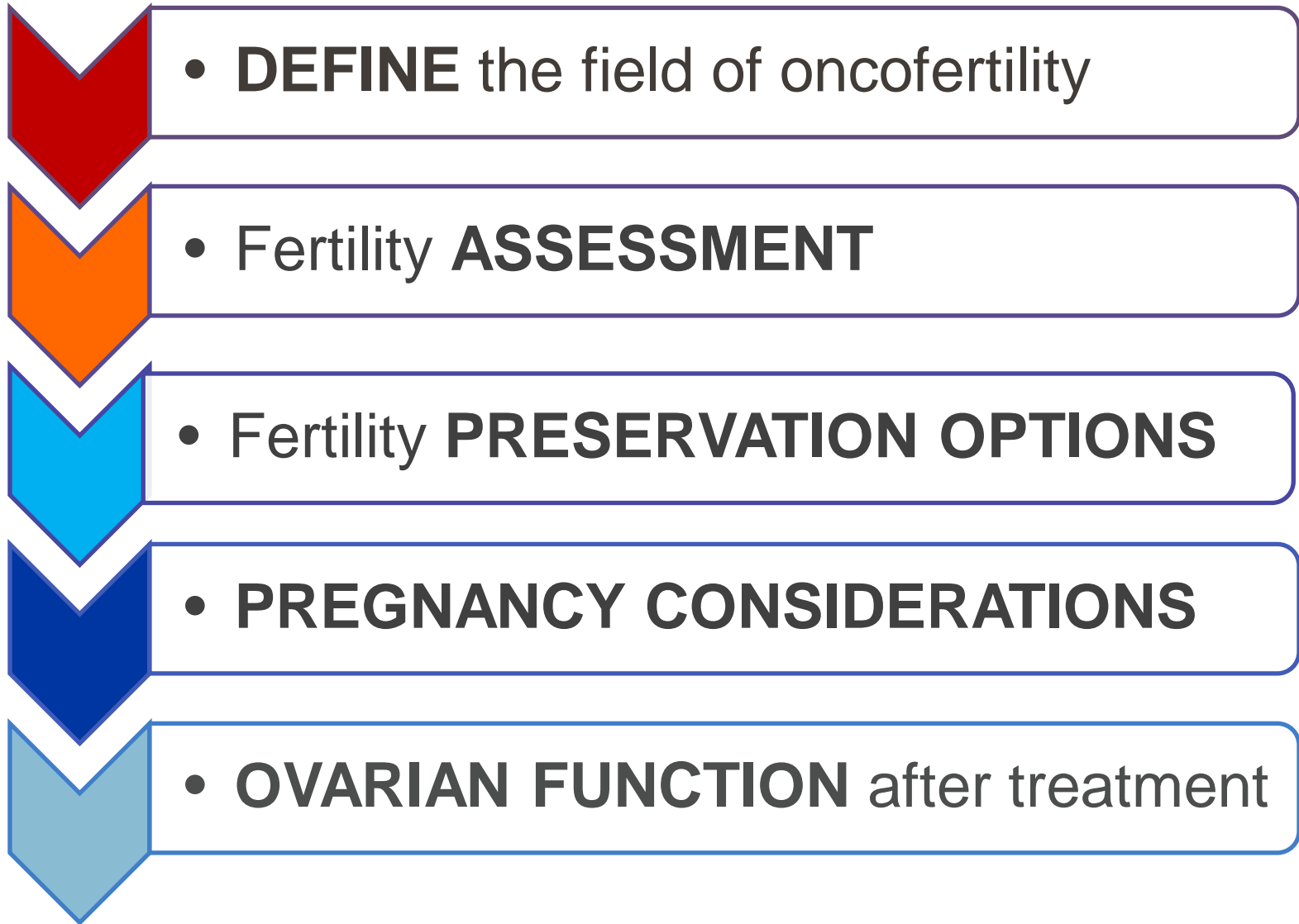
*The University of Texas MD Anderson Cancer Center*

*Houston, Texas*

*Baylor College of Medicine*

*Division of Reproductive Endocrinology and Infertility*

*Houston, Texas*



**Bridge between oncology and reproductive medicine to expand the reproductive options for those affected by cancer**

**WHAT IS ONCOFERTILITY?**

- ❖ >80% of children diagnosed with cancer become long-term survivors
- ❖ Cancer patients have a strong desire to have biologic children in addition to considering other options such as adoption or egg and sperm donation
- ❖ Reproductive counseling is associated with decreased long term regret and improved quality of life
- ❖ Fundamental tenet of survivorship care

## Primary determinants of fertility impact:

- Age of patient
- Type of agents utilized
- Dose
- Number of cycles of chemotherapy
- If radiation is utilized
- Baseline fertility status

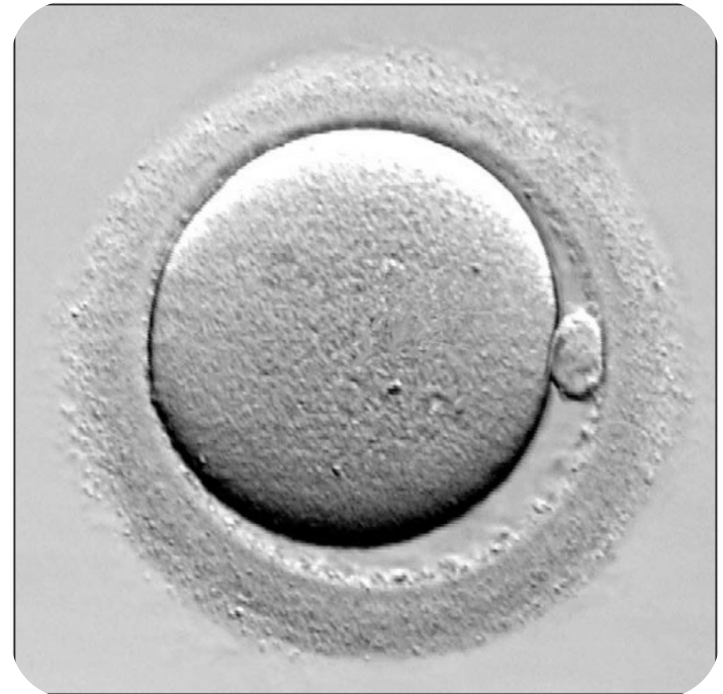


# Ovarian Reserve

Capacity of the ovary to provide eggs that are capable of fertilization resulting in a healthy and successful pregnancy

Determined indirectly:

- Follicle Stimulating Hormone and Estradiol (FSH/E2)
- Inhibin B
- **Antimullerian Hormone (AMH)**
- **Antral Follicle Count (AFC)**



# Male Fertility

The single most important test of male fertility is a semen analysis

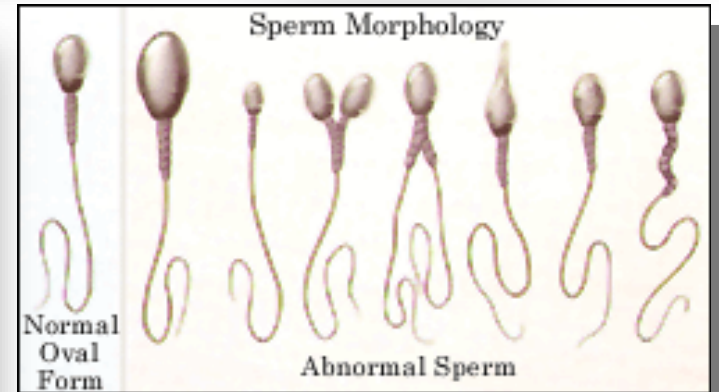
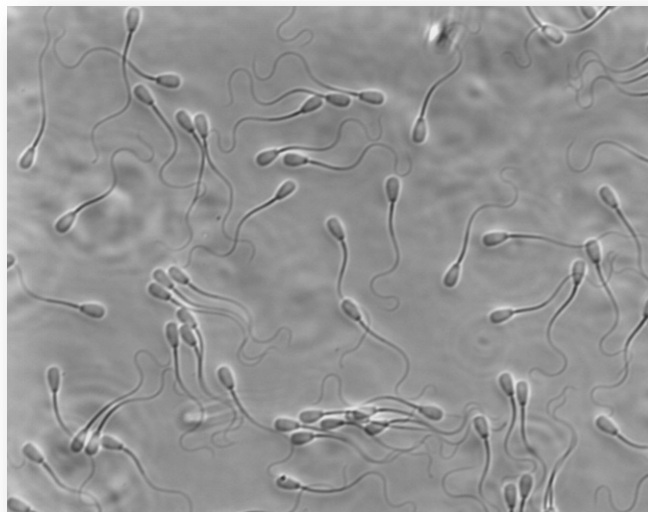
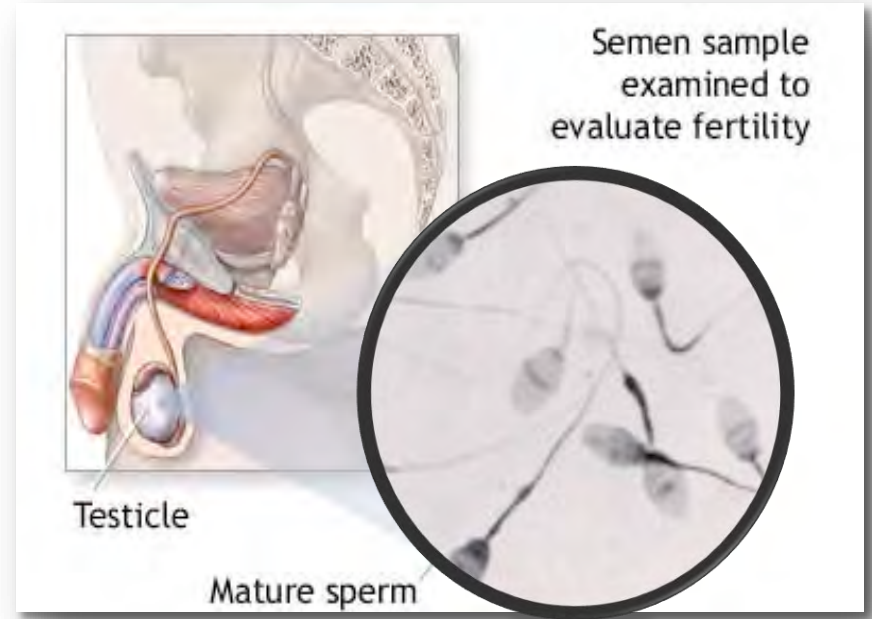
## What is it we are looking for?

Total semen volume

Sperm count

Ability of sperm to swim (motility)

Size and shape of the sperm (morphology)





# Fertility Preservation Options



- Gamete cryopreservation



- Surgical considerations



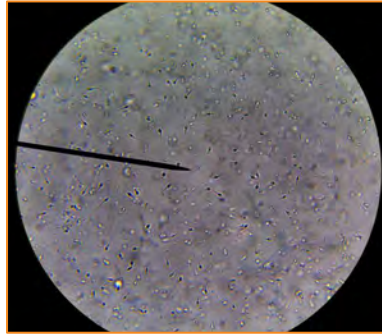
- Hormonal manipulation

# GAMETE

## CRYOPRESERVATION

Process of preserving reproductive tissue to increase the likelihood of having biological children in the future

## Not a new concept



**1953**  
First child  
via cryo  
**sperm**



**1984**  
First child  
via cryo  
**embryo**



**1986**  
First child  
via cryo  
**oocyte**

Over 900 births from cryopreserved oocytes show no increased malformation risk in offspring (Noyes et al., Repro Biomed Online 2009)

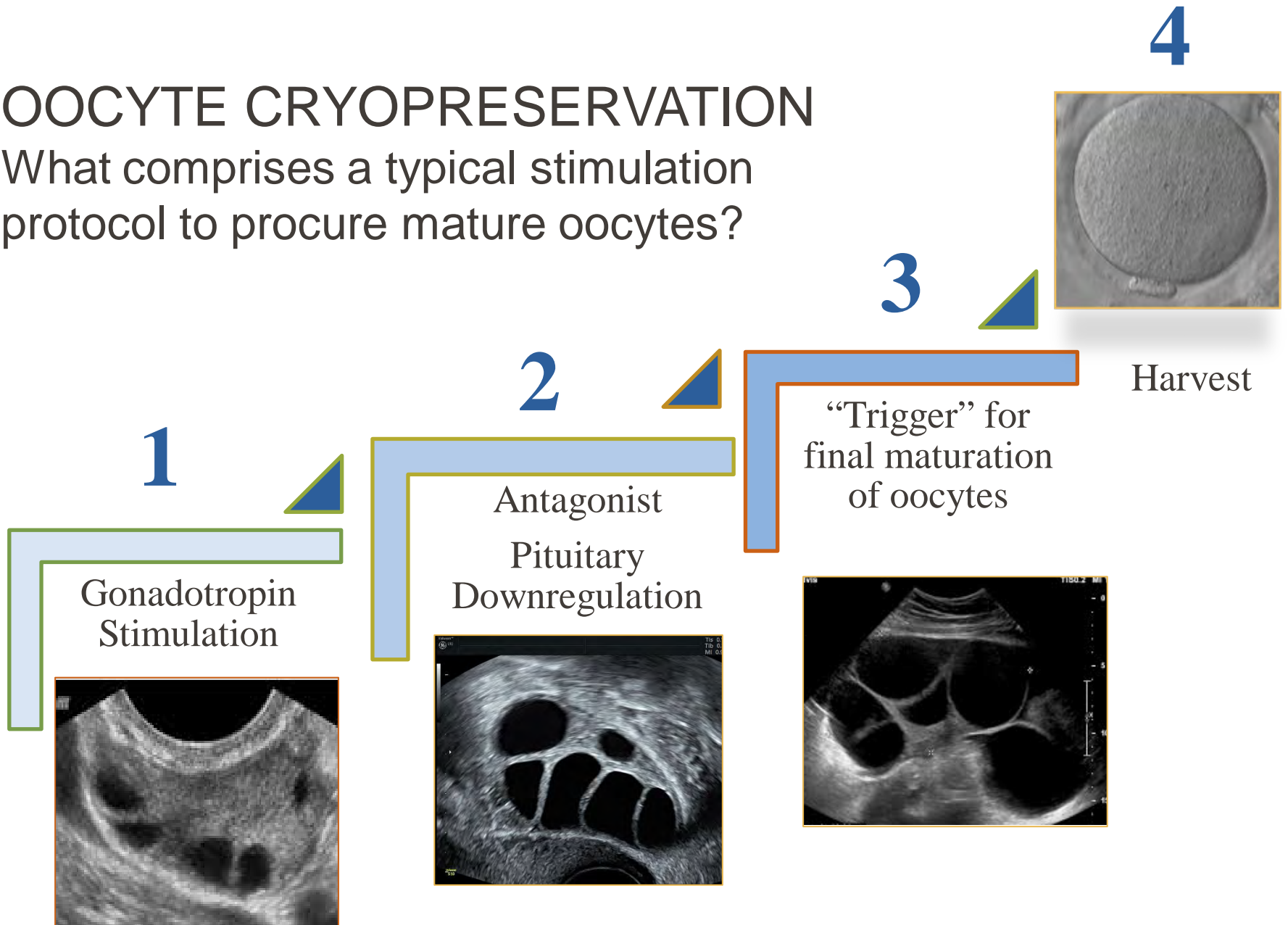
Tends to be less moral sensitivity surrounding the storage and fate of gametes, and as genetic material originates from one individual, there are fewer issues surrounding ownership

# SPERM CRYOPRESERVATION

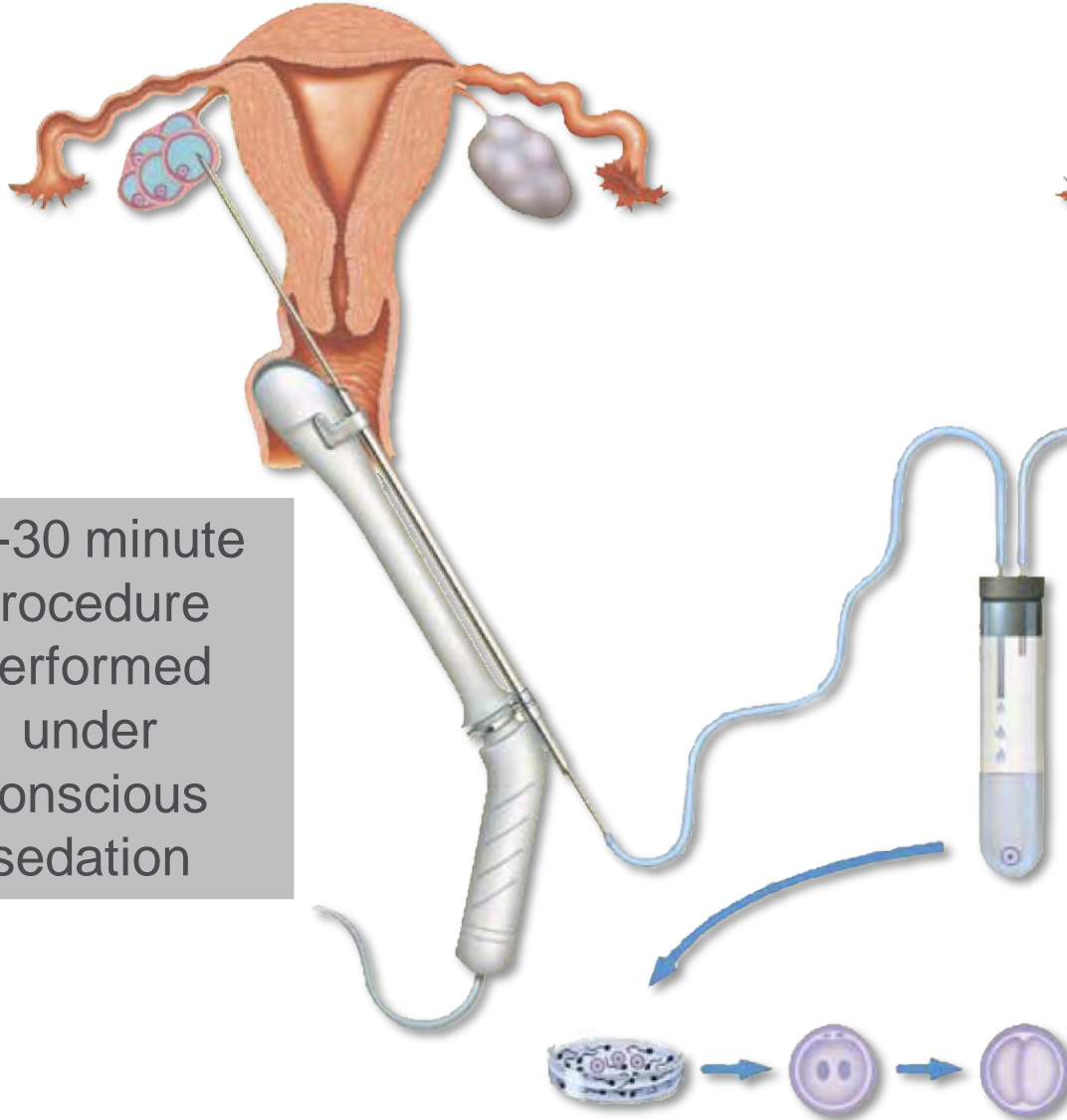
- **PRIOR** to onset of chemotherapy
- Sperm can be cryopreserved indefinitely
- The sperm parameters are important; the sample will be cryopreserved in aliquots or “vials”.
- Each sample with greater than 5 million motile sperm after thaw can be used for less aggressive fertility therapies in the future
- Consider more than one collection
- **ASK FOR A COPY OF THE REPORT**

# OOCYTE CRYOPRESERVATION

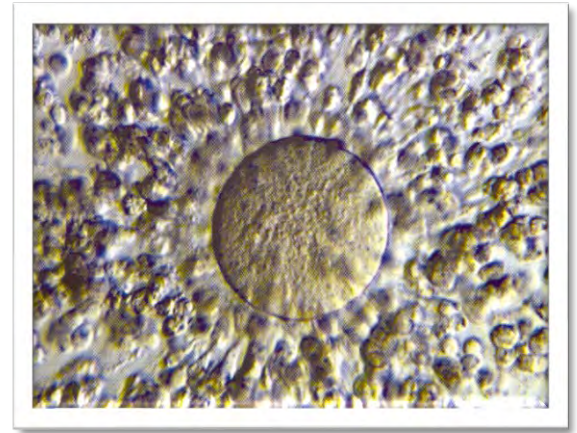
What comprises a typical stimulation protocol to procure mature oocytes?



# Transvaginal aspiration of oocytes



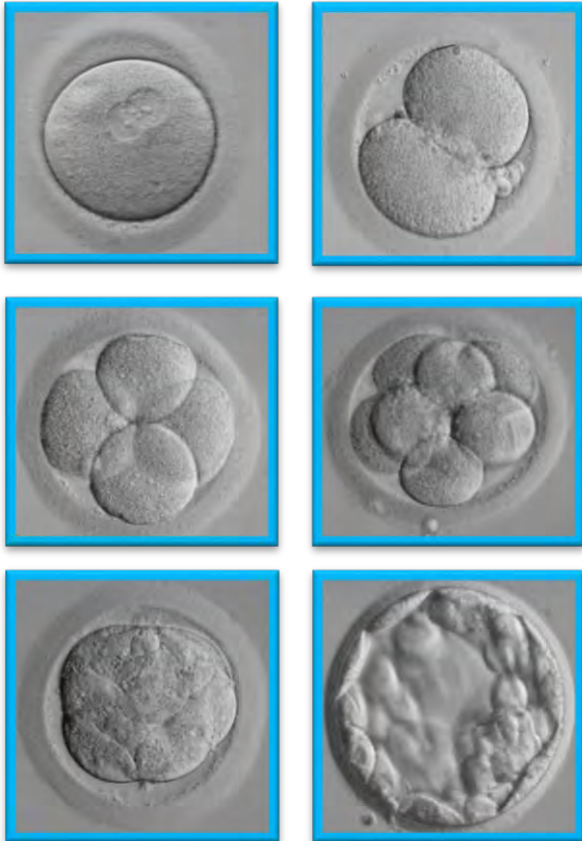
20-30 minute procedure performed under conscious sedation



Surrounding cumulus cells are stripped from the oocytes

Follicular Fluid is aspirated and the oocyte recovered from each follicle

# Embryo scoring and cryopreservation



Characteristic growth rates

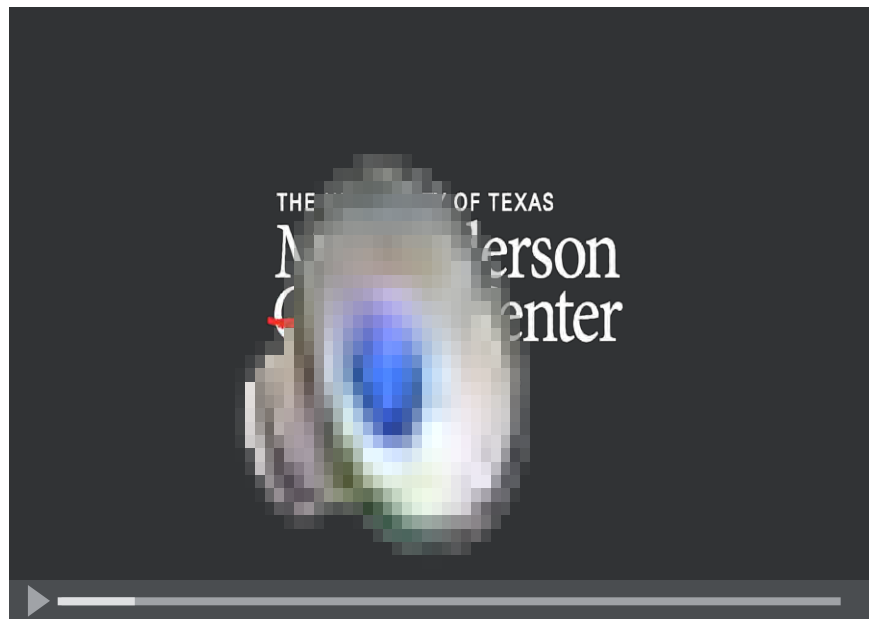


Scoring criteria based on degree of fragmentation, cell symmetry

Extending culture to day 5 improves implantation potential by facilitating embryo selection

# Preimplantation genetic testing (PGT)

- Hereditary causes occurring due to pathogenic gene sequence variants and defects comprise a significant number of all colorectal cancers and breast-ovarian cancers
- Genetic testing of embryos can be performed to avoid passing the gene of interest to offspring



Mutational analysis performed on single blastomere or trophoectoderm



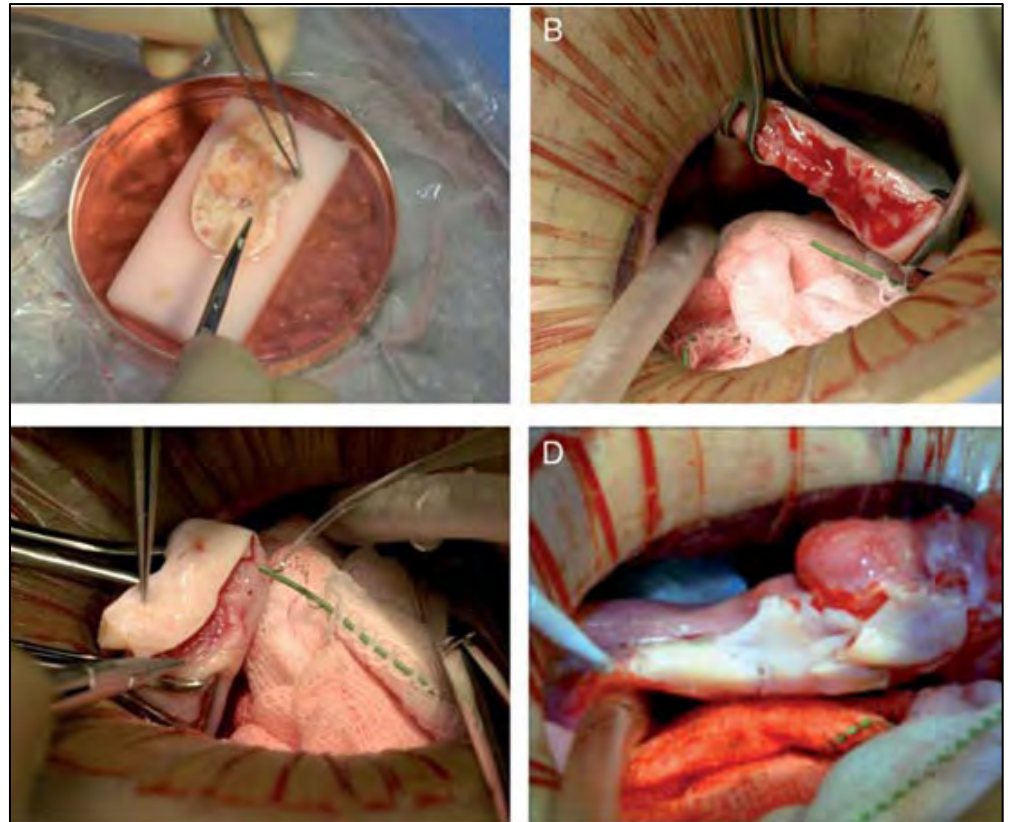
# Ovarian Tissue Cryopreservation

Over 130 live births with cryopreserved ovarian tissue have been reported as of June 2017<sup>1</sup>; as a result of orthotopic (pelvic) transplantation of thawed pieces of ovarian cortex

Amount of ovarian tissue removed varied from cortical biopsies measuring  $\sim 1.0 \times 0.5$  cm to removal of an entire ovary

Concern for metastatic cells

Was considered “experimental” until January 2020



Images courtesy of Sherman Silber, M.D.

<sup>1</sup>Donnez J, Dolmans MM. Fertility preservation in women. N Engl J Med 2017;377:1657–65.

## Surgical



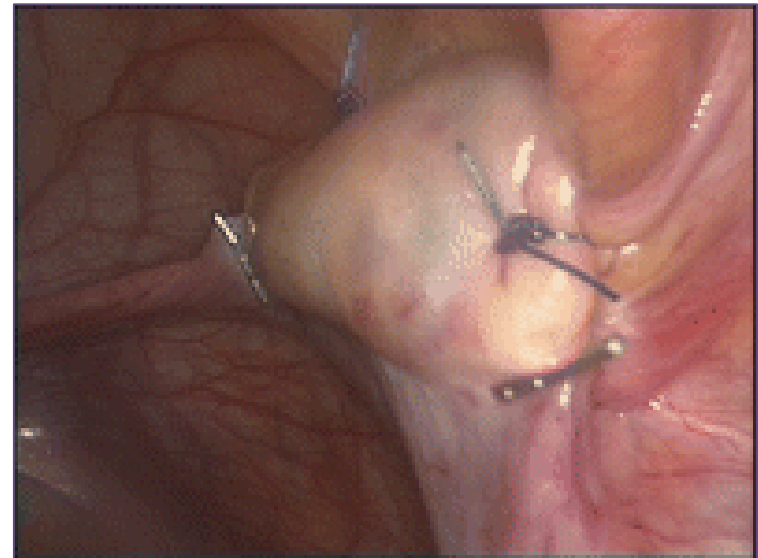
**Fertility sparing surgery to increase likelihood of having biological children in the future**

## Ovarian Transposition

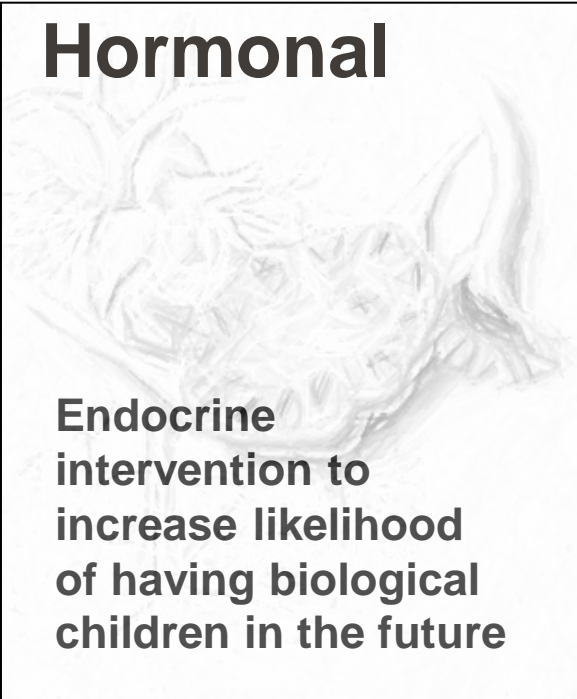
Repositioning the ovaries outside of XRT field prior to gonadotoxic pelvic or craniospinal radiation

XRT of 2 Gray: Loss of 50% of primordial follicles

15 Gray: Nearly 100% chance of POF



## Hormonal



Endocrine intervention to increase likelihood of having biological children in the future

## Ovarian Suppression

Does induction of a “quiescent” state of the ovary render it resistant to gonadotoxic chemotherapy?

Gonadotropin releasing hormone analogues

Effectiveness of GnRH is still not resolved  
J Clin Oncol ASCO Guidelines 2018

Menstrual suppression may be useful  
irrespective of ovarian protection

### Regimens:

Luprolide acetate 3.75 mg SQ monthly or 11.25 mg IM q 3 months

Goserelin (Zoladex) 3.6 mg SQ monthly or 10.8 mg SQ q 3 months

# **PREGNANCY OUTCOMES**

# Offspring of cancer survivors

Childhood Cancer Survivor Study, a large multi-centre cohort investigation, showed **no increased risk of congenital anomalies** in the offspring of survivors, including those exposed to ovarian irradiation or alkylating agents



# Radiotherapy and Uterine impact

- **Timing hypothesis** Women exposed to radiation after puberty have a larger uterus and greater likelihood of live birth than those exposed prepubertally
- Uterine irradiation at doses greater than 10 Gy significantly increased risk of stillbirth and neonatal death after puberty (OR 9.1, 95% CI 3.4–24.6)
- Girls treated before menarche, doses as low as 1–2.5 Gy associated with a significant increase in the risk of still- birth and neonatal deaths (OR 4.7, 95% CI 1.2–19)



Pregnancy  
Contraindication:  
Prepubertal XRT  
>25Gy  
Adult XRT > 45 Gy  
*Tech et al., 2014*

# Premature Ovarian Insufficiency

Premature (versus Primary) Ovarian Insufficiency (versus Failure) is a clinical syndrome defined by loss of ovarian activity before the age of 40

POI is characterized by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins (FSH, LH) and low estradiol

def·i·ni·tion

defə<sup>l</sup>niʃH(ə)n

## SEQUELAE

### BONE HEALTH

Estrogen deficiency results in increased bone remodeling

- Increased osteoclast activity results in increased bone resorption, and that in turn induces an increase in osteoblast activity and bone formation, however with resorption exceeding formation

Rapid remodeling of estrogen deficiency means there is a net loss of bone, amounting to 2-3% per year after menopause

Have reduced BMD, and this has been associated with the presence, degree, and duration of estrogen deficiency

DEXA





# SEQUELAE

## CARDIOVASCULAR DISEASE

Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease

Prospective U.S. Cohort of >6,000 women followed over 12 years, those that underwent menopause at age 35-40 had a **50% greater subsequent risk of ischemic heart disease related death** (after adjusting for confounders such as diabetes, hypertension, activity level, etc.) compared to those between 49 and 51 years of age ( Jacobsen et al., 1999)

Women with POI should be advised on how to reduce cardiovascular risk factors by not smoking, taking regular exercise, and maintaining a healthy weight



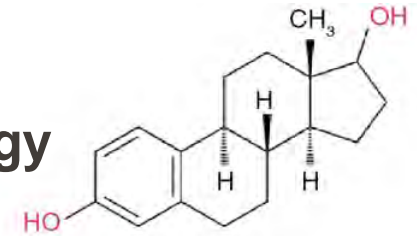
# TREATMENT STRATEGY

**ONE: To provide enough E to mimic normal physiology**

## ESTROGENS

3 types of estrogen that are available for hormone replacement:

1. Estradiol (the main ovarian estrogen 17 $\beta$ -estradiol is the active component)
2. Ethinyl estradiol (a synthetic estrogen)
3. Conjugated equine estrogens (CEE - derived from pregnant mare urine)

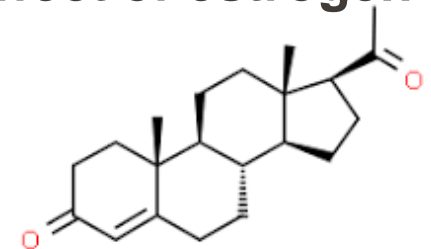


17 $\beta$ -estradiol (E2)

**TWO: Protect the endometrium from the mitogenic effect of estrogen**

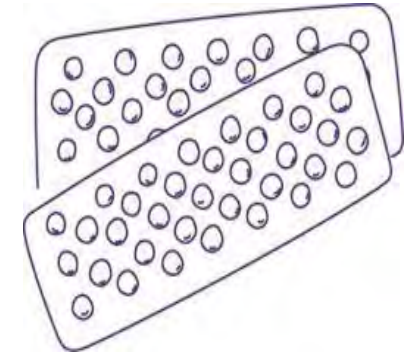
## PROGESTAGENS

1. Synthetic progestogens: Medroxyprogesterone acetate
2. Progesterone: Micronized progesterone



## TREATMENT

### CONSIDERATIONS: OCPS versus HT



Combination oral contraceptives are typically easier

Yet recall these are not replacement; they are more potent

- Perhaps higher clot risk
- Atrophic effect on the endometrium of the pill may also be a reason to avoid its use for RT in younger group, at least until after a period of treatment with a cyclical combined regime
- Are contraceptive

HT may still allow a spontaneous ovulation & pregnancy

- Albeit rates are modest

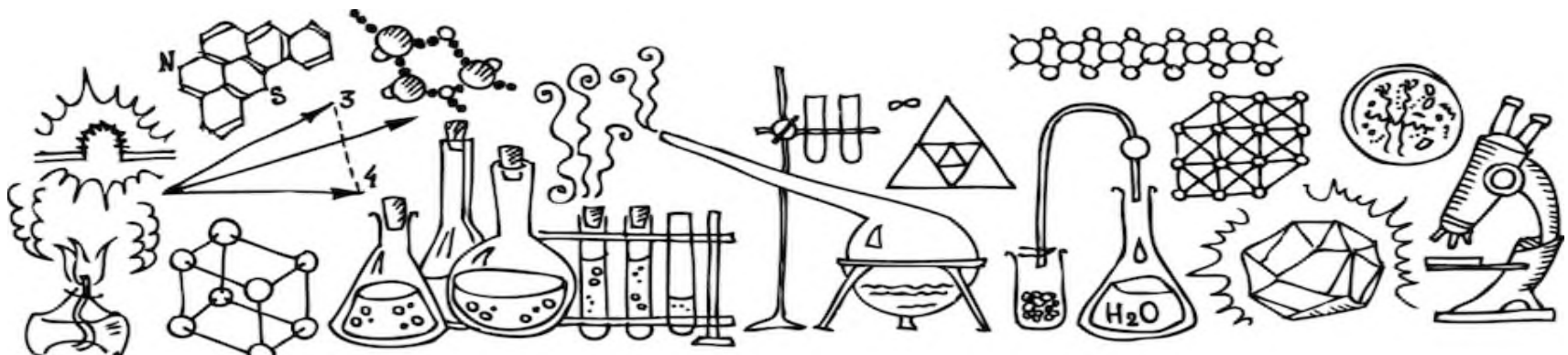
# MONITORING

Currently, there is no evidence regarding the optimum HT monitoring strategy

Estrogen dosage should be titrated to achieve symptom control and adequate bone density

Serum estradiol is not helpful in clinical practice and does not measure ethinyl estradiol (in OCPs) or estrone (the predominant estrogen in some HRTs)

There is no value in monitoring FSH levels, as they may not normalize



<https://mdanderson.org/patient-education>

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## Fertility Options for Women Diagnosed with Cancer

Certain types of cancer treatments can affect a woman's fertility. Fertility is a woman's ability to get pregnant or carry a pregnancy to term.

Many young women who face a cancer diagnosis want to have children in the future. There are options to help protect your fertility. The best time to preserve your fertility is before you begin cancer treatments.

Ask your health care team about fertility-saving options as soon as possible after your cancer diagnosis.

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PATIENT EDUCATION

## Fertility Options for Men Diagnosed With Cancer Sperm Banking

### Cancer Treatment and Fertility

For men, fertility means being able to produce healthy sperm cells that can fertilize an egg to try to make a woman pregnant.

It is common for men with cancer to have a temporary drop in semen quality. Semen quality includes:

- Sperm count (how many sperm are in a man's semen)
- Sperm motility (ability of sperm to swim to the egg)
- Sperm morphology (the percent of sperm with normal shapes)

 [Hysterosalpingogram \(HSG\)](#)

 [Fertility Options for Men Diagnosed with Cancer \(Spanish\)](#)

 [Fertility Options for Women Diagnosed With Cancer](#)

 [In Vitro Fertilization \(IVF\) with Preimplantation Genetic Testing \(PGT\) for Single Gene](#)

 [Sexuality and Chemotherapy \(Spanish\)](#)

 [Pregnancy Test](#)

 [Oocyte Cryopreservation](#)

## MDA YOCRC Seminar 2023

Livestrong Foundation: [livestrong.org](http://livestrong.org)  
Dedicated to providing reproductive information, support and hope to cancer patients and survivors whose medical treatments present the risk of infertility

855-220-7777

[www.MyOncofertility.org](http://www.MyOncofertility.org)

A patient education resource by the Oncofertility Consortium

RESOLVE [www.resolve.org](http://www.resolve.org)

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## KEY POINTS

- ❖ Fertility preservation counseling is important
- ❖ Consider baseline fertility assessment and tracking
- ❖ Many paths to parenthood
- ❖ Be aware of the long term health implications associated with prolonged hypoestrogenism; means to alleviate this

**And most importantly,**

**Addressing the reproductive and hormonal implications of treatment and providing long term expectations significantly impacts quality of life....**





Thank you!

Questions?