Family Building and Cancer

Elizabeth Constance, MD, FACOG *(she/her)*
Director, Fertility Preservation Program and LGBTQ+ Health Services
Heartland Center for Reproductive Medicine
Assistant Professor, University of Nebraska Medicine
Department of OB/GYN

Heartland Center
for Reproductive Medicine

Disclosures

- No financial conflicts or disclosures
- This presentation will discuss the off-label use of medications involved in standard fertility treatments

Objectives

1. Review natural fertility and reproductive function

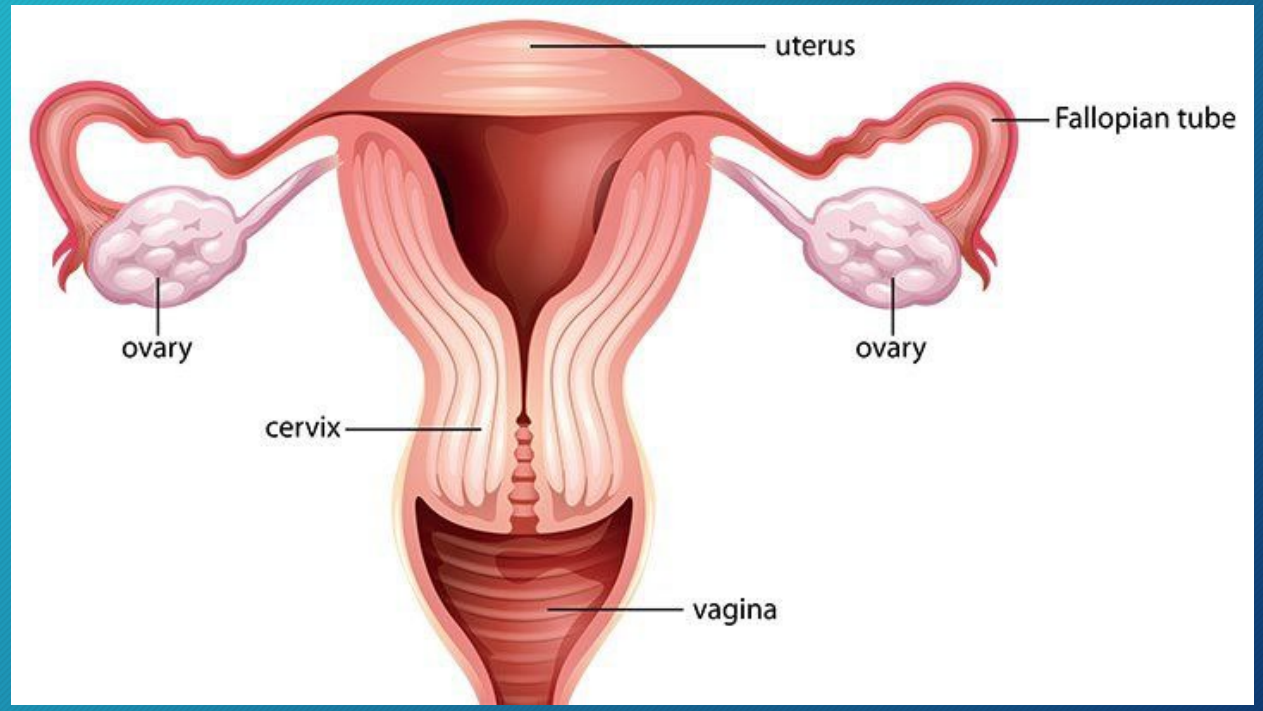
2. Describe how various cancer therapies impact fertility potential and reproductive timeline

3. Discuss options for fertility preservation before cancer treatment

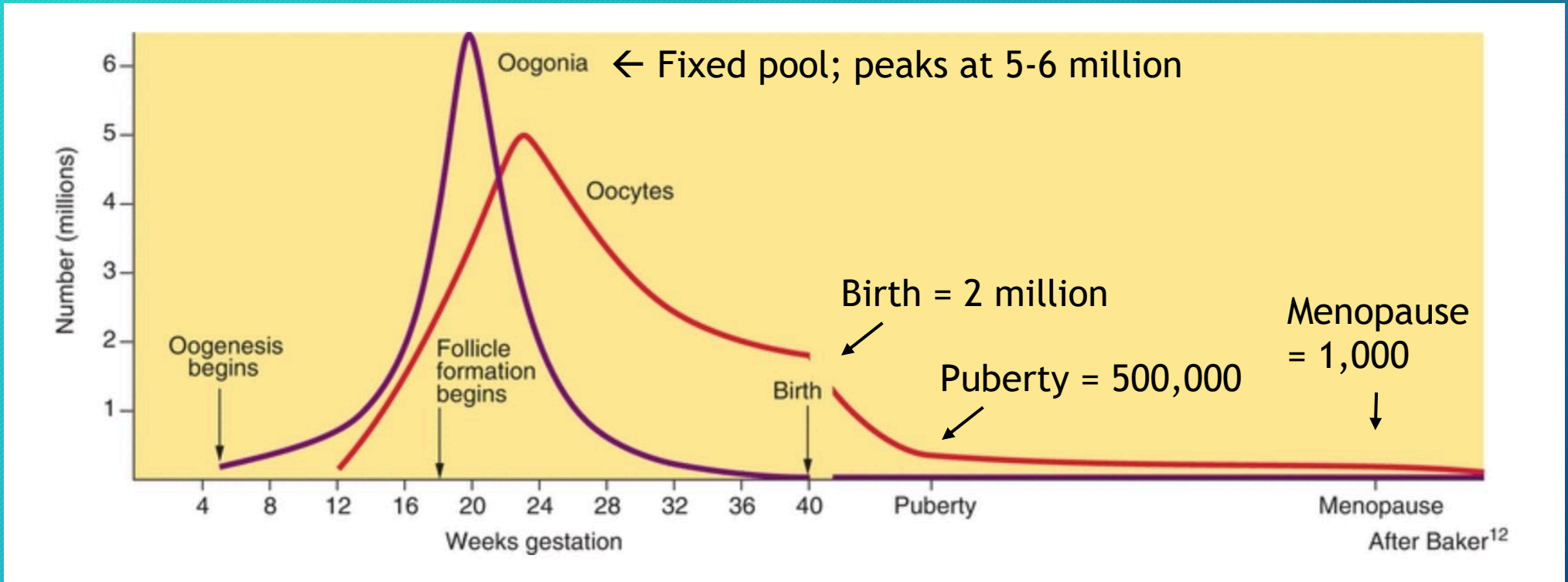
4. Explore strategies for monitoring post-treatment reproductive function and family building options

Female Fertility 101

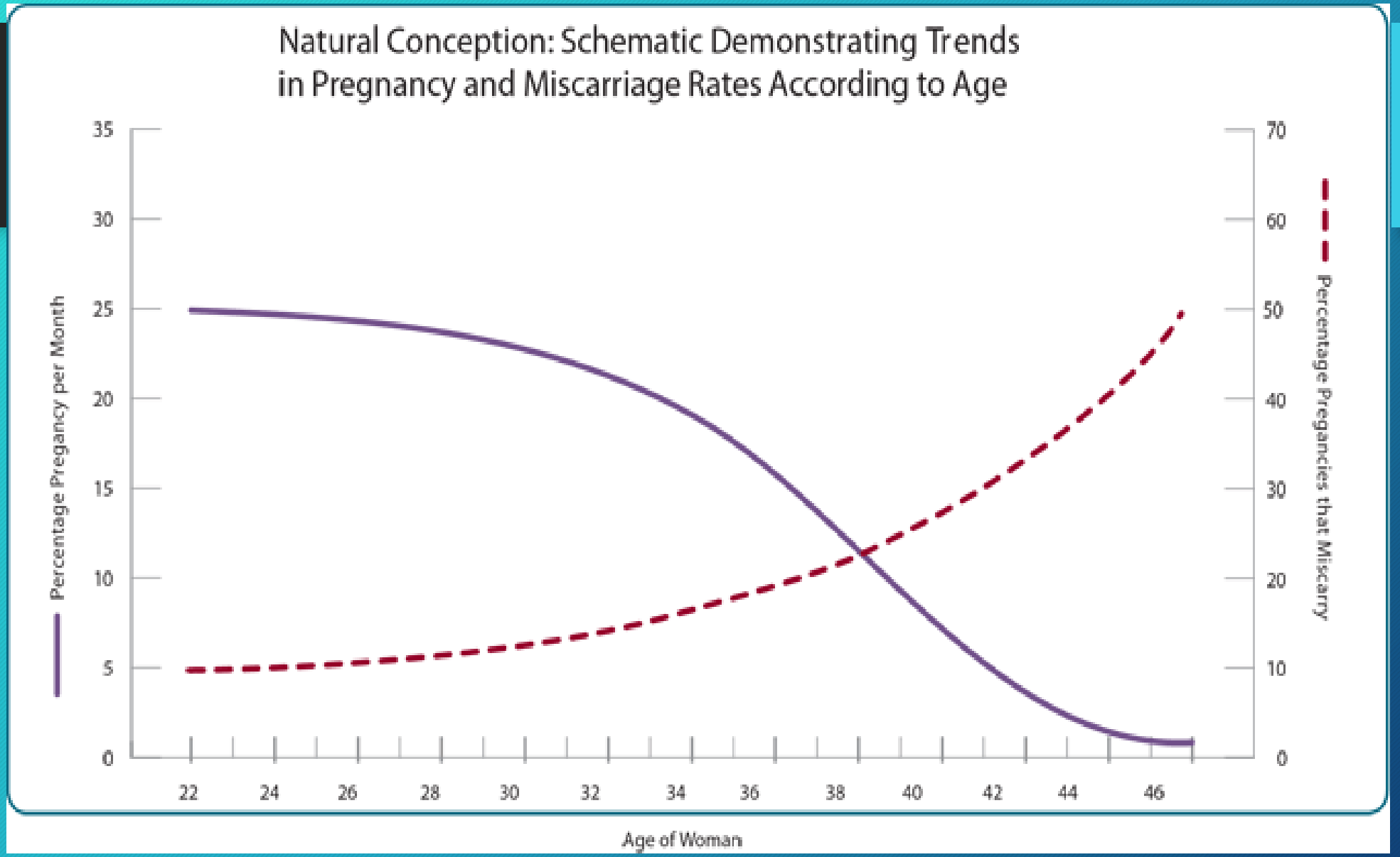
- Egg number
  - Determined before birth
  - Number goes down over time
  - Varies from person to person
    - Genetics, environment, etc.
- Egg quality
  - Most closely associated with age
  - Declines over time
- Tubes
  - Highway from ovaries to uterus
- Uterus
  - Where pregnancy implants and grows



Ovarian Reserve (Egg Number)



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


Natural Conception: Schematic Demonstrating Trends in Pregnancy and Miscarriage Rates According to Age
Percentage Pregancy per Month
Percentage Pregancies that Miscarry
Age of Woman
0
5
10
15
20
25
30
35
0
10
20
30
40
50
60
70
22
24
26
28
30
32
34
36
38
40
42
44
46

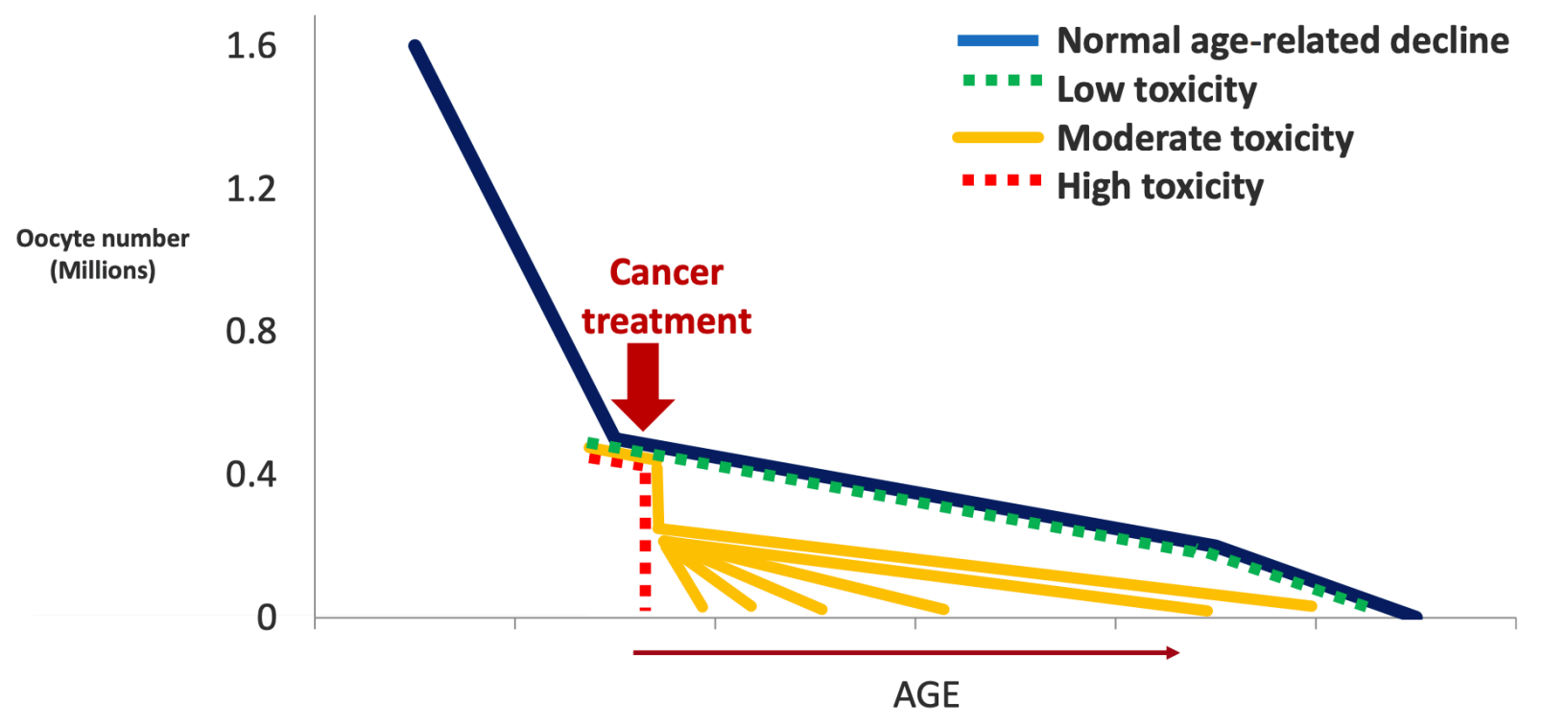
How Does Cancer Therapy Affect Female Fertility?

- Chemotherapy
  - Cause damage to blood vessels, supporting cells in ovary
  - Ovarian damage will result in follicle death
  - Age and dose dependent
- Radiation
  - Abdominal/pelvic radiation
  - TBI doses of > 10 Gy results in ovarian failure in 90% of females
  - Risk of infertility is related to number of follicles in reserve and dose of XRT
  - Radiation injury to the uterus can affect ability to conceive and carry a pregnancy
- Surgery
  - Abdomen/Pelvis
  - Hypothalamus/Pituitary

Risk of Ovarian Failure (early menopause)

High Risk	>80%	• Whole abdominal or pelvic radiation doses >6 Gy in adult women • Total body irradiation (TBI) • Cranial/brain irradiation >40 Gy • CMF, CEF, or CAF x 6 cycles in women >40 years • Total cyclophosphadmide 5 g/m2 in women >40 years • Total cyclophosphadmidey > 7.5 g/m2 <20 years • Alkylating chemotherapy (e.g., cyclophosphamide, busulfan, melaphan) conditioning for transplant • Any alkylating agent (e.g., cyclophosphamide, ifosfamide, busulfan, BCNU [carmustine], CCNU [lomustine]) + TBI or pelvic radiation • Protocols containing procarbazine: MOPP, MVPP, COPP, ChlVPP, ChlVPP/EVA, BEACOPP, MOPP/ABVD, COPP/ABVD
Intermediate Risk	30-70%	• Abdominal/pelvic radiation • CMF, CEF, or CAF x 6 cycles in women 30-40 year • Spinal radiation doses >25 Gy CMF, CEF, or CAF x 6 cycles in women 30–40 years • Bevacizumab (Avastin) • Protocols containing cisplatin • FOLFOX4 • Total cyclophos-phamide 5 g /m2 in women age 30- 40
Low Risk	<30%	• CMF, CEF, or CAF x 6 cycles in women <30 years • Nonalkylating chemotherapy: ABVD • Anthracycline + cytarabine
No Risk		• Radioactive iodine • MF • Multi-agent therapies using vincristine
Unknown Risk		• Monoclonal antibodies, e.g., cetuximab (Erbitux) • Tyrosine kinase inhibitors, e.g., erlotinib (Tarceva), imatinib (Gleevec)

Female Fertility Risk



The Guidelines

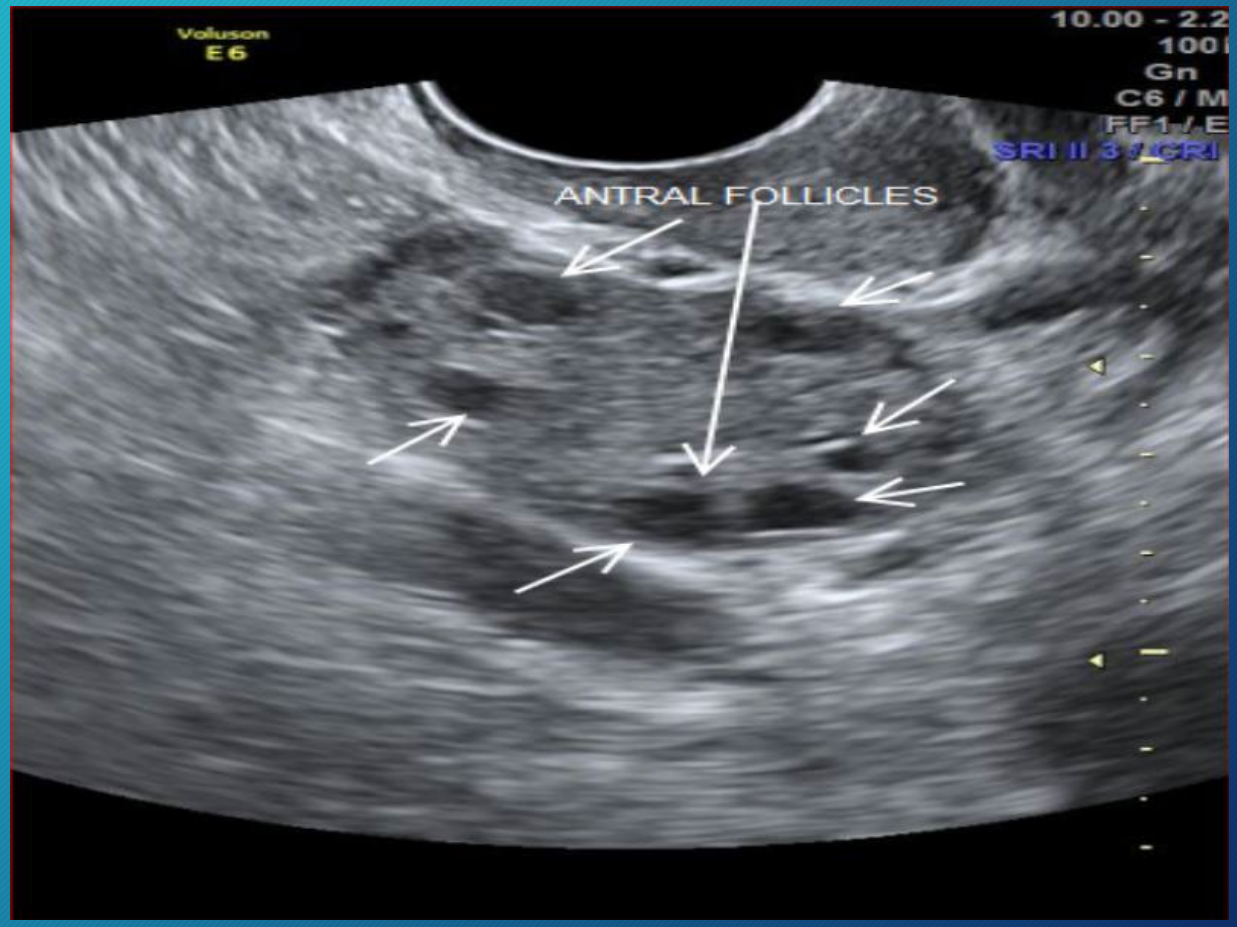
- **ASCO**: "…*health care providers (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons) should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists…as early as possible in the treatment process*"

- **ASRM**: *"When damage to reproductive organs due to cancer treatment are unavoidable, cancer specialists should inform patients of options for storing gametes, embryos, or gonadal tissue and refer them to fertility specialists who can provide or counsel them about those services."*

- **AAP**: "*Oncologists have a responsibility to inform parents and age-appropriate patients about the likelihood that treatment will permanently affect their fertility*"

Ovarian Reserve Testing

- Ultrasound for Antral Follicle Count (AFC)
- Anti-Mullerian Hormone (AMH)
- Cycle Day 3 Follicle Stimulating Hormone (FSH) with Estradiol (E2)



Ovarian Reserve Testing

AMH ng/ml	Clinical Situation	Implications
Very Low (< 0.5)	Impending onset of premature menopause	Predicts low ovarian response to stimulation
Low (≥ 0.5 - < 1.0)	Limited egg supply Diminished reserve	Shortened reproductive window
Normal (≥ 1.0 - 3.5)	Normal testing	Suggests good response to ovarian stimulation
Elevated (> 3.5)	Polycystic ovaries	Risk of hyperstimulation during ovarian stimulation
FSH mIU/ml		**Implications**
< 10		Normal
≥ 10 and < 25		Impending POI
≥ 25		POI

Modified, Toner. Fertil Steril 2013
Broer. Hum Reprod Update. 2013;19)1):26-36

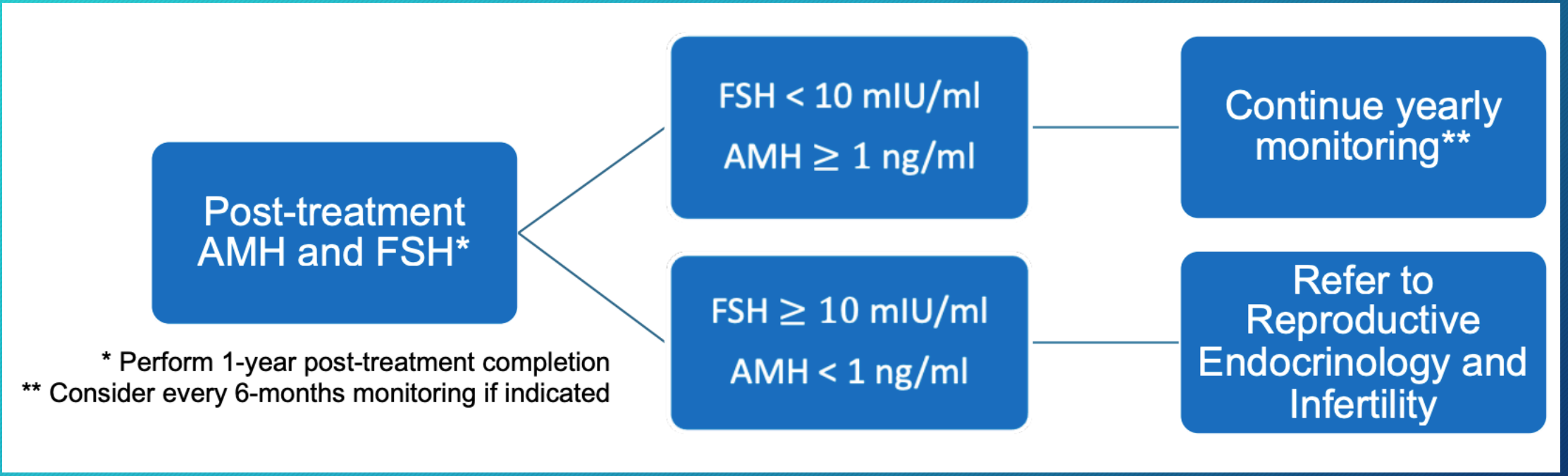
Pre-Treatment AMH and Post-Treatment Ovarian Function

- Participants with pre-treatment AMH >2 ng/ml recovered their AMH level at a rate of 11.9% per month after chemotherapy
- Participants with pre-treatment AMH <2 ng/ml recovered their AMH level at a rate of 2.6% per month

Dillon et al. Fertil Steril 2013;99:477-83.

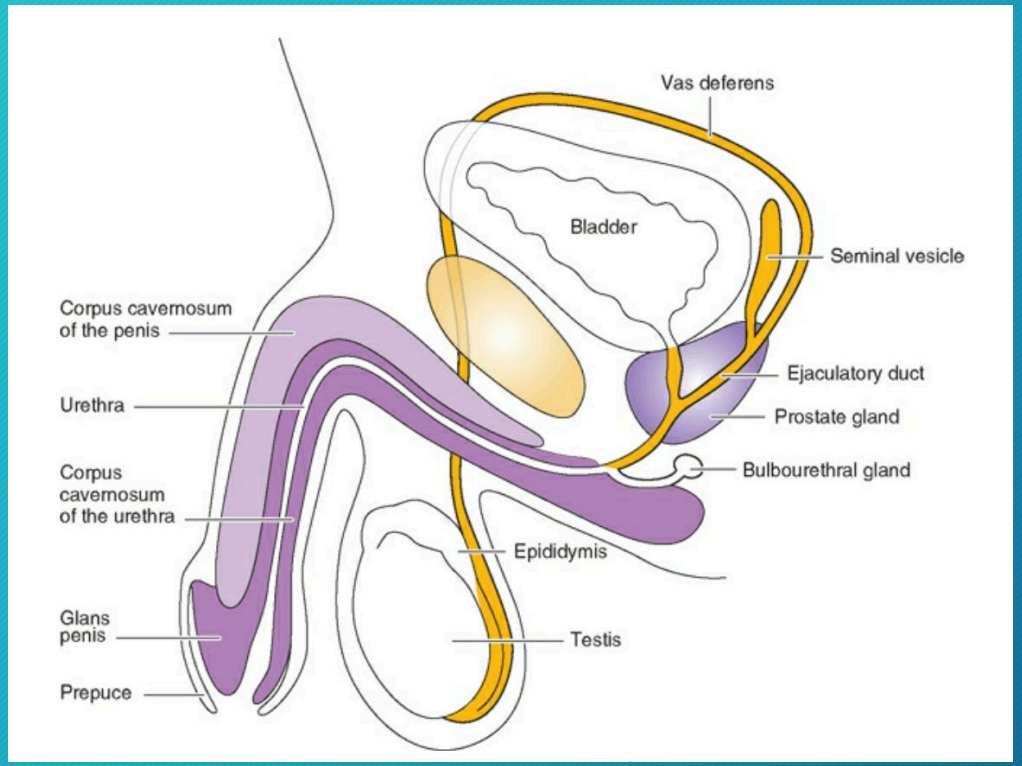
Ovarian Reserve Monitoring

- No standard of care regarding post-treatment monitoring in the absence of clinical signs of ovarian insufficiency for individuals <25 years



Guzy L, Demeestere I. Minerva Ginecol. 2017;69(1):57-67. Toner JP, Seifer DB. Fertil Steril. 2013;99(7):1825-30. George S, Meacham L. Pediatr Blood Cancer. 2019 Dec;66(12)

Male Fertility 101



Speroff. Clinical Gynecologic Endocrinology and Infertility. 8th edition

How Does Cancer Therapy Affect Male Fertility?

- Chemotherapy
  - Sperm producing cells can be damaged by chemotherapy
  - Sperm concentration decreases with increasing dose

- Radiation
  - Complete lack of sperm seen with doses >4 Gy to testes
  - TBI doses of >9 Gy have resulted in lack of sperm production
  - Cranial XRT >40 Gy will affect FSH/LH production

- Surgery
  - Disrupt normal sperm transit
  - Disrupt coordinated ejaculation with bladder neck closure

Fertility Preservation Options Before Treatment

Females

- Embryo Freezing
- Egg Freezing
- Ovarian Shielding
- Ovarian Transposition
- Ovarian Tissue Freezing
- *GnRH Agonist*

Males

- Sperm Freezing
- Testicular Sperm Extraction
- Testicular Shielding
- *Testicular Tissue Freezing*

Oocyte/Embryo Cryopreservation

Gold Standard for Female Fertility Preservation in adults/adolescents

- A frozen egg = a fresh egg
- Random start protocol – 2 weeks to complete
- Aromatase inhibitor for hormone-sensitive cancers
- Can be done with IUD or Nexplanon in place
- No difference in long-term cancer outcomes

Oocyte/Embryo Cryopreservation Considerations

- Post-puberty only
- Emotionally/psychologically ready for multiple USNs, blood draws, etc
- Must be able to delay cancer treatment for at least 2 weeks
- Must be healthy enough to undergo oocyte retrieval
- Requires hormonal stimulation
- Legal considerations with embryos

Safety Data

- 2005 – Okta: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation

  Outcomes: Recurrence rate in the **29** women that did FP was similar to the **31** patients who did not undergo FP

- 2008 – Azim lation with letroz prospective

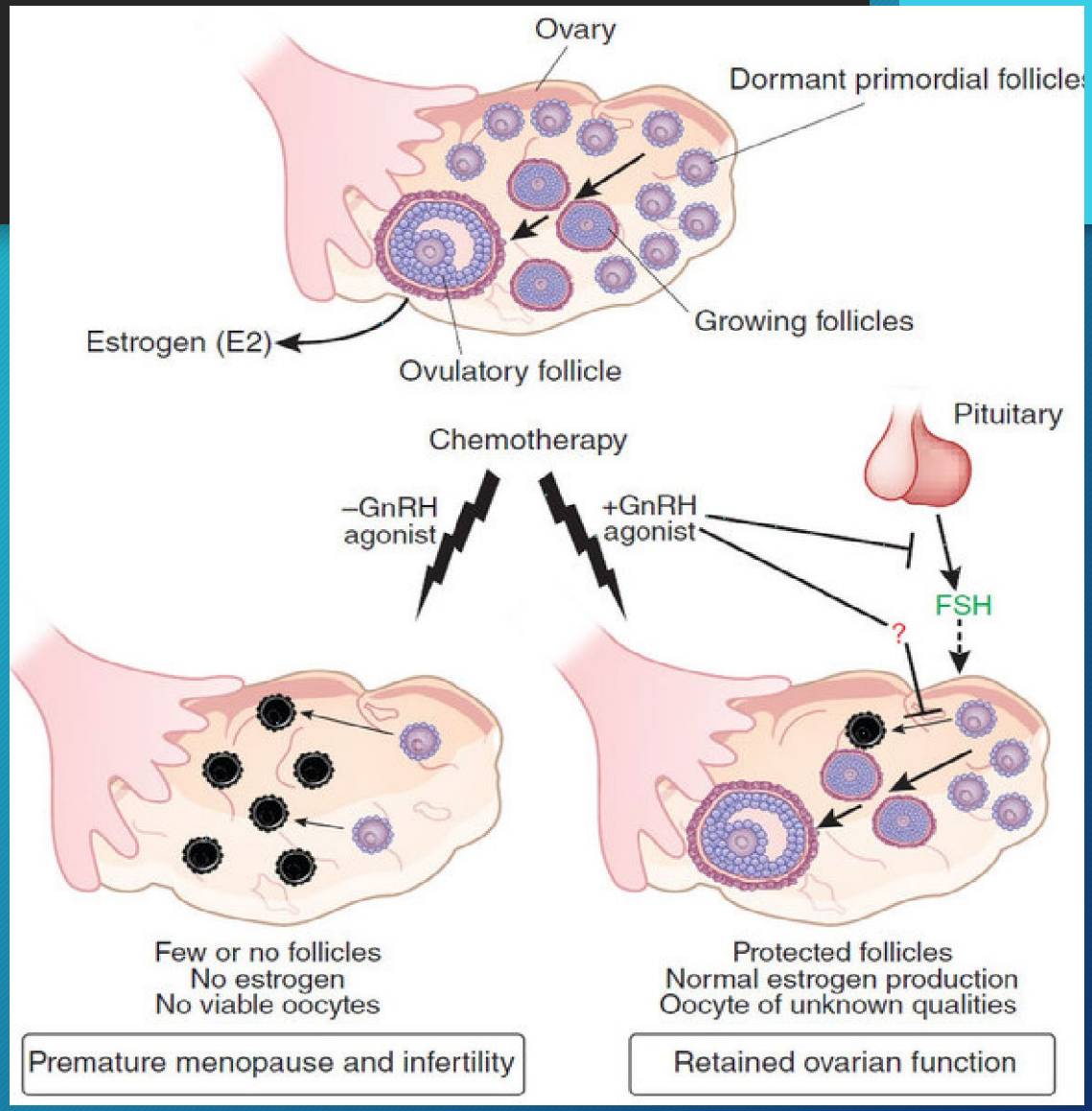
  Outcomes: no increase in recurrence or death in 79 breast cancer patients who chose to have embryos stored before treatment using letrozole compared with 136 patients who were evaluated but declined FP

- 2012 – Westphal – Gyn Onc - Integration and safety of fertility preservatio

  Outcomes: 2 local breast cancer recurrences out of the 44 breast cancer patients who underwent ovarian stimulation with a mean follow up of 47 months.

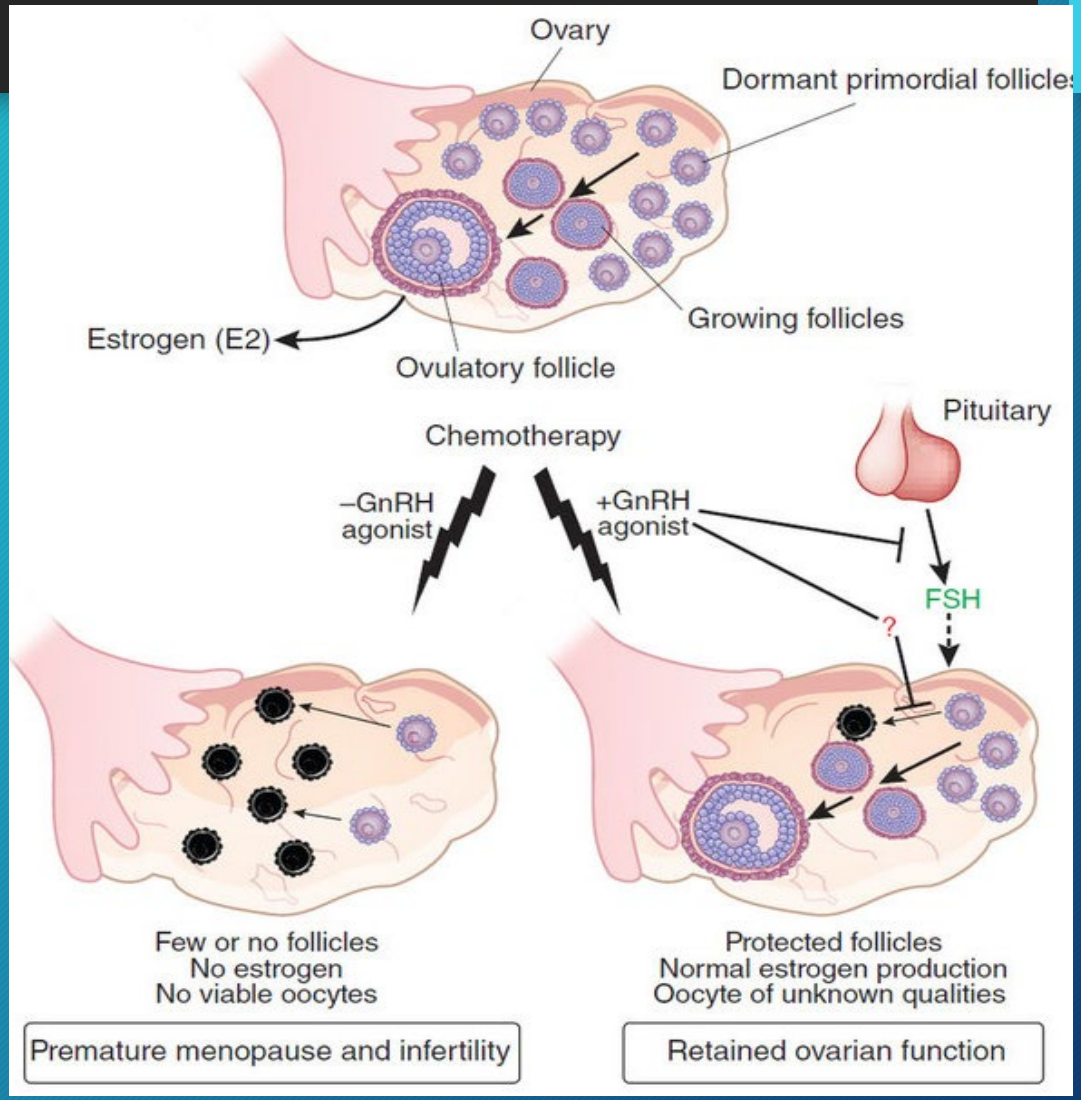
GnRH agonist

- Experimental
- POEMS and PROMISE studies show efficacy in breast cancer patients
- Study in lymphoma patients showed no benefit
- Timing important to avoid Flare effect



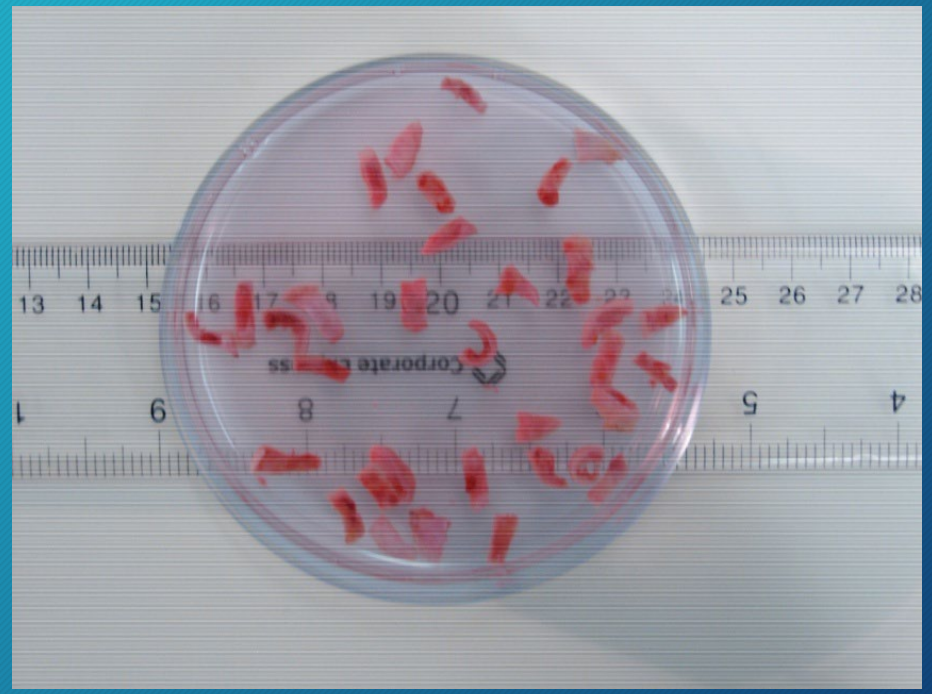
GnRH agonist – How to Administer

- Timing
  - 7-10 days **before** initiation of chemotherapy
    - Exceptions: OCPs or luteal phase of menstrual cycle
  - Any time after chemotherapy (day of discharge ok)
- Dosing
  - 3.75 mg Q month
  - 11.25 mg Q 3 months
- Continue for duration of chemotherapy
  - Caution >6 months



Ovarian Tissue Cryopreservation

- **Experimental designation removed 2019**
- Only option for pre-pubertal girls
- Removal of part or all of one ovary
- Strips of ovarian tissue frozen
- Tissue can be re-implanted in the pelvis or under the skin in the arm/abdomen



Sperm Cryopreservation

- Gold Standard for adolescents/adults

- Methods for retrieval of sperm
  - Masturbation
  - Testicular sperm extraction

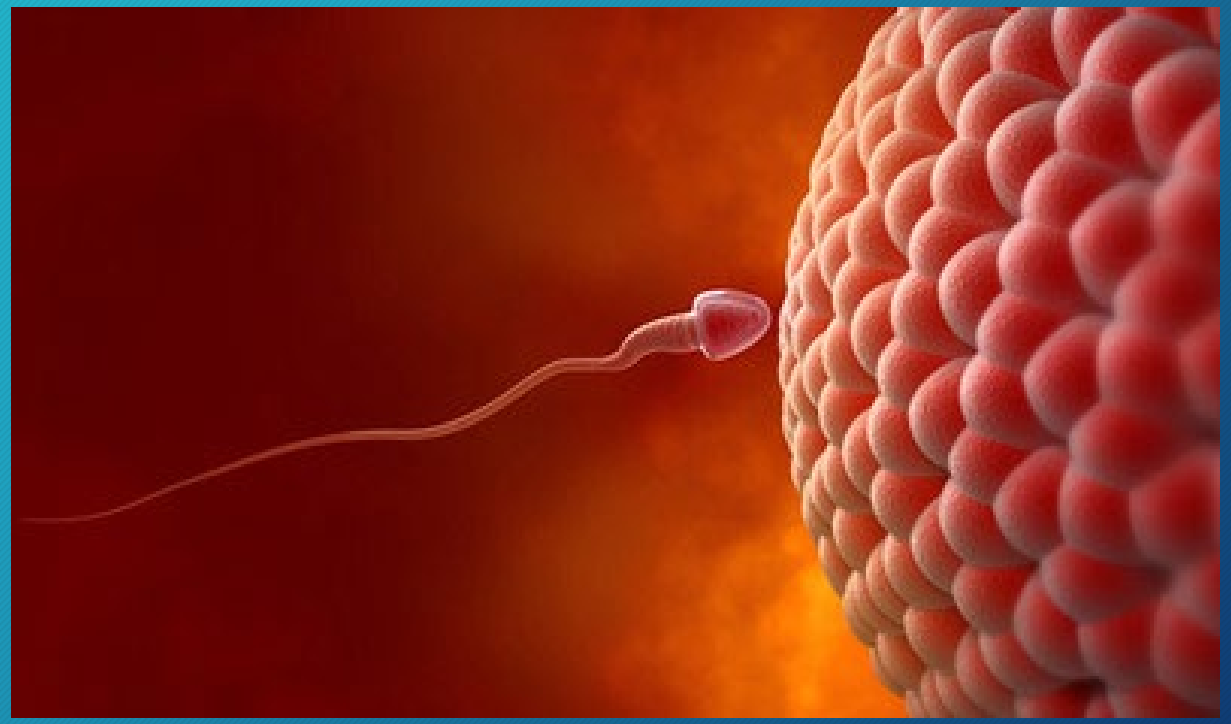
Testicular Tissue Cryopreservation

- No pregnancies reported (yet) in humans

- Possible future options:
  - Transplantation of spermatogonial stem cells
  - In vitro maturation
  - Testicular tissue autografting
  - Induced pluripotent stem cells

Fertility Options After Cancer Treatment

- Unassisted Conception
- Hormonal therapies
- Intrauterine insemination (IUI)
- *In Vitro* Fertilization (IVF)
- 3rd party reproduction



Impact of Cancer/Cancer Treatment on Pregnancy

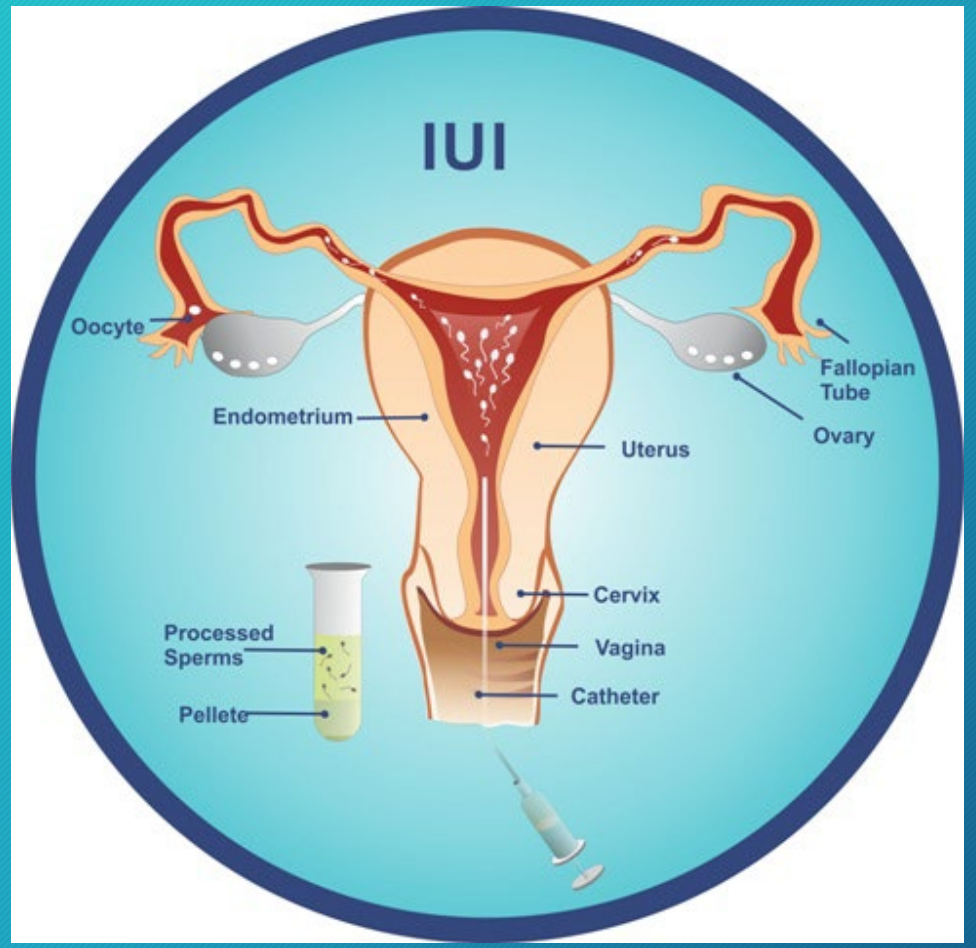
- 6-12 months delay post treatment recommended
- Babies born to mothers with prior treatment are not at risk from mother's treatment
- Increased pregnancy complication rate and timing
  - Overall, pregnancy after cancer goes as expected and is safe
  - Increased pre-term birth if ≤ 1 year after chemo ended in cervical & breast cancer

- POSITIVE Study: Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine RespponsIVE Breast Cancer

Hormone Therapies

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

Intrauterine Insemination (IUI)

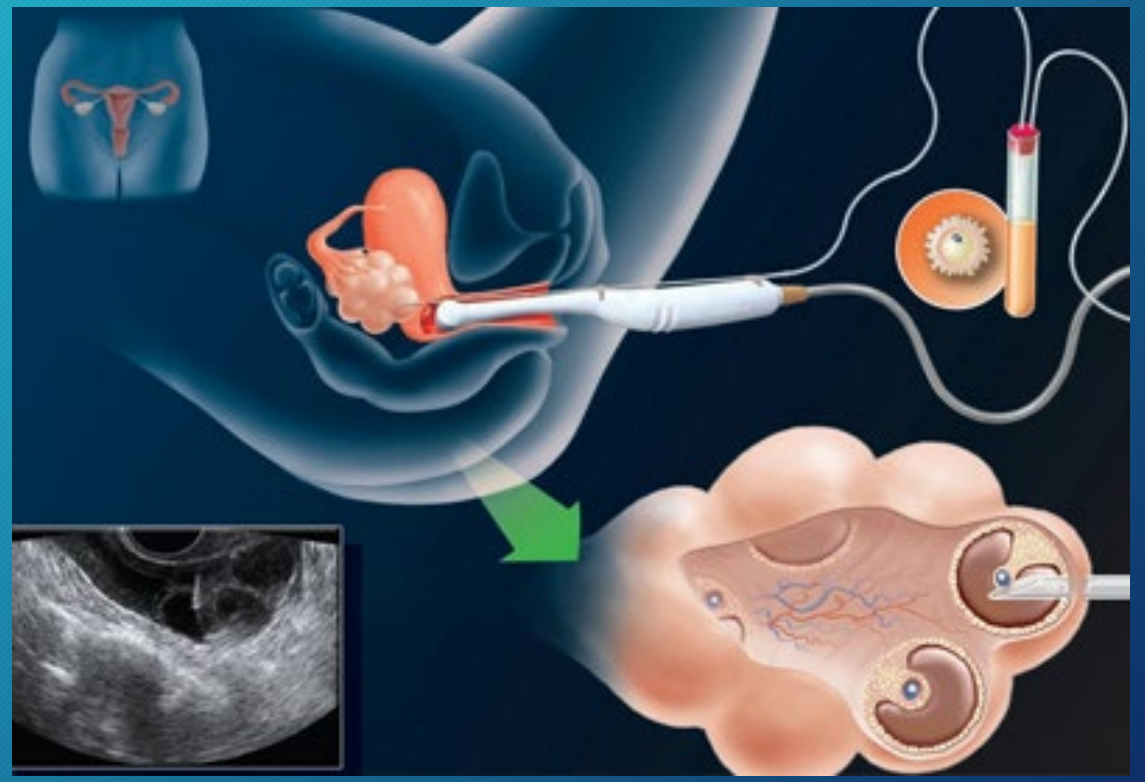


IVF and Egg/Embryo Freezing

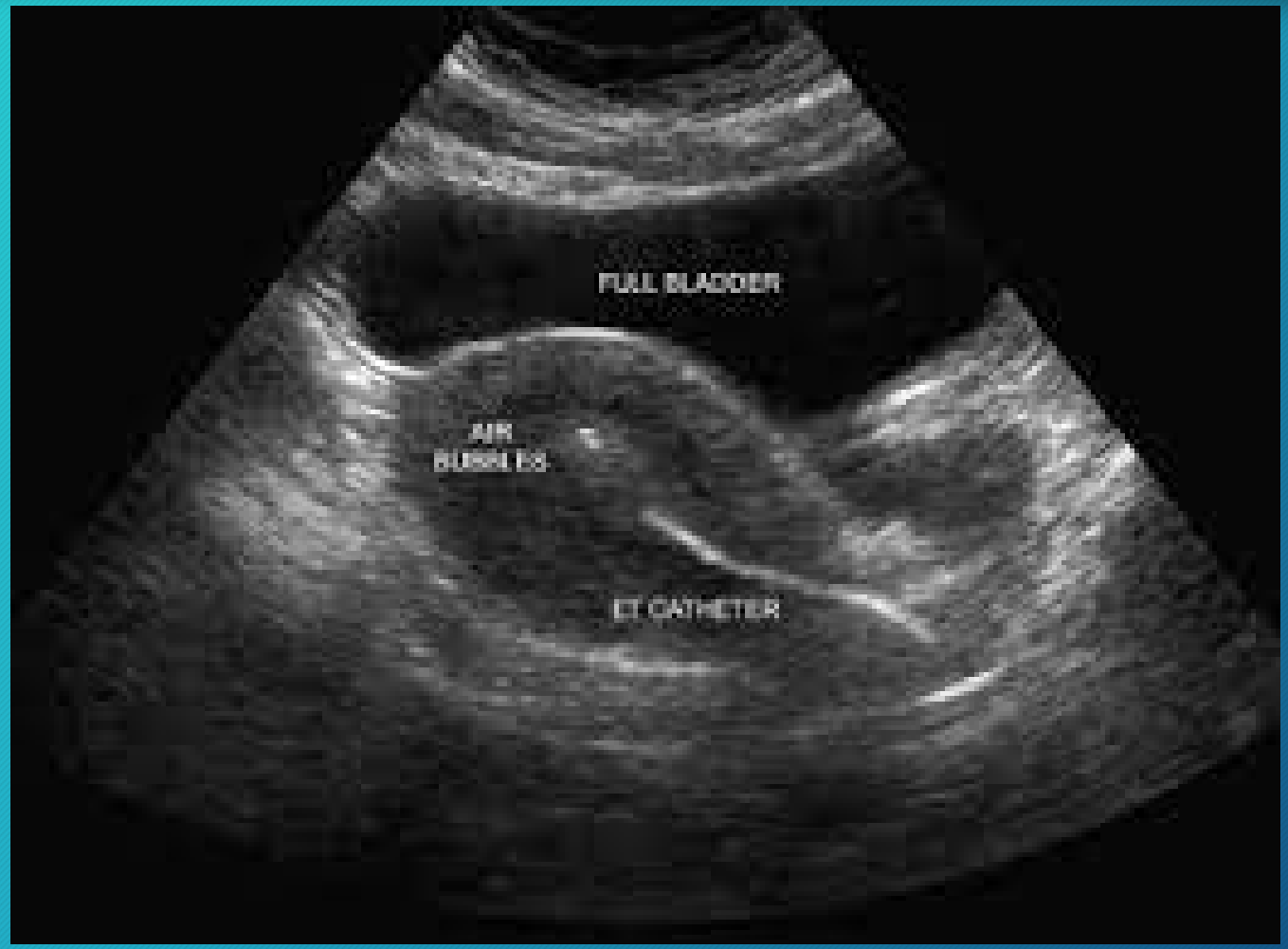
- Injectable medications for 10-14 days to stimulate ovaries
  - Overlap with letrozole in breast cancer patients
- Medication to prevent ovulation
- HCG triggers ovulation ~36 hours before egg retrieval

Egg Retrieval

- Done under conscious sedation or general anesthesia
- Vaginal ultrasound and needle guide
- Know immediately # of eggs
- Find out how many eggs successfully fertilized the following day



Embryo Transfer



Maines. Fert Stert. 2010

Preimplantation Genetic Testing

Third Party Reproduction

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

Thank You!

the Oncofertility® Consortium

AT HEARTLAND CENTER FOR REPRODUCTIVE MEDICINE