Fertility Preservation

Mary Peavey, MD, MSCI

Assistant Professor
Director of UNC Fertility Preservation
UNC Reproductive Endocrinology and Infertility
Department of Ob/Gyn

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Learning Objectives

1. Discuss the importance of conveying the risk of infertility due to cancer treatments
2. Review treatment options available to reproductive age males & females both before and after their cancer treatments
3. Provide an overview of Fertility Preservation services if patients need them

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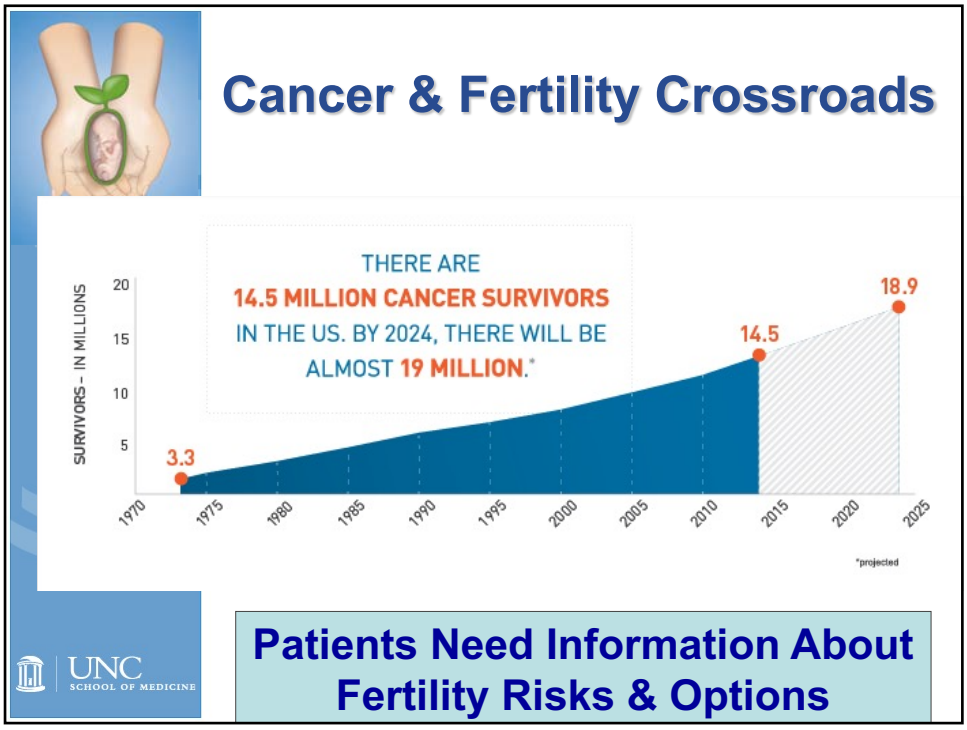
Cancer & Fertility Crossroads
THERE ARE
14.5 MILLION CANCER SURVIVORS
IN THE US. BY 2024, THERE WILL BE
ALMOST 19 MILLION.*
SURVIVORS – IN MILLIONS
20
15
10
5
3.3
14.5
18.9
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
2020
2025
*projected
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Patients Need Information About Fertility Risks & Options

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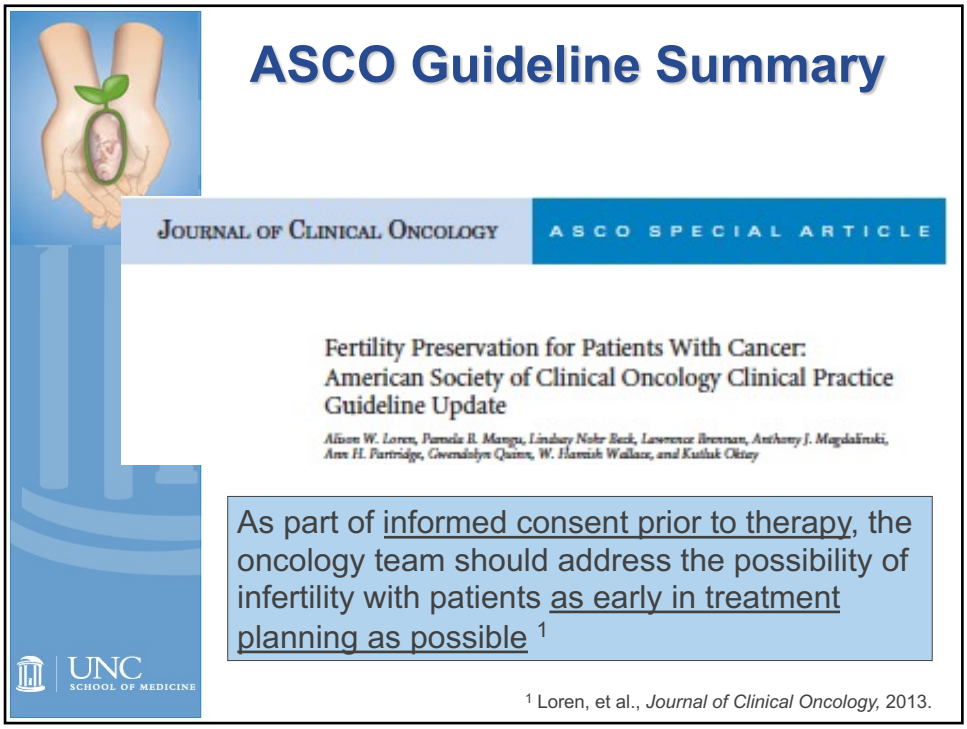
ASCO Guideline Summary
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE
Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update
Alison W. Loren, Pamela B. Mangu, Lindsay Nohr Beck, Lawrence Brennan, Anthony J. Magdalinski, Ann H. Partridge, Gwendolyn Quinn, W. Hamish Wallace, and Kutluk Oktay
As part of informed consent prior to therapy, the oncology team should address the possibility of infertility with patients as early in treatment planning as possible [1]
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[1] Loren, et al., Journal of Clinical Oncology, 2013.

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What is Fertility Preservation?

- Fertility Preservation
  - » Fertility management for cancer patients of reproductive age
  - » Oncology teams and fertility specialists work together through issues of both cancer treatment as well as potential fertility threats in that immediate moment of diagnosis

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Women, Cancer and Fertility

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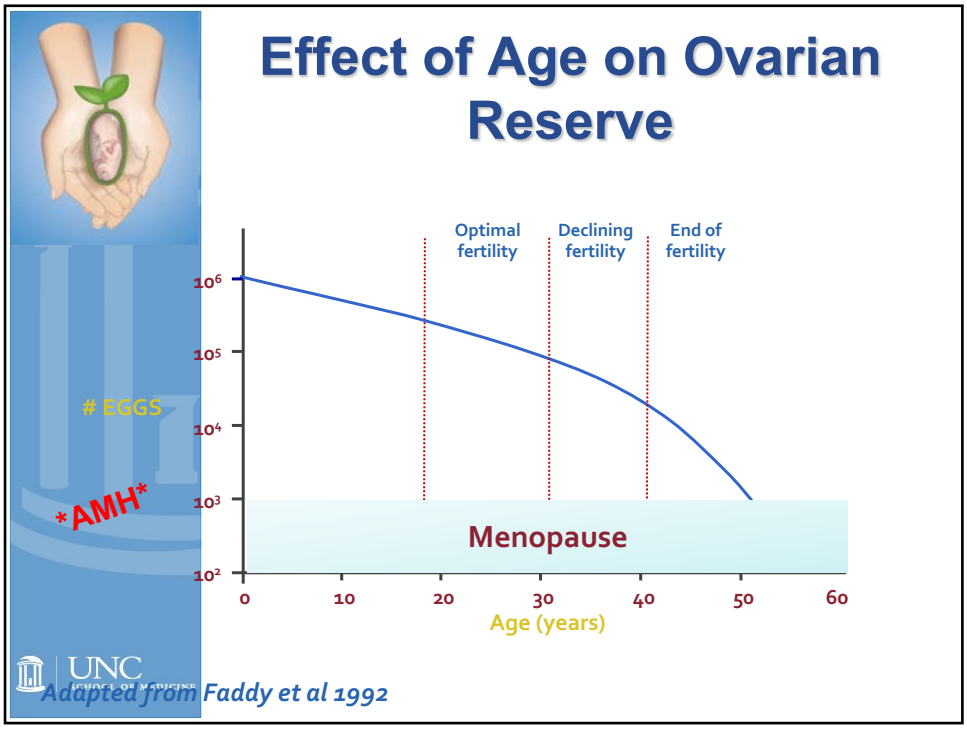
Effect of Age on Ovarian Reserve
Optimal fertility
Declining fertility
End of fertility
EGGS
AMH
10^6
10^5
10^4
10^3
10^2
Menopause
0
10
20
30
40
50
60
Age (years)
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Adapted from Faddy et al 1992

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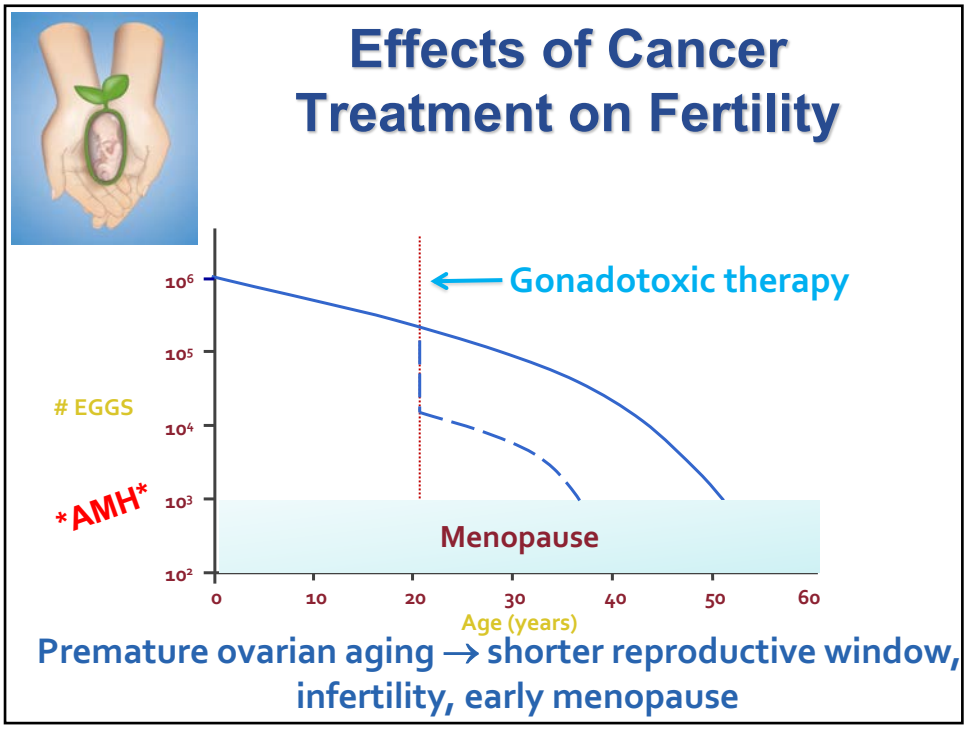
Effects of Cancer Treatment on Fertility
Gonadotoxic therapy
EGGS
AMH
10^6
10^5
10^4
10^3
10^2
Menopause
0
10
20
30
40
50
60
Age (years)
Premature ovarian aging → shorter reproductive window, infertility, early menopause

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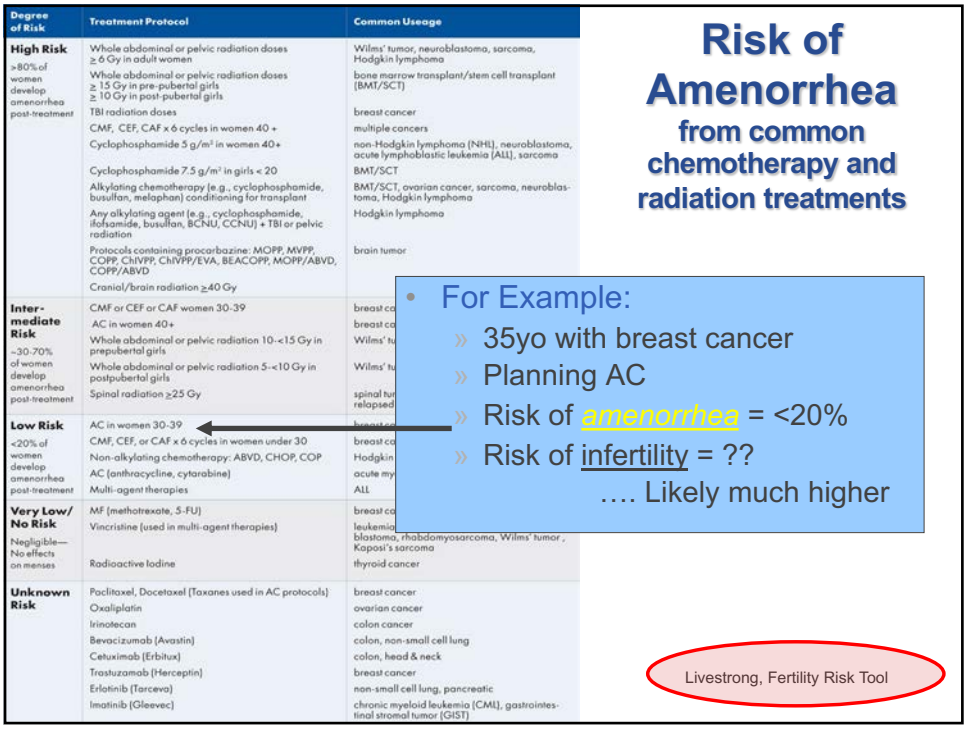

Degree of Risk	Treatment Protocol	Common Useage
High Risk >80% of women develop amenorrhea post-treatment	Whole abdominal or pelvic radiation doses ≥ 6 Gy in adult women	Wilms' tumor, neuroblastoma, sarcoma, Hodgkin lymphoma
	Whole abdominal or pelvic radiation doses ≥ 15 Gy in pre-pubertal girls ≥ 10 Gy in post-pubertal girls	bone marrow transplant/stem cell transplant (BMT/SCT)
	TBI radiation doses	breast cancer
	CMF, CEF, CAF x 6 cycles in women 40 +	multiple cancers
	Cyclophosphamide 5 g/m² in women 40+	non-Hodgkin lymphoma (NHL), neuroblastoma, acute lymphoblastic leukemia (ALL), sarcoma
	Cyclophosphamide 7.5 g/m² in girls < 20	BMT/SCT
	Alkylating chemotherapy (e.g., cyclophosphamide, busulfan, melaphan) conditioning for transplant	BMT/SCT, ovarian cancer, sarcoma, neuroblastoma, Hodgkin lymphoma
	Any alkylating agent (e.g., cyclophosphamide, ifosfamide, busulfan, BCNU, CCNU) + TBI or pelvic radiation	Hodgkin lymphoma
	Protocols containing procarbazine: MOPP, MVPP, COPP, ChlVPP, ChlVPP/EVA, BEACOPP, MOPP/ABVD, COPP/ABVD	brain tumor
	Cranial/brain radiation ≥40 Gy	
Inter-mediate Risk ~30-70% of women develop amenorrhea post-treatment	CMF or CEF or CAF women 30-39	breast ca
	AC in women 40+	breast ca
	Whole abdominal or pelvic radiation 10-<15 Gy in prepubertal girls	Wilms' tu
	Whole abdominal or pelvic radiation 5-<10 Gy in postpubertal girls	Wilms' tu
	Spinal radiation ≥25 Gy	spinal tu relapsed
Low Risk <20% of women develop amenorrhea post-treatment	AC in women 30-39	breast ca
	CMF, CEF, or CAF x 6 cycles in women under 30	breast ca
	Non-alkylating chemotherapy: ABVD, CHOP, COP	Hodgkin
	AC (anthracycline, cytarabine)	acute my
	Multi-agent therapies	ALL
Very Low/ No Risk Negligible— No effects on menses	MF (methotrexate, 5-FU)	breast ca
	Vincristine (used in multi-agent therapies)	leukemia, blastoma, rhabdomyosarcoma, Wilms' tumor, Kaposi's sarcoma
	Radioactive Iodine	thyroid cancer
Unknown Risk	Paclitaxel, Docetaxel (Taxanes used in AC protocols)	breast cancer
	Oxaliplatin	ovarian cancer
	Irinotecan	colon cancer
	Bevacizumab (Avastin)	colon, non-small cell lung
	Cetuximab (Erbitux)	colon, head & neck
	Trastuzamab (Herceptin)	breast cancer
	Erlotinib (Tarceva)	non-small cell lung, pancreatic
	Imatinib (Gleevec)	chronic myeloid leukemia (CML), gastrointestinal stromal tumor (GIST)

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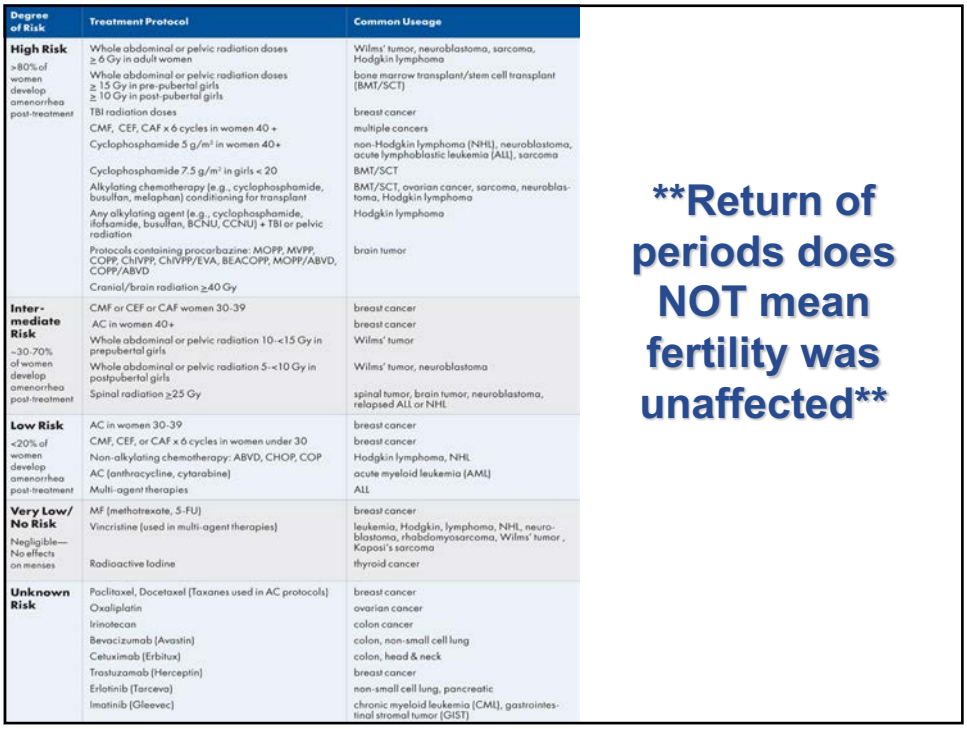

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	Whole abdominal or pelvic radiation 10-<15 Gy in prepubertal girls	Wilms' tumor
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	Spinal radiation ≥25 Gy	spinal tumor, brain tumor, neuroblastoma, relapsed ALL or NHL
Low Risk <20% of women develop amenorrhea post-treatment	AC in women 30-39	breast cancer
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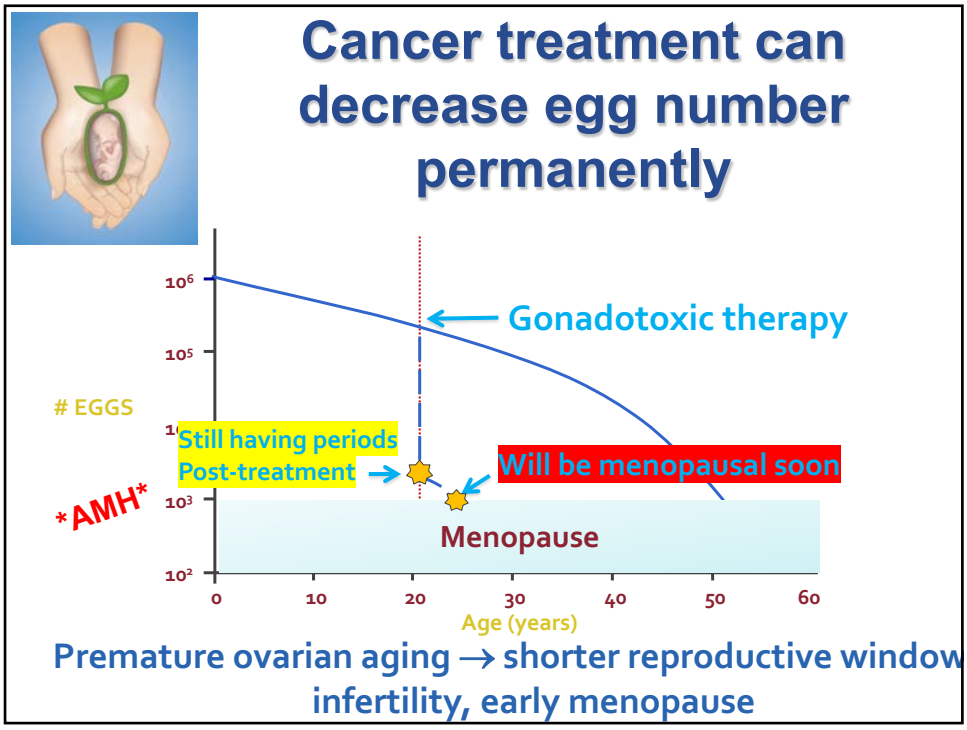
Cancer treatment can decrease egg number permanently
EGGS
AMH
Still having periods
Post-treatment
Gonadotoxic therapy
Will be menopausal soon
Menopause
Age (years)
Premature ovarian aging → shorter reproductive window
infertility, early menopause

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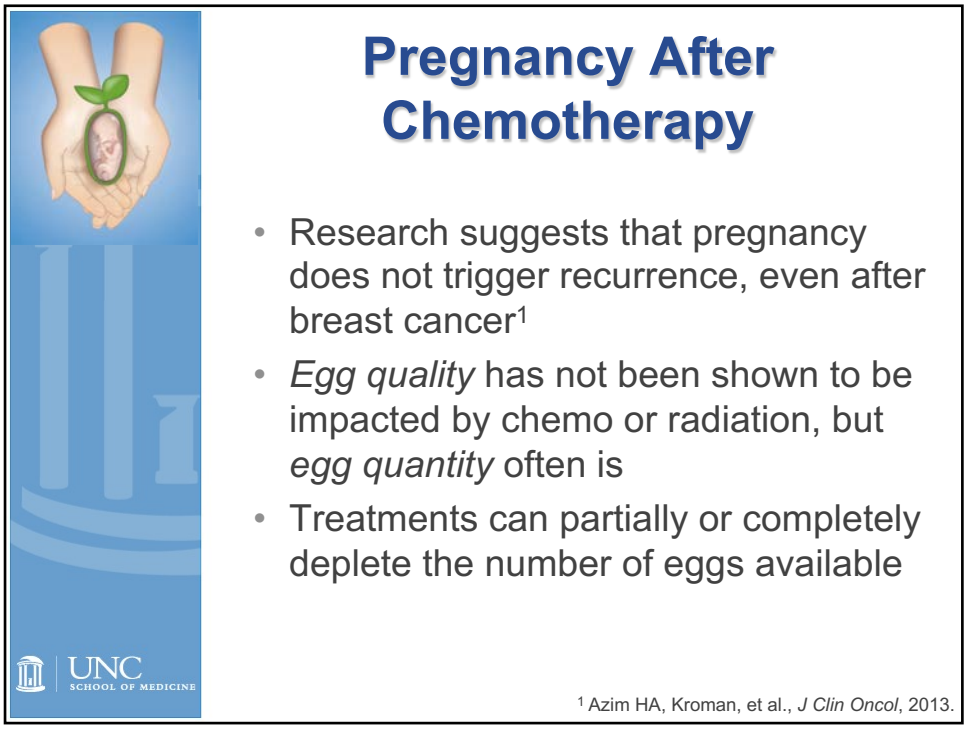
Pregnancy After Chemotherapy
Research suggests that pregnancy does not trigger recurrence, even after breast cancer[1]
Egg quality has not been shown to be impacted by chemo or radiation, but egg quantity often is
Treatments can partially or completely deplete the number of eggs available
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[1] Azim HA, Kroman, et al., J Clin Oncol, 2013.

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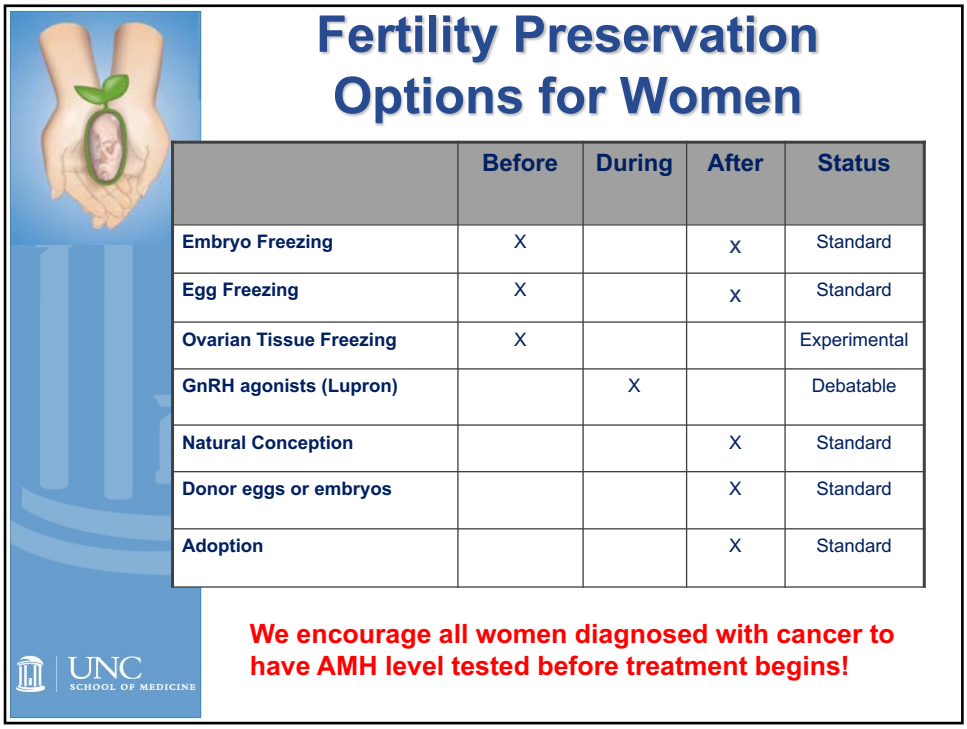

Fertility Preservation Options for Women

	Before	During	After	Status
Embryo Freezing	X		X	Standard
Egg Freezing	X		X	Standard
Ovarian Tissue Freezing	X			Experimental
GnRH agonists (Lupron)		X		Debatable
Natural Conception			X	Standard
Donor eggs or embryos			X	Standard
Adoption			X	Standard

We encourage all women diagnosed with cancer to have AMH level tested before treatment begins!

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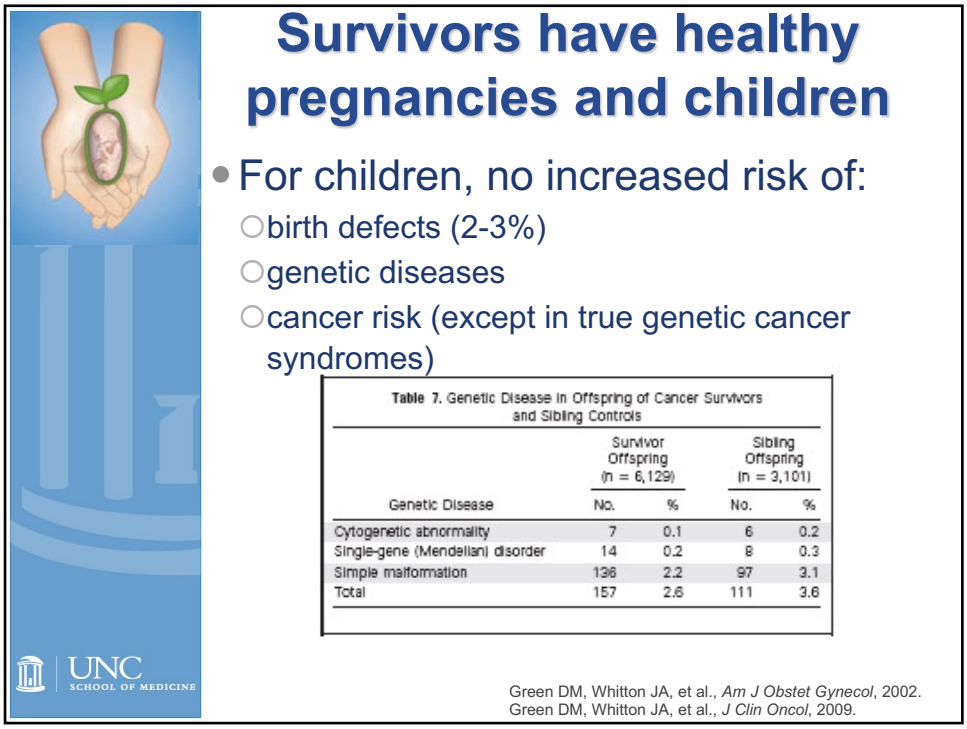

Survivors have healthy pregnancies and children

- For children, no increased risk of:
  - birth defects (2-3%)
  - genetic diseases
  - cancer risk (except in true genetic cancer syndromes)

Table 7. Genetic Disease in Offspring of Cancer Survivors and Sibling Controls

	Survivor Offspring (n = 6,129)		Sibling Offspring (n = 3,101)	
Genetic Disease	No.	%	No.	%
Cytogenetic abnormality	7	0.1	6	0.2
Single-gene (Mendelian) disorder	14	0.2	8	0.3
Simple malformation	136	2.2	97	3.1
Total	157	2.6	111	3.6

Green DM, Whitton JA, et al., *Am J Obstet Gynecol*, 2002.
Green DM, Whitton JA, et al., *J Clin Oncol*, 2009.

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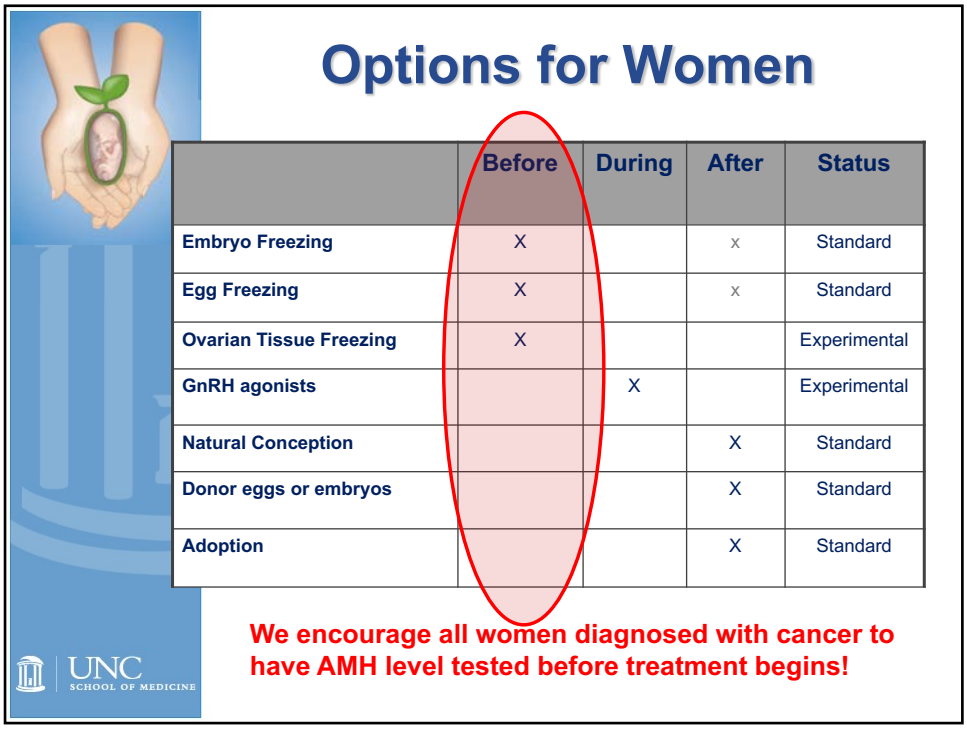
Options for Women
Before
During
After
Status
Embryo Freezing
X
x
Standard
Egg Freezing
X
x
Standard
Ovarian Tissue Freezing
X
Experimental
GnRH agonists
X
Experimental
Natural Conception
X
Standard
Donor eggs or embryos
X
Standard
Adoption
X
Standard
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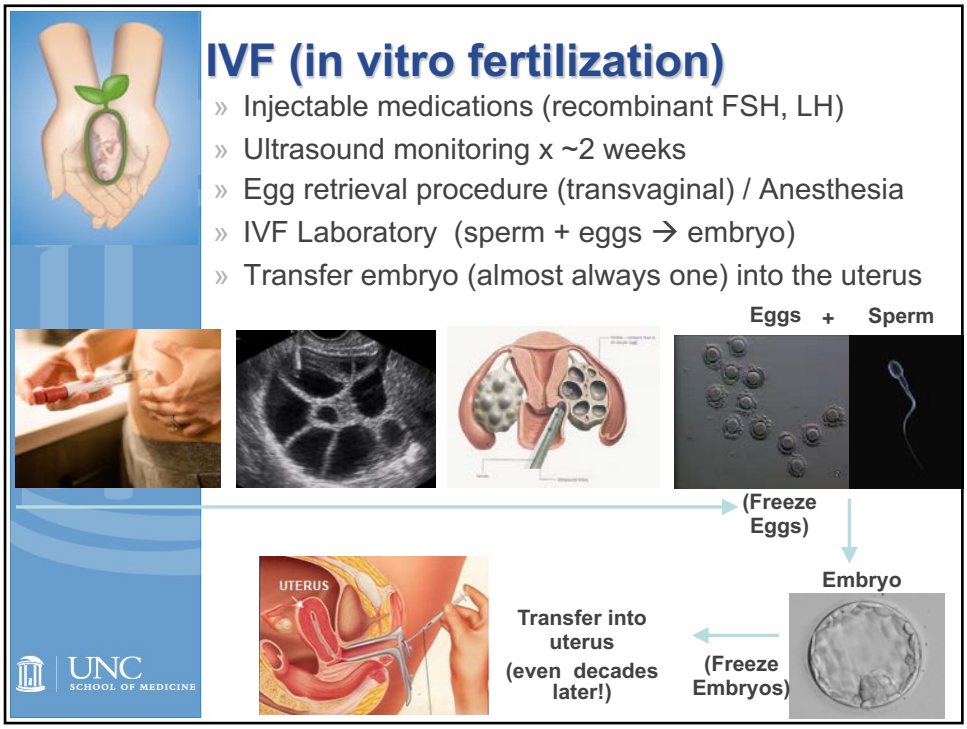
IVF (in vitro fertilization)
» Injectable medications (recombinant FSH, LH)
» Ultrasound monitoring x ~2 weeks
» Egg retrieval procedure (transvaginal) / Anesthesia
» IVF Laboratory (sperm + eggs → embryo)
» Transfer embryo (almost always one) into the uterus
Eggs + Sperm
(Freeze Eggs)
Embryo
UTERUS
Transfer into uterus
(even decades later!)
(Freeze Embryos)
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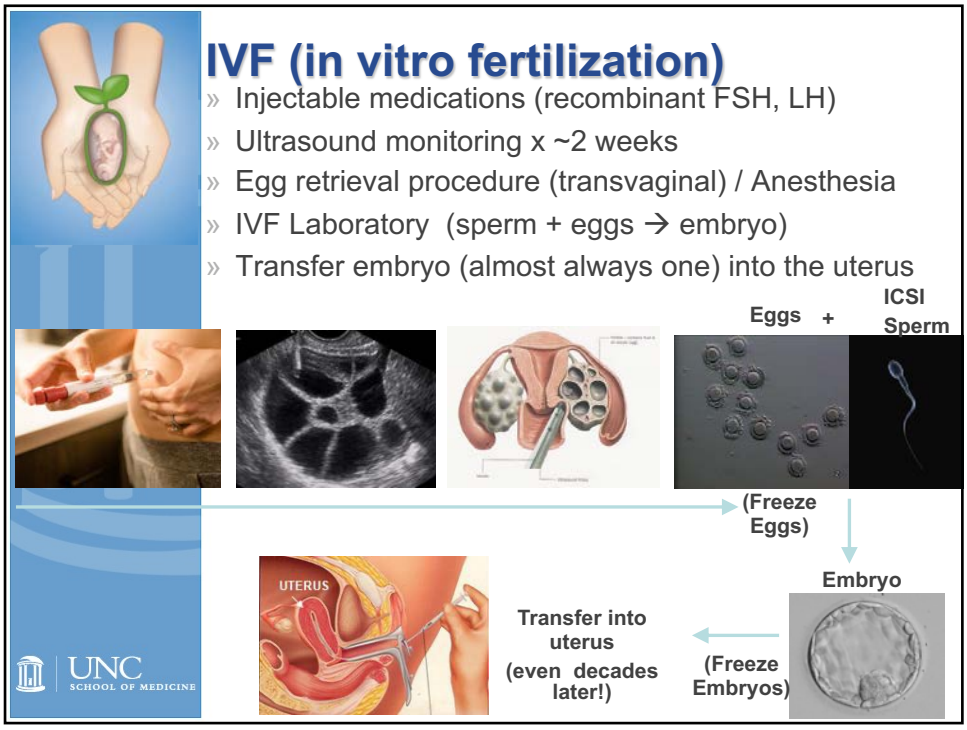
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Eggs + ICSI Sperm
(Freeze Eggs)
Embryo
UTERUS
Transfer into uterus (even decades later!)
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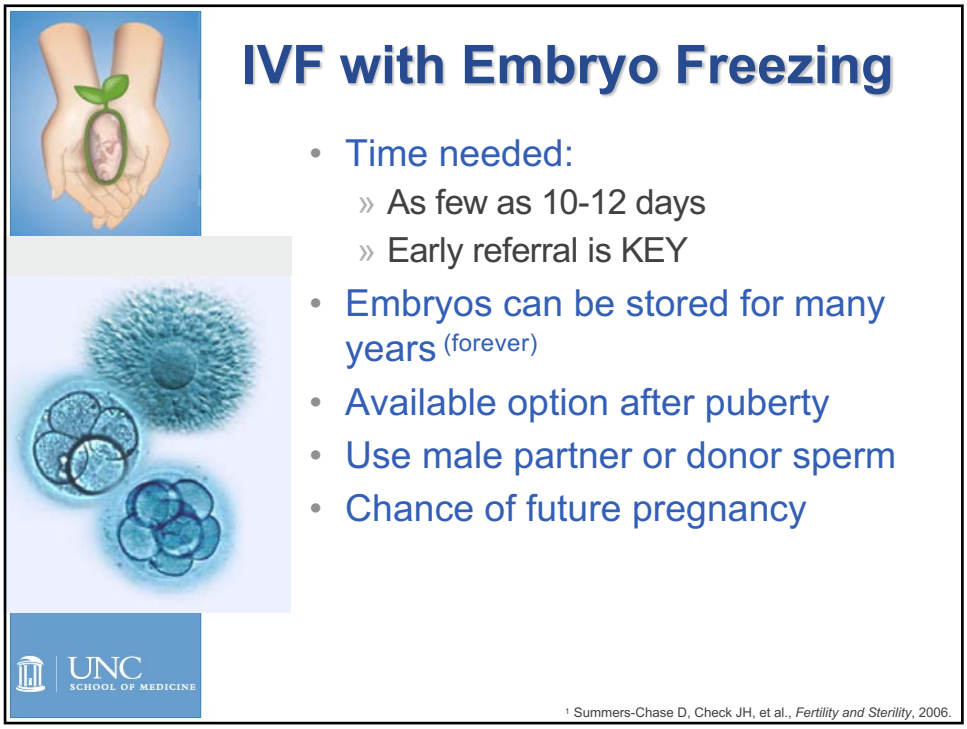
IVF with Embryo Freezing
• Time needed:
» As few as 10-12 days
» Early referral is KEY
• Embryos can be stored for many years (forever)
• Available option after puberty
• Use male partner or donor sperm
• Chance of future pregnancy
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[1] Summers-Chase D, Check JH, et al., Fertility and Sterility, 2006.

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Egg Freezing

- Ovarian stimulation (similar to IVF)
- Mature eggs removed, frozen unfertilized
- Standard care (not experimental)
- Was *previously* technically challenging
  - » Newer technique: vitrification → > 90% eggs survive thaw
- >10,000 babies born worldwide[1]

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[1] Noyes et.al, Reprod Biomed Online 2009

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Why Choose Egg Freezing?

- Doesn't require a male partner
- Doesn't require donor sperm
- Costs less
- Moral / ethical concerns about embryo freezing

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[1] Cobo et al, Human Reproduction, 2010

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GnRH Agonists (Lupron)

- Administered before/during chemo to induce pre-pubertal state
- *May* limit damage to immature follicles, possibly reducing chance of infertility
- Del Mastro, JAMA, 2011
  - » RCT, multi-center Italian study
  - » 282 women, breast cancer
  - » Primary outcome: no menses 12 months after final chemotherapy, some with FSH and estradiol levels

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GnRHa – Standard Treatment?

- Benefits:
  - » Possible improvement in future ovarian function
  - » May minimize menstrual symptoms during chemotherapy
- Concerns:
  - » Not entirely benign medication – side effects
  - » Cost
  - » Falsely reassuring?
- When to start medication? Unclear data

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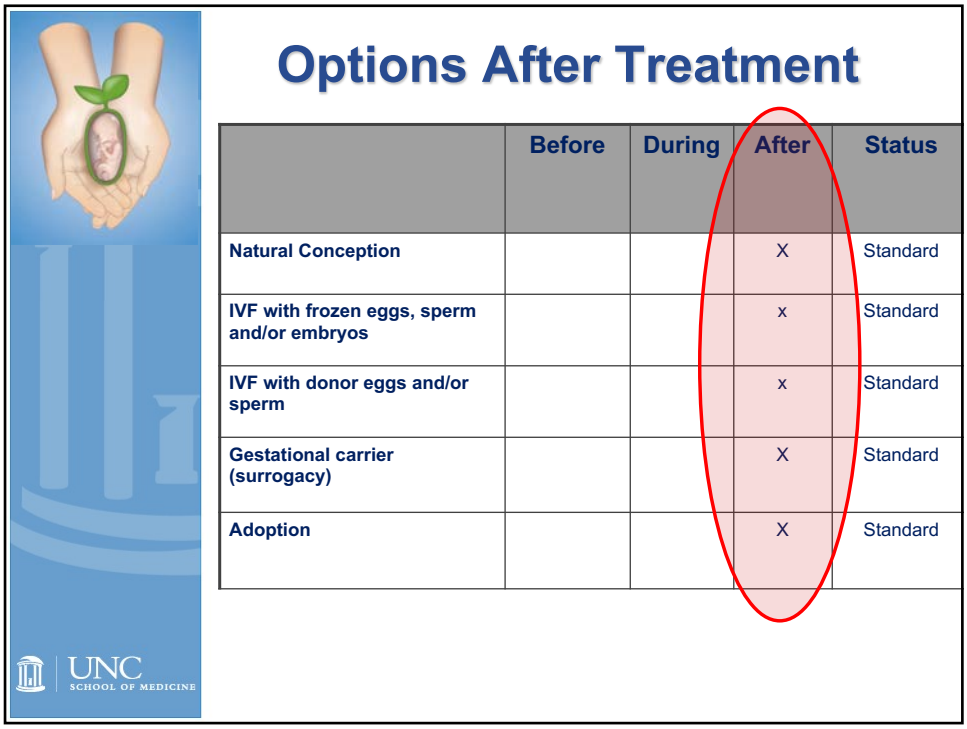
Options After Treatment
Before
During
After
Status
Natural Conception
X
Standard
IVF with frozen eggs, sperm and/or embryos
x
Standard
IVF with donor eggs and/or sperm
x
Standard
Gestational carrier (surrogacy)
X
Standard
Adoption
X
Standard
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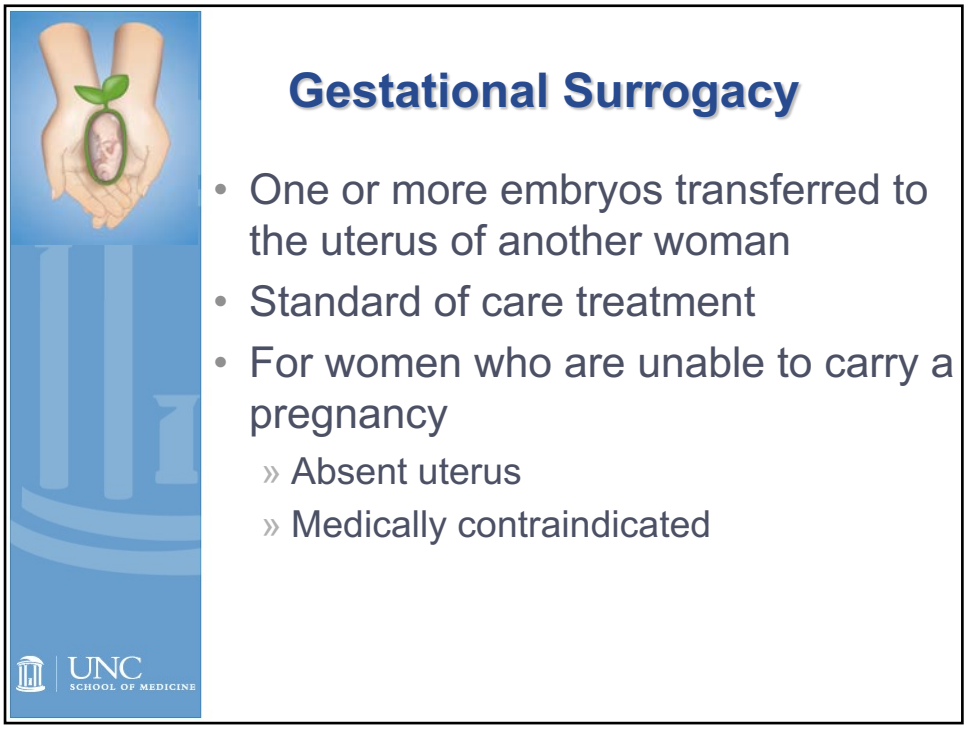
Gestational Surrogacy
• One or more embryos transferred to the uterus of another woman
• Standard of care treatment
• For women who are unable to carry a pregnancy
» Absent uterus
» Medically contraindicated
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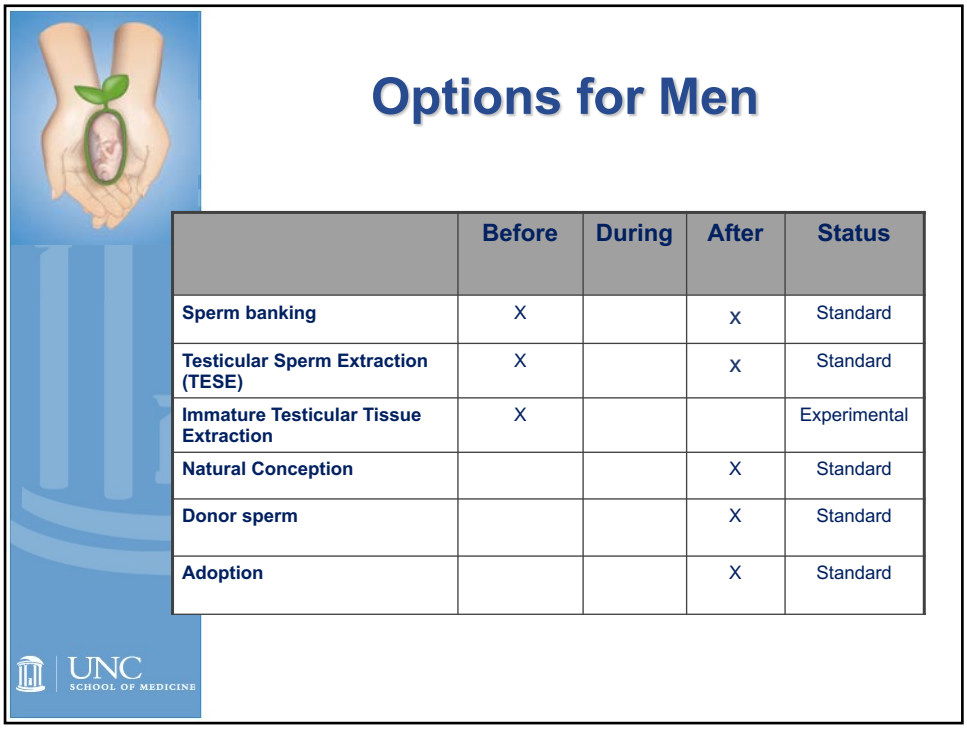
Options for Men
Before
During
After
Status
Sperm banking
X
X
Standard
Testicular Sperm Extraction (TESE)
X
X
Standard
Immature Testicular Tissue Extraction
X
Experimental
Natural Conception
X
Standard
Donor sperm
X
Standard
Adoption
X
Standard
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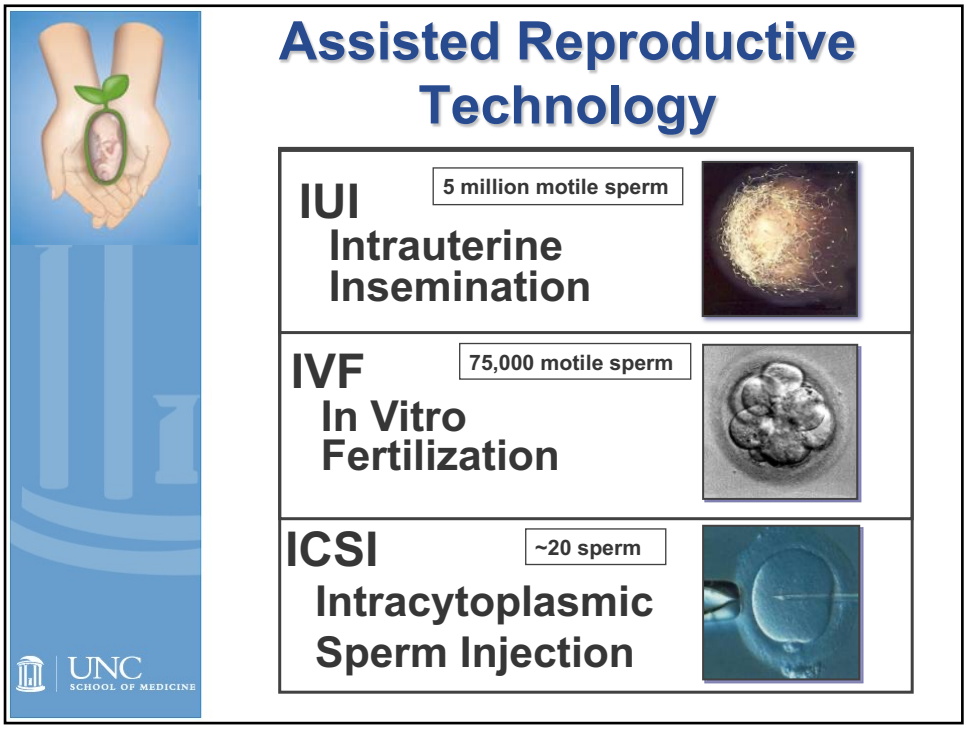
Assisted Reproductive Technology
IUI
Intrauterine Insemination
5 million motile sperm
IVF
In Vitro Fertilization
75,000 motile sperm
ICSI
Intracytoplasmic Sperm Injection
~20 sperm
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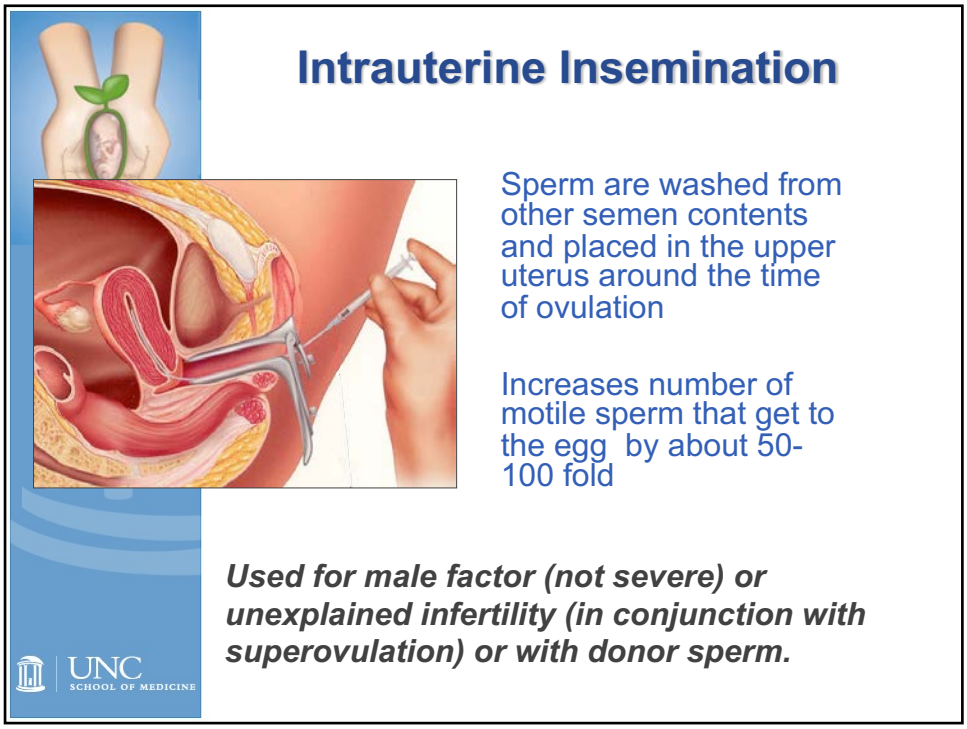
Intrauterine Insemination
Sperm are washed from other semen contents and placed in the upper uterus around the time of ovulation
Increases number of motile sperm that get to the egg by about 50-100 fold
Used for male factor (not severe) or unexplained infertility (in conjunction with superovulation) or with donor sperm.
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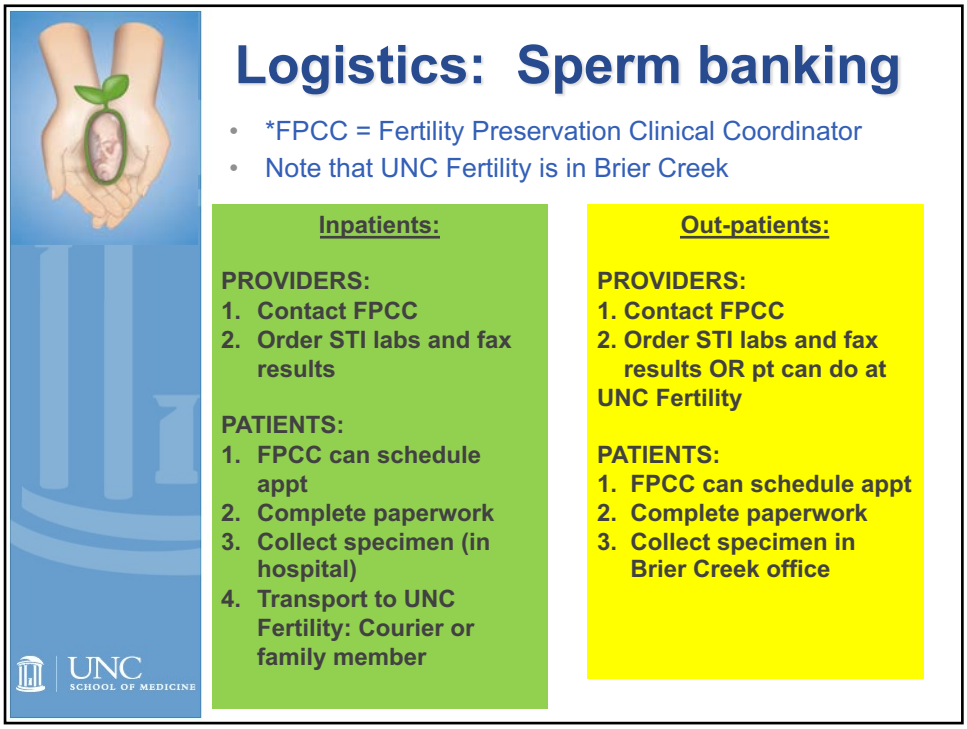
Logistics: Sperm banking
*FPCC = Fertility Preservation Clinical Coordinator
Note that UNC Fertility is in Brier Creek
Inpatients:
PROVIDERS:
1. Contact FPCC
2. Order STI labs and fax results
PATIENTS:
1. FPCC can schedule appt
2. Complete paperwork
3. Collect specimen (in hospital)
4. Transport to UNC Fertility: Courier or family member
Out-patients:
PROVIDERS:
1. Contact FPCC
2. Order STI labs and fax results OR pt can do at UNC Fertility
PATIENTS:
1. FPCC can schedule appt
2. Complete paperwork
3. Collect specimen in Brier Creek office
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So my patient needs to collect sperm right now??

- Mentally re-framing: emphasize the fact that this is a medical procedure
- Embrace the potential for awkwardness
- CLEAR THE WHOLE ROOM
  - » Take this responsibility off the patient
  - » **Put a substantial sign on the door**
  - » **Determine how you'll know it's okay to come back**

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What if the patient cannot produce a semen sample?

- Adolescents, hormone derangements, nerve damage, ED, emotional inability
  - » Penile vibratory stimulation (PVS)
  - » Electroejaculation (EEJ)
  - » Surgical sperm extraction
    - Testicular sperm extraction (TESE)
    - Epididymal sperm aspiration (MESA)

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What if the patient is Azoospermic (no sperm)?

- Azoospermia is not an end-point for Fertility Preservation!!!
- Surgical sperm extraction necessary
  - » Overall ~50% sperm retrieval rate for azoospermic cancer patients

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Schrader M, et al, *Urology,* 61:421-425, 2003.

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Male Fertility After Chemotherapy

- Male fertility should be reassessed about 2 years after treatment ends with semen analysis
- If no sperm are present (azoospermia), frozen sperm can be utilized
- If sperm are present and appear normal, natural conception or sperm banking is an option

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Time Needed for Sperm Banking

- UNC Fertility is open Monday – Friday, and can generally accept patients / specimen deliveries from 7am – 3pm
- Appointments must be scheduled in advance; often available same day
- For inpatients, sperm specimen can be delivered to UNC Fertility by a loved one
- Surgical sperm extraction requires Urology consult

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Average Treatment Cost

Embryo Freezing	~$5-6,000	$10,000 [illegible]eds
Egg Freezing	~$4-5,000	$8,000 [illegible]ds
GnRHa Treatments		$500/month
Sperm Banking		$141 + storage
Testicular Tissue Freezing		$10,000
Donor sperm, eggs or embryos		$3,000 - 5,000
Adoption (domestic, international, public, private)		$2,500 - 35,000
Surrogacy		$20,000 -100,000

- Submit to insurance
- Livestrong Fertility & Walgreen's HeartBeat program
  - » Medications may be free or discounted to qualifying patients

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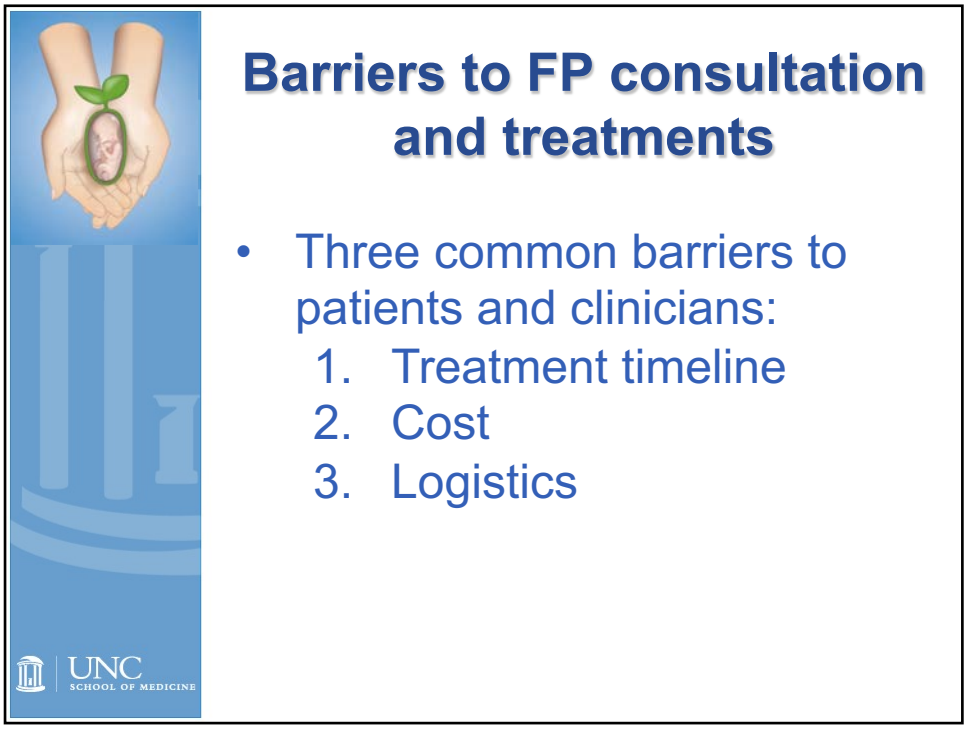
Barriers to FP consultation and treatments
Three common barriers to patients and clinicians:
1. Treatment timeline
2. Cost
3. Logistics
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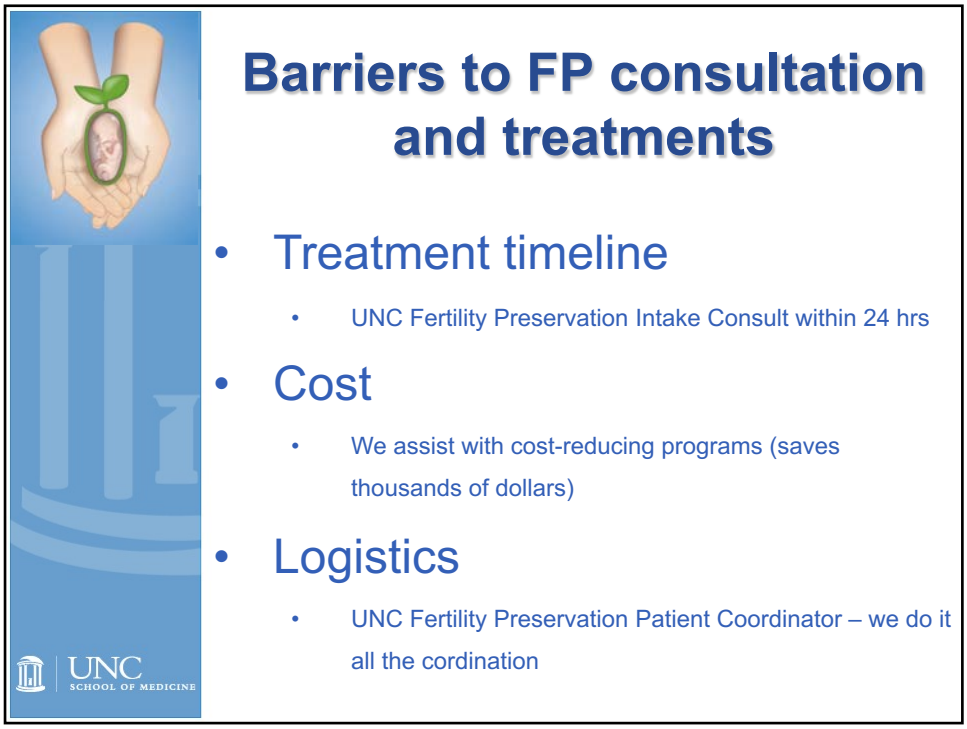
Barriers to FP consultation and treatments
Treatment timeline
UNC Fertility Preservation Intake Consult within 24 hrs
Cost
We assist with cost-reducing programs (saves thousands of dollars)
Logistics
UNC Fertility Preservation Patient Coordinator – we do it all the cordination
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How to Utilize UNC Fertility Preservation for Your Patients

Great question!

- Discuss treatment's likelihood to impact fertility
- Assess interest in learning more about fertility preservation
- Refer to FPCC if interested in discussing options further

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Fertility Preservation Clinical Coordinator role

- Review risk to future fertility
- Empower patient to consider all FP options
- Facilitate referral process to REI Team @ UNC Fertility
- Connect patient with financial supports
- Communicate with treatment team
- Follow up with patient throughout & after treatment

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Summary

- Fertility preservation opportunities are essential with cancer treatment for young women & men
- Fertility can be preserved in the majority of post-pubertal patients
- All patients with a new diagnosis of cancer should be offered fertility preservation, regardless of the diagnosis or treatment plan

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I have a patient interested in learning more about FP

- GREAT! Contact our team ASAP
- Okay, but how?!
  - Page 919-216-6097 **"Fertility Preservation"**
  - Email Jordan_Hunt@med.unc.edu
  - Call 919-843-8246

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