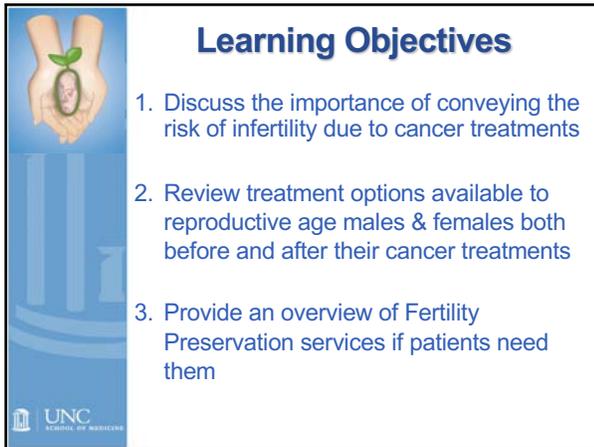


Fertility Preservation

Mary Peavey, MD, MSCI

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

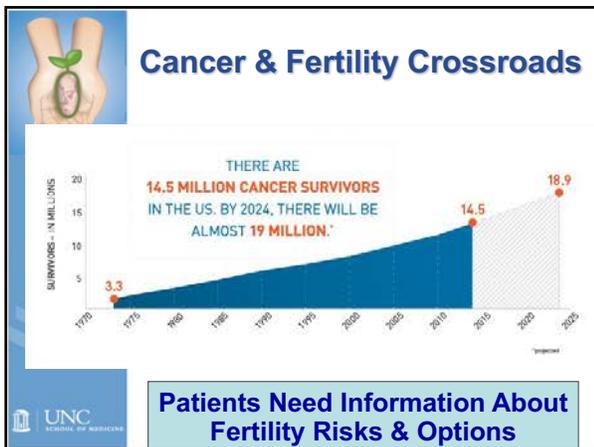
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Learning Objectives

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

2



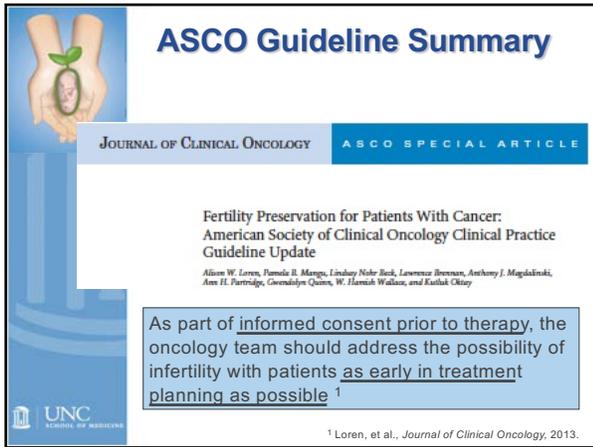
Cancer & Fertility Crossroads

THERE ARE 14.5 MILLION CANCER SURVIVORS IN THE US. BY 2024, THERE WILL BE ALMOST 19 MILLION.*

Year	Survivors (in millions)
1975	3.3
1976	3.3
1977	3.3
1978	3.3
1979	3.3
1980	3.3
1981	3.3
1982	3.3
1983	3.3
1984	3.3
1985	3.3
1986	3.3
1987	3.3
1988	3.3
1989	3.3
1990	3.3
1991	3.3
1992	3.3
1993	3.3
1994	3.3
1995	3.3
2000	3.3
2005	3.3
2010	3.3
2015	14.5
2020	14.5
2024	18.9

Patients Need Information About Fertility Risks & Options

3



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. Manjoo, Lindsay Nohr Beck, Lawrence Brennan, Anthony J. Magdalinski, Ann H. Partridge, Geraldine Quinn, W. Harish Walter, and Katiak 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

¹ Loren, et al., *Journal of Clinical Oncology*, 2013.

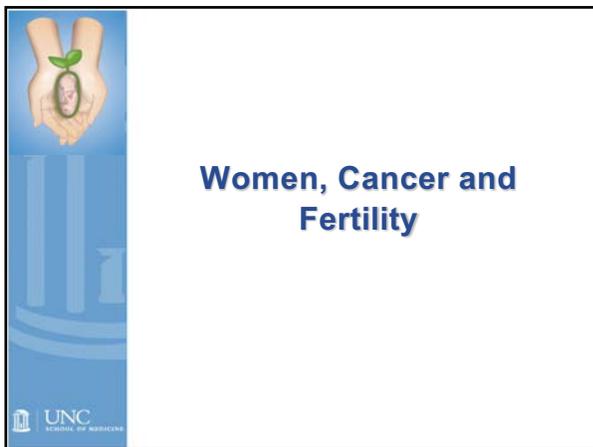
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What is Fertility Preservation?

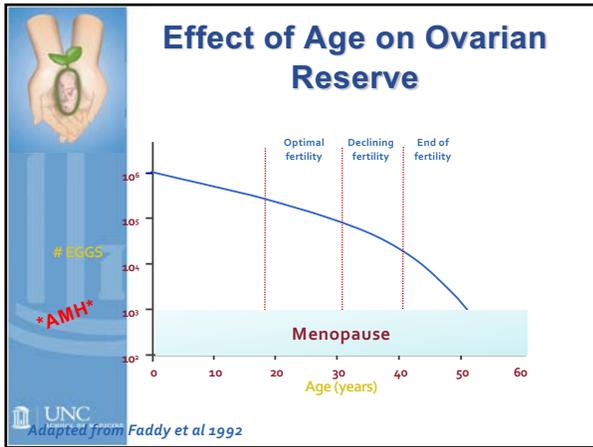
- **Fertility Preservation**
 - » Fertility management for cancer patients of reproductive age
 - » Oncology teams and fertility specialists work together through issues of both cancer treatment as well as potential fertility threats in that immediate moment of diagnosis

5

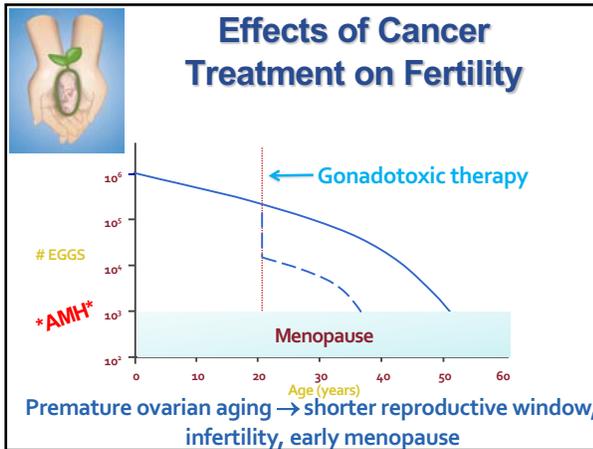


Women, Cancer and Fertility

6



7



8

Degree of Risk	Treatment Protocol	Common Usage
High Risk ~80% of women develop amenorrhea post-treatment	Whole abdominal or pelvic radiation doses > 4 Gy in adult women Whole abdominal or pelvic radiation doses > 15 Gy in prepubertal girls TBI radiation doses CMF, CE, CAF < 6 cycles in women < 40 + Cyclophosphamide 5g/m ² in women < 40 + Cyclophosphamide 7.5g/m ² in girls < 20 Alkylating chemotherapy (e.g., cyclophosphamide, busulfan, melphalan) conditioning for transplant Any alkylating agent (e.g., cyclophosphamide, ifosfamide, busulfan, BCNU, CCNU) + TBI or pelvic radiation Proteasome-inhibiting proteasomase: MDPV, MPP, COPP, CAPP, CAAPP/PA, BEACOPP, MOPP/ABVD, COPP/ABVD Central brain irradiation > 40 Gy	Wilms' tumor, neuroblastoma, sarcoma, Hodgkin lymphoma bone marrow transplant/stem cell transplant (MST/SCT) breast cancer multiple cancers non-Hodgkin lymphoma (NHL), neuroblastoma, acute lymphoblastic leukemia (ALL), sarcoma BM/ST BM/ST ovarian cancer, sarcoma, neuroblastoma, Hodgkin lymphoma Hodgkin lymphoma brain tumor
Intermediate Risk ~30-70% of women develop amenorrhea post-treatment	CMF or CE or CAF women 30-39 AC in women < 40 Whole abdominal or pelvic radiation 10-15 Gy in prepubertal girls Whole abdominal or pelvic radiation 5-10 Gy in postpubertal girls Spinal irradiation > 25 Gy	breast of breast of Wilm's Wilm's spinal cord re-irradiation
Low Risk ~10% of women develop amenorrhea post-treatment	AC in women 30-39 CMF, CE or CAF < 6 cycles in women under 30 Non-alkylating chemotherapy: ABVD, CHOP, CCP AC: interferon-α, tyrosine kinase Anti-HER2 therapy	breast of Hodgkin ovary ALL
Very Low/No Risk Hodgkin-like No effects on ovaries	MF (interferon-α, 5-FU) Vincristine (used in multi-agent therapy) Radioactive iodine	breast of breast of blastoma, rhabdomyosarcoma, Wilms' tumor, Rhabdomyosarcoma thyroid cancer
Unknown Risk	Paclitaxel, Docetaxel (Taxanes used in AC protocols) Oestradiol Imatinib Bortezomib (Avastin) Capecitabine (Eliquis) Trastuzumab (Herceptin) Erlotinib (Tarceva) Irinotecan (Oncoxin)	breast cancer ovarian cancer colon cancer colon, non-small cell lung colon, head & neck breast cancer breast cancer non-small cell lung, pancreatic thrombocytopenic purpura (TTP), gemtuzumab intracerebral (GIMT)

Risk of Amenorrhea from common chemotherapy and radiation treatments

• For Example:

- » 35yo with breast cancer
- » Planning AC
- » Risk of amenorrhea = <20%
- » Risk of infertility = ??
- Likely much higher

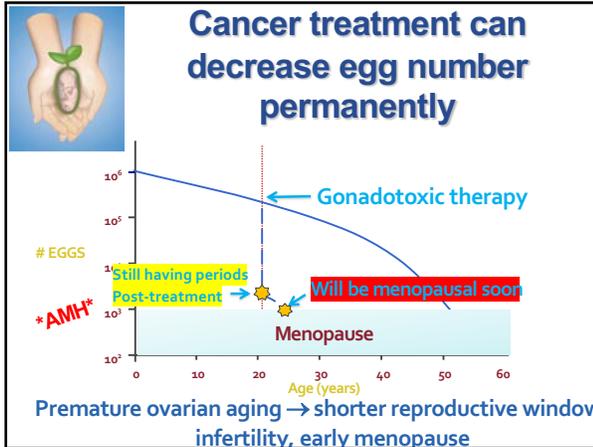
Livestrong, Fertility Risk Tool

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Degree of Risk	Treatment Protocol	Common Usage
High Risk ≥80% of women develop amenorrhea post-treatment	Whole abdominal or pelvic radiation doses ≥ 8 Gy in adult women Whole abdominal or pelvic radiation doses ≥ 15 Gy in pre-pubescent girls TBI radiation doses: CMF, CMF + CAF x 4 cycles in women ≥ 40+ Cyclophosphamide 5g/m ² in women ≥ 40+ Cyclophosphamide 7.5g/m ² in girls < 20 Alkylating chemotherapy (e.g., cyclophosphamide, busulfan, melphalan) conditioning for transplant Any alkylating agent (e.g., cyclophosphamide, ifosfamide, busulfan, E-SU, CCNU) + TBI or pelvic radiation Protonid conditioning protocol: MOPP, MOPP/CCOP, CCOP, CHOP/ESH, BEACOPP, MOPP/ABVD, CHOP/ABVD Ovarian brain radiation ≥ 40 Gy	Wilm's tumor, neuroblastoma, sarcoma, Hodgkin lymphoma bone marrow transplant/stem cell transplant (BM/SCIT) breast cancer multiple cancers non-Hodgkin lymphoma (NHL), neuroblastoma, acute lymphoblastic leukemia (ALL), sarcoma BM/SCIT BM/SCIT ovarian cancer, sarcoma, neuroblastoma, Hodgkin lymphoma Hodgkin lymphoma brain tumor
Inter-mediate Risk ~30-70% of women develop amenorrhea post-treatment	CMF or CMF or CAF women 30-39 AC in women ≥ 40 Whole abdominal or pelvic radiation 10-15 Gy in prepubertal girls Whole abdominal or pelvic radiation 5-10 Gy in postpubertal girls Spinal radiation ≥ 25 Gy	breast cancer breast cancer Wilm's tumor Wilm's tumor, neuroblastoma spinal tumor, brain tumor, neuroblastoma, relapsed ALL or NHL
Low Risk 10-25% of women develop amenorrhea post-treatment	AC in women 30-39 CMF, CMF or CAF x 4 cycles in women under 30 Non-alkylating chemotherapy: ABVD, CHOP, CCOP, AC (paclitaxel, cyclophosphamide) Multi-agent therapies	breast cancer breast cancer Hodgkin lymphoma, NHL, acute myeloid leukemia (AML) ALL
Very Low/No Risk negligible/no effects on women	MF (methotrexate, 5-FU) Vincristine (used in multi-agent therapies) Radioactive iodine	breast cancer lyukemia, Hodgkin lymphoma, NHL, neuroblastoma, histiocytosis, Wilm's tumor, Kaposi's sarcoma thyroid cancer
Unknown Risk	Paclitaxel, Docetaxel (Taxanes used in AC protocols) Oxaliplatin Irinotecan Borizoximide (Avenite) Cetuximab (Erbitux) Trastuzumab (Herceptin) Erlotinib (Tarceva) trametinib (Trometin)	breast cancer ovarian cancer colon cancer colon, non-small cell lung colon, head & neck breast cancer breast cancer non-small cell lung, pancreatic chronic myeloid leukemia (CML), glioblastoma, breast cancer (BRCA)

****Return of periods does NOT mean fertility was unaffected****

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Pregnancy After Chemotherapy

- Research suggests that pregnancy does not trigger recurrence, even after breast cancer¹
- *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


1 Azim HA, Kroman, et al., J Clin Oncol, 2013.

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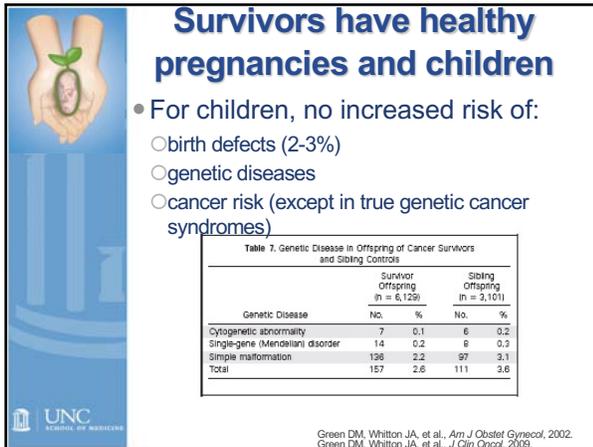


Fertility Preservation Options for Women

	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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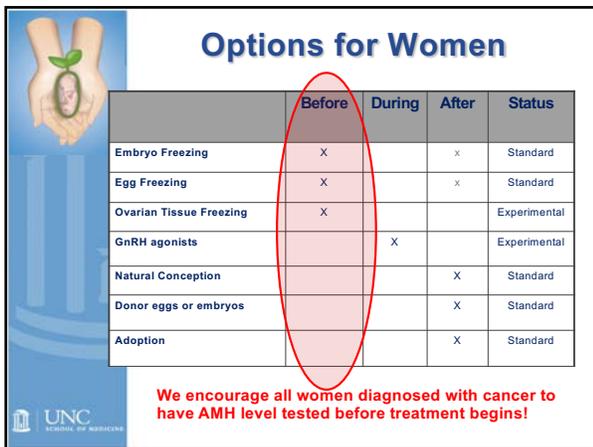
Survivors have healthy pregnancies and children

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

Genetic Disease	Survivor Offspring (n = 6,129)		Sibling Offspring (n = 3,101)	
	No.	%	No.	%
Cytogenetic abnormality	7	0.1	6	0.2
Single-gene (Mendelian) disorder	14	0.2	8	0.3
Simple malformation	196	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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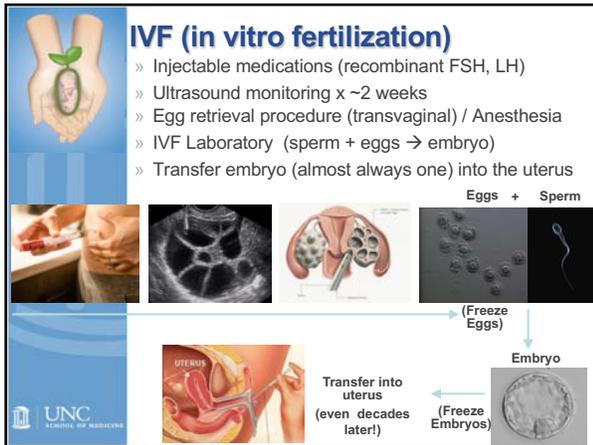


Options for Women

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Ovarian Tissue Freezing	X			Experimental
GnRH agonists		X		Experimental
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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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

(Freeze Embryos)

Transfer into uterus (even decades later!)

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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 ICSI

(Freeze Eggs)

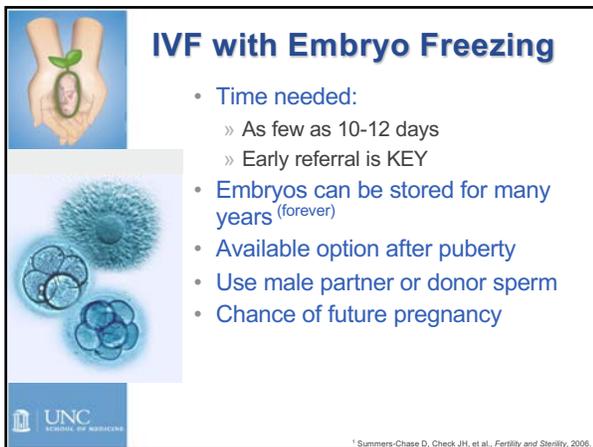
Embryo

(Freeze Embryos)

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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© 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 worldwide¹

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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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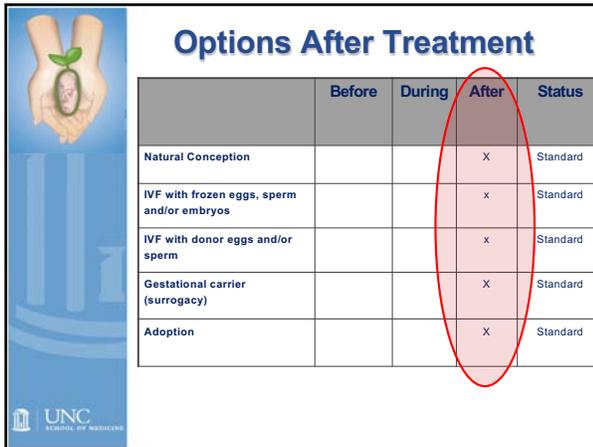


GnRHa – Standard Treatment?

- **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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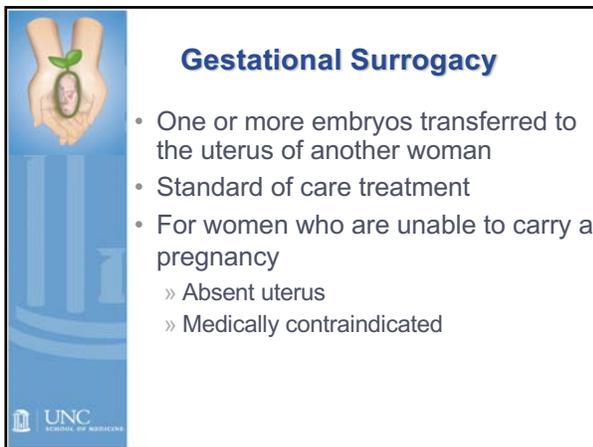


Options After Treatment

	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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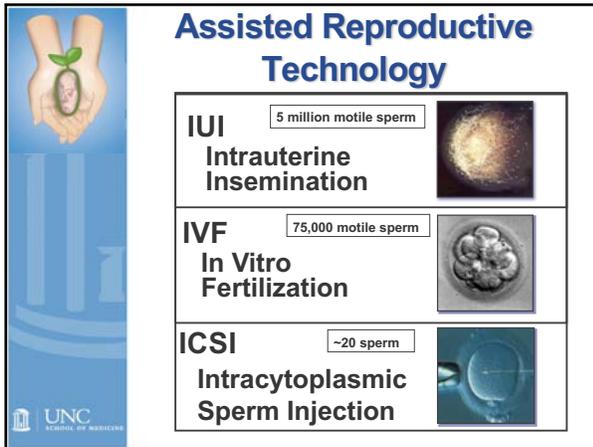
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Options for Men

	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

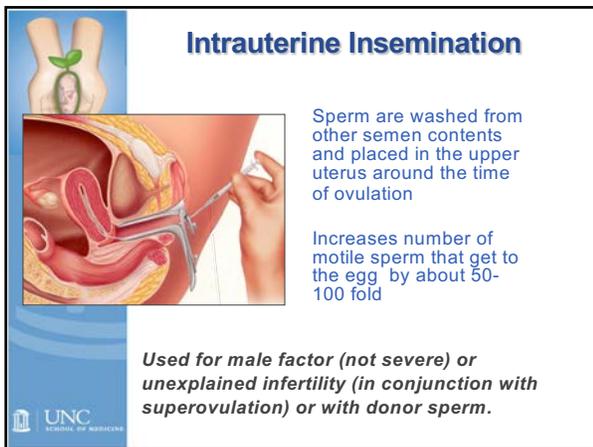
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Assisted Reproductive Technology

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:	Out-patients:
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	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 + meds
Egg Freezing	~\$4-5,000	\$8,000 + meds
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 coordination

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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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THANK YOU!

Questions?



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