Fertility Preservation for Cancer Patients

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I do not have any disclosures
Objectives

• Discuss the impact of gonadotoxic treatments or diagnoses on fertility in women and men

• Explain available fertility preservation options for females and males, both established and experimental

• Increase knowledge about reproductive care for cancer survivors

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Cancer and Fertility

• Survival rates are at an all-time high

• Treatment is often detrimental to reproductive function
  – Resumption of menses ≠ fertility
  – Earlier age at menopause (shortened fertile window)

• An infertility diagnosis has equivalent psychosocial effects as a cancer diagnosis

Partridge AH et al. Fertil Steril 2010
Letourneau JM et al. Cancer 2012
The cure rate from pediatric cancer is approaching 80%; 75% young adult survivors desire parenthood.

Several studies confirm that adult survivors of pediatric cancer:
- wish they had been given more information and options about fertility
- are often uncertain about their fertility status or feel regret about no longer having an option
As of 1/1/16, there were >15.5 million cancer survivors in the US*

Former focus: Primarily on survival alone

Demographic changes & improved detection/survival led to shifts:
- Parenthood later in life
- Second families after divorce, death of spouse

Current focus: Survival and quality of life after treatment

*ACS Cancer Treatment and Survivorship Facts and Figures 2016-2017
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”
This isn’t easy!

“The unique duality involved in confronting a life-threatening diagnosis while simultaneously considering the deeply human desire to have a child presents a struggle both for patients with cancer and for clinicians.”

Jeruss and Woodruff, NEJM 2009
Oncofertility Consortium

- 2-way exchange of ideas, methods, technologies, and issues
- Multi-disciplinary
- Promulgate best practices and strong referrals to local centers
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

• Surgery
How Does Cancer Therapy Affect Male Fertility?

- **Chemotherapy**
  - Sertoli cells and spermatogonia can be damaged by chemotherapy
  - Leydig cells are not typically affected
  - Sperm concentration decreases with increasing CED

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

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

Initial Evaluation

- History
  - Dx, treatment hx, treatment plan
  - Menstrual
  - Fertility
  - Family/Genetics
  - Partner

- General Physical Exam

- Endocrine blood tests
Natural Conception: Schematic Demonstrating Trends in Pregnancy and Miscarriage Rates According to Age
Initial Counseling

• Present risk of treatment protocol (if known)

• Provide an understandable menu of options
  – Include risks/benefits/alternatives

• Discuss cost/financial assistance

• Offer mental health support/counseling
Potential Hurdles Unique to Pediatrics

• Proxy decision-making

• Potential for decisional regret
  • Patient or parent

• Assisted reproductive technologies in evolution
  • Facilitate patient/parent knowledge and decision-making in the face of uncertainty

• Disposition of gametes
<table>
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<tr>
<th>Risk Level</th>
<th>Characteristics</th>
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| High Risk  | - Whole abdominal or pelvic radiation doses >6 Gy in adult women  
- Whole abdominal or pelvic radiation doses >10 Gy in postpubertal girls  
- Total body irradiation (TBI)  
- Cranial/brain irradiation >40 Gy  
- CMF, CEF, or CAF x 6 cycles in women >40 years  
- Cyclophosphamide 5 g/m² in women >40 years  
- Cyclophosphamide 7.5 g/m² in girls <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, CHVPP, CHVPP/EVA, BEACOPP, MOPP/ABVD, COPP/ABVD |
| Intermediate Risk | - Whole abdomina or pelvic radiation 5 to <10 Gy in postpubertal girls  
- Spinal radiation doses >25 Gy CMF, CEF, or CAF x 6 cycles in women 30–39 years  
- AC in women >40 years |
| Low Risk    | - AC in women 30–39 years  
- CMF, CEF, or CAF x 6 cycles in women <30 years  
- Nonalkylating chemotherapy: ABVD, CHOP, COP  
- AC |
Options

**Females**
- Embryo Cryopreservation
- Oocyte Cryopreservation
- Ovarian Shielding
- Ovarian Transposition
- GnRH Agonist
- Ovarian Tissue Cryopreservation

**Males**
- Sperm banking
- Testicular sperm extraction
- Testicular shielding
- Testicular tissue cryopreservation
GnRH agonist

• “Experimental”

• POEMS and PROMISE studies show efficacy in breast cancer patients

• Flare effect
Embryo/Oocyte Cryopreservation

• Most commonly used fertility preservation techniques

• Caveats:
  – Post pubertal 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
  – Oncology must be ok with hormonal stimulation
Oocyte/Embryo Cryopreservation

- FSH/LH medications for 8-13 days
  - Overlap with letrozole in breast cancer patients

- GnRH Antagonist midcycle to prevent ovulation

- HCG triggers ovulation 36 hours prior to retrieval
• Retrieval done under conscious sedation with TVUS and needle guide

• Know immediately # of eggs

• Find out how many eggs successfully fertilized the following day
Points for Counseling

• A frozen egg = a fresh egg

• Partners have legal rights over embryos

• Random start protocol – 2 weeks for cycle

• No difference in long-term cancer outcomes
Safety Data


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


  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 preservation in a breast cancer program.

  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.
Preimplantation Genetic Diagnosis
Cost

• Fertile Hope through Livestrong

• Walgreen’s – Heartbeat

• Reprotech – Verna’s Purse
Ovarian Tissue Cryopreservation

- Ovarian tissue frozen worldwide for over a decade without knowledge of how it could be used
- Strips of cortical tissue now frozen
- Still considered experimental
- Sample protocols and support through the National Physician’s Cooperative of
Orthotopic Transplantation – Ovarian Fossa

Donnez et al. Frontiers in Bioscience 2012

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Orthotopic Transplantation – Contralateral Ovary

A

B

Donnez et al. Hum Reprod Update 2006

Slides are the property of the presenter. Do not reproduce without written consent.
Heterotopic Transplantation – Forearm

Oktay et al. Fertility and Sterility 2003

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Future Directions – Ovarian Tissue

• In vitro maturation into mature follicles

• Engineered environments for follicle or tissue transplantation
Important Counseling Points

• Graft survival

• Reseeding risk

• Autologous transplant only

• Role of pubertal development
Testicular Tissue Cryopreservation

• No spermatogenic recovery or pregnancies reported

• Possible future options:
  – Transplantation of spermatogonial stem cells
  – In vitro maturation
  – Testicular tissue autografting
  – Induced pluripotent stem cells
Options After Cancer Treatment

- Intra-Uterine Insemination
- *In Vitro* Fertilization +/- ICSI
- 3rd party reproduction
- Hormone manipulation
- Surgical sperm extraction
Third Party Reproduction

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

- **Domestic**
  - Agency
  - 2/3 of adoptions involving a newborn take at least 7 months and cost an average of $40,000
  - Department of Children and Family Services
    - Foster Care and Adoption Resource Center (FCARC)

- **International**
  - Dependent on country regulations
  - Can cost up to $100,000 and take up to 2 years or longer
  - Some countries may have health regulations/requirements

- **Being a Cancer Survivor**
Perinatal Risks

• Miscarriage - CNS (3x) or pelvic (2x) radiation

• Preterm Birth – trachelectomy (2-3x), pelvic radiation (3x), chemotherapy (2x)

• Cardiac – chest radiation, anthracyclines

• Hypertensive disease – Pelvic radiation (2-3x)

• Unknown risks with newer therapies

Green JCO 2009; Moslehi NEJM 2016; Anderson JAMA Oncol 2017; Reulen JNCI 2017
Social, Legal, and Ethical Issues

• Waiting to be Born
  • The Ethical and Legal Implications of the Generation from Frozen and Stored Gametes

• Prepubertal Tissue Storage
  • Patient rights vs. parental rights

• Postpubertal Gamete Storage
  • Patient rights vs. parental rights

• Individual Gamete Storage
  • Disposition

• Embryo Storage
  • Relationship changes, disposition
Fertility Preservation Program

Does a dedicated program for young breast cancer patients affect the Cancer and Fertility Program Improves Patient Satisfaction With Information Received


2M9, Canada

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Ideal Model

Figure adapted from K. Smith, Northwestern University

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The Referring Physician

• “Specialists should have enough familiarity with fertility preservation to discuss the referral process and briefly overview options.”

• “The goal is not to make these specialists fertility specialists.”

• These providers “break the ice” with the patient
  • Drive patient’s care
  • Determine the time frame available to provide services
  • Their involvement and support is essential
Thank You!