Oncofertility: from now to next
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I have nothing to disclose
Cancer treatments, while life preserving, can have off-target effects

Age-related effects of cancer treatments

- Dementia, attention deficits: methotrexate, RT
- Cataracts: tamoxifen
- Hypothyroidism: methimazole, sunitinib
- Carotid artery stenosis: RT
- Systemic hypertension: cisplatin, bevacizumab
- Pulmonary fibrosis: bleomycin, carmustine
- Muscular weakness: taxol + cisplatin
- Decreased bone mineral density/osteoporosis: glucocorticoids
- Liver disease: imatinib
- Arthritis: cyclophosphamide + tamoxifen
- Chronic kidney disease: ifosfamide
- Chronic constipation: taxol, cisplatin, vincristine
- Secondary myeloid neoplasms/leukaemia: vinca alkaloids, RT

Childhood Cancer Survivor Study – survivors first diagnosed at age 21 and followed up for a median of 24.5 years after diagnosis along with their siblings

**Fig 3.** Hazard ratios and 95% CIs of survivors versus siblings for specific chronic conditions that first occurred at or after age 35 years, adjusted for age, race, and sex. CHF, congestive heart failure.

Cupit-Link CT et al, ESMO Open, 2017

Armstrong GT et al, JCO, 2014
Cancer treatments can affect all aspects of the reproductive axis.

**Female**
- Loss of follicle reserve
- Ovarian hormone dysfunction
- Abnormal cyclicity
- Uterine dysfunction
- Failed pregnancy

**Male**
- Hypogonadism
- Decreased semen parameters
- Increased sperm DNA damage
- Erectile dysfunction
- Ejaculatory dysfunction

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**Infertility or Sterility**
Who is at risk?

- More than **1.4 million** people are diagnosed with cancer in the US annually and **10 million** globally.
- **10%** of these individuals are in their reproductive years.
- **1 in 750** in the US is a childhood cancer survivor.
- Survivors are significantly more likely to be **infertile** or have **difficulty getting pregnant** than their siblings.
- **Fertility and sexual functioning** are key health related quality of life concerns in young adult survivors of childhood cancer.

Jeruss and Woodruff, *NEJM*, 2009
Howlader N, SEER Cancer Statistics Review 1975-2012
Phillips et al, CEBP, 2015 NCI Office of Cancer Survivorship
Nightingale et al, *JAYAO*, 2011
The Oncofertility Consortium - a New Paradigm

A global 10+ year NIH-funded interdisciplinary initiative to explore and expand the reproductive future of cancer survivors

Health Professionals
(oncologists, reproductive endocrinologists, gynecologists, nurses, social workers, patient navigators)

Patients
(men, women, children, families, and friends)

Fertility Preservation

Researchers
(biologists, chemists, bioengineers)

Scholars
(social scientists, bioethicists, future scientists)

Additional Stakeholders
(lawyers, insurance experts, religious leaders, advocacy groups, the public)

Duncan et al, Reproductive Endocrinology, 8th Edition
Fertility Preservation Options for Men

For men, standard methods include:

1. Testis Shielding
2. Sperm Banking
3. Sperm Extraction

Experimental method:
4. Testicular Tissue Cryopreservation

Cancer Treatment Methods:

1. Radiation
2. Surgery
3. Chemotherapy

Duncan et al., Reproductive Endocrinology, 8th Edition
Fertility Preservation Options for Women

**CLINICAL FERTILITY PRESERVATION OPTIONS**

For women, standard methods include:

1. **PELVIC SHIELDING**
2. **OVARIAN TRANSPOSITION**
3. **EMBRYO BANKING**
4. **EGG BANKING**

Experimental methods include:

5. **GONADAL SUPPRESSION**
6. **OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION**
7. **IN VITRO MATURATION**

**CANCER TREATMENT**

1. **RADIATION**
2. **SURGERY**
3. **CHEMOTHERAPY**

Starting the Conversation...

**FERTILITY PRESERVATION**

FOR WOMEN DIAGNOSED WITH CANCER

Duncan et al, Reproductive Endocrinology, 8th Edition
Fertility Preservation Options for Children

- Radiation shielding
- Ovarian transposition
- Ovarian/testicular tissue cryopreservation*

*Investigational
Challenges of making the decision

- Existential crisis about self, survival, and future
- Decision peripheral to primary diagnosis
- Time constraints
- Overwhelming array of options
- Access to care
- Financial constraints

Challenges of navigating the decision

- Sex
- Age
- Diagnosis
- Treatment type
- Stage of treatment
- Baseline fertility

Duncan et al, Reproductive Endocrinology, 8th Edition

The Fertility Preservation Decision Making Process is Complex
Oncofertility resources for diverse stakeholders

Websites, materials, branding

Conferences, virtual grand rounds, training programs

Patient navigation

AT [YOUR INSTITUTION HERE]

the Oncofertility Consortium

Oncofertility.northwestern.edu
Savemyfertility.org
Preservefertility.northwestern.edu

The Multinational Association of Supportive Care in Cancer • Annual Meeting 2019 • www.mascc.org/meeting
A clinical and field-wide infrastructure to support fertility preservation

- 117 US Sites
- 231 Sites Globally in 42 Countries
- 19 Pediatric Sites
- Subset perform OTC under IRB-approved protocols

The National Physicians Cooperative (NPC) and Oncofertility Professional Engagement Network (OPEN)
A focus on female fertility preservation – ovarian tissue cryopreservation

Standard ART protocols (i.e. egg and embryo banking) may not apply to those who:

- Are pre-pubertal
- Can not delay cancer treatment
- Can not tolerate hormonal stimulation

Ovarian tissue removal and cryopreservation with future use for transplantation or additional emerging technologies
OTC and tissue transplantation to restore endocrine function and fertility
OTC and tissue transplantation has been successful

- >130 live births worldwide
- 26% live birth success rate
- Hormone production up to 12 years
  - Average 5 years

Jeruss and Woodruff NEJM, Donnez NEJM 2017
Pacheco Reprod Sci 2017
Kim et al J Gynecol Oncol 2016
Armstrong et al, Future Oncology, 2018
Smith et al, Future Oncology, 2018
How do we continue to reduce the reproductive health burdens for cancer survivors?

- Make safer ("smart") cancer treatments
- Determine the fertotoxicity of cancer treatments
- Develop fertoprotective adjuvant therapies
- Engineer new fertility preservation methods
Making safer or “smart” cancer treatments

• Arsenic trioxide has serious systemic toxicities but is a front line treatment for acute promyelocytic leukemia and has shown promise in adult T-cell leukemia/lymphoma

• This therapeutic hurdle can be lowered by encapsulating drugs into liposome particles (or nanobins)

Ahn et al, PLOS One, 2013
Nano-encapsulation of arsenic trioxide enhances efficacy against lymphoma in a murine model while minimizing reproductive toxicity.

Ahn et al, PLOS One, 2013
Using microphysiologic platforms to screen for the fertoxicity of cancer treatments

Xiao et al, Nature Communications, 2017
Identifying the reproductive toxicity of chemotherapeutics

Doxorubicin

Xiao et al, Toxicol Sci, 2017
Development of fertoprotective adjuvant therapies

Ovarian pre-treatment with anti-apoptotic agents protects against radiation damage and preserves follicles and fertility.
Engineering new fertility preservation methods

Ovarian tissue transplantation – while successful - may be contraindicated.

Laronda et al, Biomaterials, 2015
Bioinspired scaffold serves as an ovarian soft tissue transplant

Bioprosthesis, bursa

Multiple generations

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The Future: where we are going

- **No More Cancer**
  - Treatments are changing in real time

- **Full Fertility**
  - Interventional options to preserve fertility
  - Mitigation strategies

- **Fully Accessible**
  - Low/no resource environments

- **Fully Considered by all Stakeholders**
  - Providers, patients, partners, public

- **Eliminate the field**
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2019 Oncofertility Conference
Pediatric Oncofertility: At the Intersection of Oncology, Fertility Preservation, and Patient Care

November 11-13, 2019
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Visit www.oncofertility.northwestern.edu for more details