FERTILITY AND REPRODUCTION IN FEMALE CHILDHOOD CANCER SURVIVORS

BO YU, MD, MS
ASSISTANT PROFESSOR

GENEVIEVE NEAL-PERRY, MD PHD
ASSOCIATE PROFESSOR, CHIEF
REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
1% OF CANCER OCCURS IN CHILDREN

Estimated number of Persons Alive in the U.S. Who Were Diagnosed With Cancer, by Current Age – More Detail (as of January 1, 2014) (Invasive/1st Primary Cases Only, N = 14.5 M survivors)

Cancer Incidence and Death Rates* in Children 0-19 Years, 1975-2009

*Age-adjusted to the 2000 Standard population.

BETTER TREATMENT = BETTER SURVIVAL

Figure 1. Estimated and projected number of cancer survivors in the United States from 1977 to 2022 by years since diagnosis.
MANY LONG-TERM HEALTH IMPACTS

- Growth and development
  - Skeletal maturation
  - Linear growth
  - Emotional and social maturation
  - Intellectual function
  - Sexual development

- Psychosocial
  - Mental health
  - Education
  - Employment
  - Health insurance
  - Social interactions
  - Chronic symptoms
  - Physical and body image

- Carcinogenesis
  - Recurrent primary cancer
  - Subsequent neoplasms

- Organ function
  - Cardiac
  - Endocrine
  - GI and hepatic
  - Genitourinary
  - Musculoskeletal
  - Neurological
  - Pulmonary

- Fertility and reproduction
  - Fertility
  - Health of offspring
  - Sexual functioning

Nature Reviews | Cancer
Communication between the brain and the ovaries and the uterus allow women to have menstrual cycles and to conceive.
MENSTRUAL CYCLE

The menstrual cycle consists of several phases:

1. Menstruation
2. Follicular phase (Proliferative phase)
3. Ovulation
4. Luteal phase (Secretory phase)
5. Next cycle begins

Hormones involved in the menstrual cycle include:

- FSH (Follicle-Stimulating Hormone)
- LH (Luteinizing Hormone)
- Estrogen
- Progesterone

Key events include:

- Developing follicle
- Mature follicle
- Ovulation
- Developing corpus luteum
- Regressing corpus luteum
- Menses

Days 1-28 represent one menstrual cycle.
BEGINNING OF A PREGNANCY

- **DAY 0**: Ovulation, Ovary, Oocyte
- **DAY 1**: Fertilized Egg (zygote)
- **DAY 2**: First Cleavage, 2-cell stage, 4-cell stage
- **DAY 3-4**: 8-cell uncompacted morula, 8-cell compacted morula
- **DAY 4**: Early blastocyst
- **DAY 5**: Late-stage blastocyst (hatching)
- **DAY 6-7**: Implantation of the blastocyst
- **DAY 8-9**:
FEMALE FERTILITY DECLINES NATURALLY WITH AGE: DUE TO LOSS OF EGGS

- Born with 1 million eggs → release 300-400 eggs over lifetime → 1000 eggs remain at menopause

- Egg quantity and quality decrease with age → fertility decline from 30s

CDC, 2012
HOW DO CANCER TREATMENTS AFFECT FEMALE REPRODUCTION?

• Many cancer treatments adversely affect:
  • egg quantity and quality
  • blood supply to the uterus
  • hypothalamus/pituitary function

• Many cancer survivors experience:
  • Decreased fertility
  • Premature menopause (premature ovarian failure)
  • Sexual dysfunction
  • Precocious or delayed puberty
REDUCED FERTILITY
Compared to siblings, survivors have:

- Reduced chance for pregnancy and birth rate (82%)
- Busulfan, lomustine, and very high dose cyclophosphamide reduced pregnancy and birth rate
• Pelvic radiation ≥ 30 Gy
  • Decrease uterine blood flow
• Wilm’s tumor: 10% with abnormal uterus
  • Increased miscarriage, preterm birth, malpresentation, low birth weight
• Evaluation by REI: ultrasound, MRI
• Primary: Direct damage to ovaries
  • Certain chemotherapy: alkylating agents (busulfan, cyclophosphamide)
  • Radiation: Abdomen, pelvis, spine, total body; especially after puberty
  • Removal of ovary
• Secondary or Central: Hypothalamic/pituitary damage
  • Brain radiation >30Gy
IMPAIRED OVARIAN FUNCTION: PRESENTATIONS

- Delayed or arrested puberty
- Acute ovarian failure:
  - Never had period, or stop period within 5 yrs after diagnosis
- Premature ovarian failure:
  - Menopause before 40yo
- Infertility
IMPAIRED OVARIAN FUNCTION: WHAT TO DO?

• Before or during Ca treatment:
  • Freeze eggs or ovarian tissue
  • Move ovaries out of radiation field
  • Lupron shots during chemo

• After Ca treatment:
  • Annual visit: follow puberty, periods, sexual function, pregnancy
  • Labs: baseline FSH, LH, Estrodiol, (AMH) at age 13, and if clinically indicated
  • Refer to GYN or REI as indicated
  • Freeze eggs if desires, before ovarian failure
  • Hormone replacement if ovarian failure
EGG FREEZING
(OOCYTE CRYOPRESERVATION)

- Pre-Screening and Pre-Testing
- Hormone Injections
  - Stimulate Ovaries to Ripen Multiple Eggs
- Ultrasound Guided Procedure to Retrieve Eggs
- Egg Retrieval under Sedation

Freeze and store in liquid nitrogen
EMBRYO FREEZING

1. Eggs harvested from ovary
2. Eggs fertilised in the lab with sperm
3. Embryos undergo a number of cell divisions
4. Embryos transferred to the womb
ICSI (INTRA CYTOPLASM SPERM INJECTION)
EMBRYO DEVELOPMENT BEFORE TRANSFER

Day 1

Day 2

Day 3

Day 4

Day 5

UW Medicine
EARLY FERTILITY PRESERVATION IS KEY!

• Damage to ovaries is not reversible
• Normal periods ≠ normal fertility
• Fertility decline especially prominent after age 30-35
• Standard embryo or egg freezing takes ~ 4 to 6 weeks
• Success not guaranteed
IVF SUCCESS RATE IN NON-CA PATIENTS

Outcomes of ART Cycles Using Fresh Nondonor Eggs or Embryos, by Stage and Age Group, 2013

National Center for Chronic Disease Prevention and Health Promotion
Division of Reproductive Health

UW Medicine
### Table III
Likelihood of conception and live birth for women after ART by cancer diagnosis, limited to women who only used autologous oocytes.

<table>
<thead>
<tr>
<th>Cancer diagnosis</th>
<th>n, women</th>
<th>Model</th>
<th>Live birth</th>
<th>Conception</th>
<th>Live birth given conception</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR/AOR 95% CI</td>
<td>OR/AOR 95% CI</td>
<td>OR/AOR 95% CI</td>
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<tr>
<td>No cancer</td>
<td>48138</td>
<td></td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
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<tr>
<td><strong>All cancers</strong></td>
<td>393</td>
<td>Unadjusted</td>
<td>0.36 0.29, 0.45</td>
<td>0.33 0.27, 0.41</td>
<td>0.93 0.55, 1.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted a</td>
<td>0.36 0.28, 0.46</td>
<td>0.34 0.27, 0.42</td>
<td>1.21 0.69, 2.11</td>
</tr>
<tr>
<td>Endocrine</td>
<td>62</td>
<td>Unadjusted</td>
<td>0.53 0.31, 0.90</td>
<td>0.52 0.31, 0.87</td>
<td>0.77 0.26, 2.25</td>
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<tr>
<td></td>
<td></td>
<td>Adjusted a</td>
<td>0.67 0.37, 1.18</td>
<td>0.65 0.38, 1.14</td>
<td>0.84 0.28, 2.56</td>
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<tr>
<td>Melanoma</td>
<td>43</td>
<td>Unadjusted</td>
<td>1.27 0.70, 2.32</td>
<td>1.14 0.62, 2.10</td>
<td>1.76 0.42, 7.45</td>
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<tr>
<td></td>
<td></td>
<td>Adjusted a</td>
<td>1.59 0.83, 3.06</td>
<td>1.33 0.69, 2.56</td>
<td>3.07 0.69, 13.6</td>
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<tr>
<td>Breast</td>
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<td>Unadjusted</td>
<td>0.18 0.11, 0.30</td>
<td>0.19 0.12, 0.29</td>
<td>0.49 0.19, 1.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted a</td>
<td>0.19 0.11, 0.30</td>
<td>0.20 0.13, 0.32</td>
<td>0.63 0.24, 1.64</td>
</tr>
<tr>
<td>Ovarian</td>
<td>12</td>
<td>Unadjusted</td>
<td>1.54 0.49, 4.86</td>
<td>1.15 0.37, 3.63</td>
<td>–   –</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted a</td>
<td>1.28 0.39, 4.16</td>
<td>0.98 0.30, 3.22</td>
<td>–   –</td>
</tr>
<tr>
<td>Cervical</td>
<td>24</td>
<td>Unadjusted</td>
<td>0.37 0.15, 0.93</td>
<td>0.41 0.18, 0.96</td>
<td>0.46 0.09, 2.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted a</td>
<td>0.33 0.13, 0.84</td>
<td>0.36 0.15, 0.87</td>
<td>0.70 0.11, 4.49</td>
</tr>
<tr>
<td>Uterine</td>
<td>15</td>
<td>Unadjusted</td>
<td>0.28 0.08, 0.98</td>
<td>0.30 0.10, 0.94</td>
<td>0.46 0.05, 4.43</td>
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<tr>
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<td></td>
<td>Adjusted a</td>
<td>0.30 0.08, 1.11</td>
<td>0.33 0.10, 1.05</td>
<td>0.38 0.04, 3.77</td>
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<tr>
<td>All female genital</td>
<td>53</td>
<td>Unadjusted</td>
<td>0.48 0.27, 0.86</td>
<td>0.50 0.29, 0.87</td>
<td>0.61 0.21, 1.83</td>
</tr>
<tr>
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<td></td>
<td>Adjusted a</td>
<td>0.47 0.25, 0.86</td>
<td>0.49 0.27, 0.87</td>
<td>0.79 0.23, 2.78</td>
</tr>
</tbody>
</table>

*Models adjusted for woman’s age, parity, cumulative FSH dosage, infertility diagnosis and number of infertility diagnoses, number of ART cycles, State of residency and year of ART treatment. Bolded values are OR/AORs and 95% CIs which are significant.

**IVF SUCCESS RATE IN CA PATIENTS LOWER**

OTHER OPTIONS TO HAVE CHILDREN

• Ovarian tissue freezing: experimental, prepubertal girls
• Donor eggs
• Donor sperms
• Gestational carrier
• Adoption
OVARIAN FAILURE
• Menopausal symptoms
  • Vasomotor symptoms
  • Sexual dysfunction
  • Atrophic vaginitis
• Long-term health after menopause
  • Bone
  • Metabolic
  • Cardiovascular
Hormone replacement therapy

- Before puberty: estrogen, monitored by pediatric endocrinologist or adolescent gynecologist
- After menarche: estrogen and progesterone, follow up with GYN

- May occasionally ovulate → pregnancy
- Osteoporosis prevention
- Symptom relief
SEXUAL DYSFUNCTION:
RISK FACTOR

- Chronic GVHD
- Low estrogen level: ovary, brain
- Spinal cord tumor or surgery
- Vaginal tumor or surgery
- Pelvic radiation
  - Prepubertal: ≥25 Gy
  - Postpubertal: ≥50 Gy
SEXUAL DYSFUNCTION: PRESENTATIONS

• Altered or diminished sensation
• Difficulty with tampon insertion
• Dyspareunia
• Vulvar pain
• Postcoital bleeding
• Vaginal fistula
SEXUAL DYSFUNCTION: TREATMENT

• Gynecologic consultation:
  • Lubrication
  • Vaginal dilators
  • Vaginal reconstructive surgery
  • Hormone replacement therapy

• Psychological consultation: for patients with emotional difficulties
• Heavy periods during ca treatment due to low platelets
  • Lupron shot, birth control pills

• Routine GYN care, HPV vaccine, contraception
PRECOCIOUS PUBERTY
• Breast development before 8 years old
• Risk factor:
  • Head/neck radiation ≥18 Gy
  • younger age at time of irradiation
• Evaluation: Pediatric Endocrinologist
  • LH, FSH, estradiol, pelvic ultrasound, bone age
• Treatment:
  • GnRH agonist (Lurpon) until normal age of puberty
1) Improved and personalized cancer treatment plans have resulted in increased numbers of young cancer patients living long lives after cancer treatment.

2) Patients diagnosed with cancer want to live a full life and not just survive after cancer therapy.

3) Many reproductive aged patients identify normal reproductive function to be an important part of life.

4) Many treatment options are available to meet reproductive needs of survivors.
### Providers and Embryologists

#### Providers
1. Emalee Danforth, NP CNM
2. Rekha Matken, NP
3. Genevieve Neal-Perry, MD PhD
4. Diane Woodford, MD
5. Bo Yu, MD MS

#### Embryologists
1. Vahida Anchamparuthy, PhD
2. Michael Eagle, BA
3. Andy Dorfmann, PhD

### Administrators
1. Rekha Matken (Nurse Manager)
2. Hannah Giese (Academic Practice Administrator)

### Program Goals
To provide comprehensive and evidence based care to:

1. Assist with the management of endocrine and reproductive tract disorders that disrupt fertility
2. Assist with the management of endocrine disorders that disrupt baseline reproductive function
3. Assist with the management of reproductive function and family planning in the context of a cancer diagnosis
SIGNATURE SERVICES

1. Infertility and family planning
2. Oncoreproductive health and oncofertility management
3. Reproductive health and nutrition
4. Reproductive health, menopause and hormones
5. Excellence in imaging studies focused on the evaluation of reproductive tract (i.e. HSG, SIS, pelvic ultrasounds)
6. Endocrine disorders and reproductive dysfunction
7. Recurrent pregnancy loss
8. Same sex and single partner fertility care
9. Donor gametes and reproduction
10. Gamete/embryo cryopreservation
11. Third party fertility management
12. Mullerian anomalies and reproductive management
URC IS DEDICATED TO PROVIDING THE HIGHEST QUALITY OF CARE

- Treatment protocols
  - Minimal stimulation IVF protocols
  - Oocyte and embryo cryopreservation
  - Oncoreproductive healthcare
  - Donor gamete services
    - Oocytes
    - Sperm
  - Preimplantation genetic diagnosis
  - Preimplantation genetic screening

**Oncofertility patient visits are prioritized and treatment is not dependent on IVF batching**
1. Onsite social services with expertise in reproductive health
2. Onsite financial counselor
   **Specially priced oncofertility packages**
3. Onsite male fertility specialist
4. Onsite pharmacy with significantly reduced cost for medications
5. Onsite laboratory facility
6. Onsite storage of gametes and embryos
7. Visits for patients diagnosed with cancer are prioritized
8. Personalized treatment plan
9. Patients have a wide range of services to select from
Rekha Matkin, Nurse Manager
rekham2@uw.edu
206-598-7529

Claire Carlson-Jurich, Patient Services Specialist
clairecj@uw.edu
(206) 598-4225

Genevieve Neal-Perry, MD PhD
Division Chief, Reproductive Endocrinology and Infertility
nealperr@uw.edu
ONLINE RESOURCES

• American Society of Reproductive Medicine: http://www.reproductivefacts.org/
• Fertile Hope/Livestrong Foundation: www.fertilehope.org
• Oncofertility Consortium: https://oncofertility.northwestern.edu/

• COG LTFU Guidelines: http://www.survivorshipguidelines.org/
• Childhood cancer survivor study: https://ccss.stjude.org/
• Coalition against childhood cancer (CAC2): https://cac2.org/
Surviving cancer is not
The end of a gruesome story
It is the beginning
Of a beautiful one...