Fertility Preservation Options for Cancer Patients and Survivors

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Introduction

• More patients are surviving cancer
• More cancer survivors are young
• With successful cancer treatment, Quality of Life Issues become more important
• Fertility is a major Quality of Life Issue
• Most patients want a genetically related baby
• Options for Fertility Preservation are available
Five-year Relative Survival

*5-year relative survival rates based on follow up of patients through 2002
Figure 1. Cancer death rates for children and adolescents aged 1–19 years, by sex: United States, 1999–2014

NOTES: Decline in rates from 1999 through 2014 was statistically significant for all groups ($p < 0.05$). Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db257_table.pdf#1. SOURCE: NCHS, National Vital Statistics System, Mortality, ICD–10 underlying cause-of-death codes malignant neoplasms (C00–C97).
Figure 2. Cancer death rates for children and adolescents aged 1–19 years, by age group: United States, 1999, 2006, and 2014

- Significantly higher than the rate for those aged 5–9 in 1999 (p < 0.05).
- Significantly higher than the rates for all other age groups (p < 0.05).

NOTES: Decline in rates from 1999 through 2014 was statistically significant for all groups (p < 0.05). Access data table for Figure 2 at: [http://www.cdc.gov/nchs/](http://www.cdc.gov/nchs/)
Causes of Infertility in Cancer Survivors

• Surgical removal of reproductive organs
  – ovarian, testicular, cervical and endometrial cancer

• Gonadal toxicity of chemo/radiotherapy
Causes of Infertility
Female
Ovarian Oocyte Depletion

- 6-7 weeks
- 20 weeks
- At birth
- Puberty
- Menopause

Oocytes (Millions)

0 1 2 3 4 5 6 7 8
Factors Contributing to Ovarian Failure

- Age of the Woman
  - Younger Women
    - Amenorrhea (21% - 71%)
    - Onset (6 – 16 months)
  - Older Women
    - Amenorrhea (49% – 100%)
    - Onset (2 – 4 months)

Factors Contributing to Ovarian Failure

- **Drug**
  - **Permanent damage**
    - Alkylating agents
      - Cyclophosphamide
      - L-phenylalanine mustard
      - Chlorambucil
    - Procarbazine
  - **No permanent damage**
    - Methotrexate
    - 5-fluorouracil
    - Etoposide
Chemotherapy: Gonadotoxic agents

- Methotrexate
- 5-Fluorouracil
- Vincristine
- Bleomycin
- Actinomycin D

- Cyclophosphamide
- Cholarambucil
- Melphalan
- Busulphan
- Nitrogen mustard
- Procarbazine

Increasing Gonadotoxicity

- Taxanes
- Oxaliplatin
- Irinotecan
- Monoclonal Antibodies
- Tyrosine kinases inhibitors

Unknown  Low  High

Factors Contributing to Ovarian Failure

- Cumulative Dose
  - Cyclophosphamide
    - Increasing rate of POF with increasing dose
    - Dose required to produce amenorrhea

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>20,400 mg</td>
</tr>
<tr>
<td>30-39</td>
<td>9,300 mg</td>
</tr>
<tr>
<td>40-49</td>
<td>5,200 mg</td>
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</tbody>
</table>
## Radiation Effects on Ovarian Function

<table>
<thead>
<tr>
<th>Ovarian Dose (RAD)</th>
<th>Age</th>
<th>% Sterilized</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>All</td>
<td>None</td>
</tr>
<tr>
<td>150</td>
<td>15 – 40</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>&gt; 40</td>
<td>Minimal</td>
</tr>
<tr>
<td>250-500</td>
<td>15 – 40</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>&gt; 40</td>
<td>100%</td>
</tr>
<tr>
<td>500 – 800</td>
<td>15– 40</td>
<td>60% – 70%</td>
</tr>
<tr>
<td></td>
<td>&gt; 40</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 800</td>
<td>All</td>
<td>100%</td>
</tr>
</tbody>
</table>

Damewood. *Fert Steril* 1986;45:443
Radiation Effects on Ovarian Function

- Median Lethal Dose to Human Oocyte: 440 cGy
- "Cut-off" for Radiation Induced Ovarian Failure: 300 cGy

<table>
<thead>
<tr>
<th>Dose (cGy)</th>
<th>Ovarian Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>11% -- 13%</td>
</tr>
<tr>
<td>&gt; 300</td>
<td>60% -- 63%</td>
</tr>
</tbody>
</table>

- Adding chemotherapy increases the risk of POF

Husseinzadeh. *Gynecol Oncol* 1984;18:373
Causes of Infertility
Male
# Radiation

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
<th>No Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Body Radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular Radiation &gt; 6 Gy</td>
<td>Testicular Radiation 1-6 Gy</td>
<td>Testicular Radiation 0.2 – 0.7 Gy</td>
<td>Testicular Radiation &lt; 0.2 Gy</td>
</tr>
<tr>
<td>Cranial Radiation &gt; 40 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Chemotherapy

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
<th>No Risk</th>
<th>Unknown Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating Agent + Radiation</td>
<td>BEP (2-4 cycles)</td>
<td>Non-alkylating agents (ABVD, CHOP, OEPA)</td>
<td></td>
<td>Monoclonal antibodies (bevacizumab, cetuximab)</td>
</tr>
<tr>
<td>Cyclophosphamide &gt; 7.5 gm/m²</td>
<td>Platinum agents Cisplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimens with procarbazine (COPP, MOPP)</td>
<td>Carboplatin</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### Surgery

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
<th>No Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal of one or both testes</td>
<td>Surgeries within the pelvis (rectum, bladder, prostate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removal of pituitary gland</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPPLND</td>
<td>Nerve sparing RPPLND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fertility Preservation Options
Spermatozoa Cryopreservation
Sperm Cryopreservation

- Timing of collection
- Specimen quality
- Storage
- Cost
- Benefit
Sperm Cryopreservation

• Insemination
• IVF
• IVF with ICSI
Other Options

• Testicular shielding
• Testicular Sperm Extraction and Cryopreservation
• Testicular Tissue Cryopreservation
  – Experimental
  – Only cryopreservation option for pre-pubertal boys
Strategies to Preserve Fertility in Female Cancer Patients

Treatment Options

• Pharmacologic Protection from Chemotherapy
  – Oral Contraceptive Pills
    • Do not appear to be effective
  – Progesterone (MPA)
    • Helps rats … but not humans
Pharmacologic Protection from Chemotherapy

- GnRH-a
  - Multiple studies show no protective effect in the male gonad
  - Some large series have shown a protective effect in the female gonad
Blumenfeld 2002

Prospective, non-randomized, some historical controls

<table>
<thead>
<tr>
<th></th>
<th>Chemo + GnRH-a</th>
<th>Chemo</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Patients</td>
<td>58</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>60%</td>
<td>60%</td>
<td>NS</td>
</tr>
<tr>
<td>Non-Hodgkin</td>
<td>40%</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>14 – 40</td>
<td>14 – 40</td>
<td>NS</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>60%</td>
<td>58%</td>
<td>NS</td>
</tr>
<tr>
<td>Dose (cGy)</td>
<td>$2320 \pm 1521$</td>
<td>$1882 \pm 1993$</td>
<td>NS</td>
</tr>
<tr>
<td>POF</td>
<td>5%</td>
<td>55%</td>
<td>&lt;.01</td>
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</table>
Prospective with two historical control groups

<table>
<thead>
<tr>
<th></th>
<th>Premenarchal</th>
<th>GnRH-a</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>5</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>3-7.5</td>
<td>14.7-20</td>
<td>15.9-20</td>
</tr>
<tr>
<td><strong>POF</strong></td>
<td>0/5</td>
<td>0/12</td>
<td>4/4</td>
</tr>
<tr>
<td><strong>Pregnancies</strong></td>
<td>5 in 3 women</td>
<td>3 in 2 women</td>
<td>0</td>
</tr>
<tr>
<td>Study or sub-category</td>
<td>GnRHa (+) n/N</td>
<td>GnRHa (-) n/N</td>
<td>OR (random) 95% CI</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>01 Randomized controlled trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waxman, 1987</td>
<td>4/8</td>
<td>6/9</td>
<td>8.32 [0.07, 3.55]</td>
</tr>
<tr>
<td>Giuseppe, 2007</td>
<td>14/14</td>
<td>8/15</td>
<td>4.50 [1.29, 5.06]45</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>61</td>
<td>63</td>
<td>26.45 [0.47, 71.03]</td>
</tr>
<tr>
<td>Total events: 53 (GnRHa (+))</td>
<td>27 (GnRHa (-))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 9.81, df = 2 (P = 0.007), I² = 79.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.36 (P = 0.17)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 02 Nonrandomized studies | | | | | |
| Pereyra Pacheco, 2001   | 12/12         | 0/4           | 2.67 [3.86, 13113.77] | 16.21 [5.93, 44.32] |                     |
| Blumenfeld, 2005        | 70/75         | 38/82         | 15.80 [4.09, 120.69] |         |                     |
| Dann, 2005              | 7/7           | 5/6           | 3.66 [0.14, 120.69]  |         |                     |
| Somers, 2005            | 19/20         | 14/20         | 7.01 [0.88, 74.48]   |         |                     |
| Castelo-Branco, 2007    | 27/30         | 6/26          | 11.33 [6.68, 134.68] |         |                     |
| Brumenfeld, 2008        | 63/65         | 29/68         | 11.11 [4.00, 85.26]  |         |                     |
| Huser, 2008             | 57/72         | 13/45         | 17.30 [3.96, 22.10]  |         |                     |
| Nitzschke, 2009         | 9/10          | 9/10          | 4.66 [0.05, 18.57]   |         |                     |
| Subtotal (95% CI)       | 291           | 239           | 73.55 [7.37, 22.92]  |         |                     |
| Total events: 264 (GnRHa (+)), 114 (GnRHa (-)) | | | | | |
| Test for heterogeneity: Chi² = 7.81, df = 7 (P = 0.37), I² = 8.0% | | | | | |
| Test for overall effect: Z = 8.86 (P < 0.00001) | | | | | |
| Total (95% CI)           | 352           | 302           | 100.00 [5.22, 21.39] |         |                     |

Q: Why Should GnRH-a Work?

A: We don’t know

Theories

- GnRH receptors on oocyte or cumulus
- Decreased gonadotropin concentrations
- Decreased ovarian perfusion due to hypoestrogenic state
Ovarian Transposition
Ovarian Transposition

The transposed ovaries are depicted according to their position on MRI. Each number represents a single patient. The shaded area represents the radiation field.

*Cancer* 1994;74:775
Ovarian Transposition

• MOT vs LOT
  – Study of irradiation for Hodgkin’s
    • 3600 cGy external beam to the pelvis
    • 3524 cGy to the ovaries normally positioned
    • 534 cGy to the ovaries transposed medially
    • 319 cGy to the ovaries transposed laterally
  – Ovarian failure compiled from small studies
    • 50% with medial transposition
    • 14% with lateral transposition
Laparoscopic Ovarian Transposition
Laparoscopic Ovarian Transposition
Laparoscopic Ovarian Transposition
<table>
<thead>
<tr>
<th></th>
<th>Brachy (60 Gy)</th>
<th>Ext Beam (25-30 Cy)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Pts</td>
<td>27</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>#Pregnant Pts</td>
<td>4 (15%)</td>
<td>8 (80%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>#Pregnancies</td>
<td>7</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Spontaneous w/o repositioning</td>
<td>3</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Spontaneous w/ repositioning</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>IVF</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SAB</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Ovarian Transposition -- Issues

- Ovarian transposition and hysterectomy may cause ovarian failure without radiation.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% POF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical Hysterectomy</td>
<td>4.1%</td>
</tr>
<tr>
<td>Radical Hysterectomy + LOT</td>
<td>4.3%</td>
</tr>
<tr>
<td>Radical Hysterectomy + LOT + XRT</td>
<td>29%</td>
</tr>
</tbody>
</table>

Chambers. *Gynecol Oncol* 1990;39:155

- The onset of menopause is, on average, five years earlier following devasularization of the ovary (45.4 vs 49.5 years).
Ovarian Transposition -- Issues

• Ovarian Cyst Formation
  – Hysterectomy for benign disease (1% – 5.2%)
  – Radical hysterectomy (4.9 – 7.6%)
  – Ovarian transposition (24%)

• Migration to original position (39%)
Ovarian Transposition -- Issues

- No excess cases of ovarian cancer in women who received 500 – 1000 cGy to the ovaries
Pregnancy After Radiation

- No excess cases of stillbirth, congenital malformation, chromosomal abnormalities, or cancer in offspring
  - Atomic bomb survivors
  - Hodgkin’s disease treated with XRT\(^1\)
- Increase in low birth weight and spontaneous abortion if conception occurred within one year of radiation therapy\(^2\)
- Case report of uterine rupture in primigravid after radiation

2. Fenig. *Cancer Treat Rev* 2001;27:1
Embryo & Oocyte Cryopreservation
Embryo Cryopreservation

- Delay in treatment
- Absence of a spouse
- Risk of stimulation and egg retrieval
- Limited numbers of embryos
Embryo Cryopreservation

• Steps
  – Suppression
  – Ovarian stimulation
  – Oocyte maturation
  – Egg Retrieval
  – Fertilization
  – Embryo Culture
  – Cryopreservation
IVF Protocol Modifications

• Immediate Start
  – GnRH antagonist
  – Luteal Lupron

• Estradiol Minimization
  – Letrozole
Oocyte Cryopreservation

1. Standard of care since 2013
2. Vitrification
3. ICSI required
ASRM Statement 2013

There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI with fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI for young women. Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population. Evidence indicates that oocyte vitrification and warming should no longer be considered experimental.
Cryopreservation of Ovarian Tissue

Oogenesis and Fertilization

Experience with parathyroid tissue
Ovarian Tissue Cryopreservation

- Ordinarily only one ovary removed
- Cortex sectioned into thin slices and cryopreserved at –196 degrees C.
- Post thaw survivability 50-70%
- Potential for normal hormonal function and fertility
To the Editor: Studies in animals and humans have shown that cryopreserved ovarian tissue can be transplanted successfully. We report the successful transplantation of frozen, banked autologous ovarian tissue according to a protocol approved by the institutional review board at our center.
An incision was made in the patient’s forearm to transplant the ovary before radiotherapy.
The development of ovarian follicles was evident 9 weeks after the transplant procedure.
The oocytes that were retrieved from the woman’s forearm were not successfully fertilized.
Ovarian Transplant Xenograft

1. Slices of ovarian tissue, containing immature eggs, are removed and frozen in liquid nitrogen.
2. Thawed tissue is surgically implanted into mouse thigh muscle, where eggs mature.
3. Eggs are removed and fertilized with sperm in vitro.

Freezing Eggs
Scientists are trying to find ways women can freeze their eggs or ovarian tissue so they can become pregnant later in life using their own eggs. In one approach, researchers are experimenting with freezing ovarian tissue.

SCID Mouse
2014 ASRM Statement

Ovarian tissue cryopreservation is an option to preserve reproductive potential in patients who must urgently undergo aggressive chemotherapy and/or radiotherapy or who have other medical conditions requiring treatment that may threaten ovarian function and subsequent fertility. Ovarian tissue cryopreservation may be the only option available to prepubertal girls undergoing such treatments. However, these techniques are still considered to be experimental.
History of Cryobiology

• 1950’s - Human sperm successfully frozen
• 1983 - First frozen embryo pregnancy
• 1986 - First frozen mature oocyte pregnancy
• 1994 - Viable frozen thawed ovarian strips containing thousands of oocytes

NEJM Oktay et al 2000;342(25):1919
Third Party Reproduction

- Donor sperm
- Donor oocyte
- Gestational Carrier
Donor Sperm

- Anonymous
- Known Donor
  - Friend
  - His relative
Donor Sperm

BASIC SEARCH

DONOR CATEGORY
- Any Donors
- CLI Donors
- ID Options Donors
- Anonymous Donors
- Graduate Donors
- Canadian Release

ANCESTRY
- Any
- Black
- Latino
- Asian
- Caucasian
- Multi

HAIR COLOR
- Any
- Black
- Auburn
- Brown
- Blond
- Red

EYE COLOR
- Any
- Brown
- Blue
- Hazel
- Green

BLOOD TYPE
- Any
- AB
- A
- B
- O

RH FACTOR
- Any
- RH+
- RH-

HEIGHT
- Any Height

Total Donors: 418
View All Donors

Find matching donors based on hair and eye color, height and more!
Third Party Reproduction

• Use of eggs, sperm, embryos or a uterus that are donated by a third person (gamete donor or surrogate) to an infertile couple (recipient) to enable them to become parents.

• Gamete donors can be known (directed) or anonymous.

• Surrogacy Laws vary from state to state
Adoption

• Can be costly ($5,000-$40,000)
• Cancer history can be prohibitive
  – May need to wait five years
  – Letter from Oncologist
Pregnancy after Cancer

- Risk to Mother:
  - Obstetrical risks:
    - cardiovascular after cardiotoxic chemo and mantle radiation to the heart and lungs
    - pulmonary fibrosis after some chemo and pulmonary radiation
  - Recurrence of cancer:
    - in general no increased risk
    - controversial for breast
Pregnancy after Cancer

- **Risk to Offspring:**
  - No increased risk of miscarriages except after radiation
  - No increased risk for birth defects
  - No increased risk of malignancies in general except heritable cancers
    - retinoblastomas
    - Wilm’s tumors
Costs

- Typically not covered by insurance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperm Cryopreservation</td>
<td>$300</td>
</tr>
<tr>
<td></td>
<td>$500 annual storage</td>
</tr>
<tr>
<td>Donor Sperm Insemination</td>
<td>$600-$800</td>
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</tbody>
</table>
## Costs

- Typically not covered by insurance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocyte Cryopreservation</td>
<td>$6000 - $8000</td>
</tr>
<tr>
<td></td>
<td>$500 annual storage</td>
</tr>
<tr>
<td>Donor Oocyte IVF</td>
<td>$12,000 - $20,000</td>
</tr>
<tr>
<td>Gestational Carrier</td>
<td>$40,000 - $60,000</td>
</tr>
<tr>
<td>Adoption</td>
<td>$5000 - $40,000</td>
</tr>
<tr>
<td>Resources</td>
<td>Website</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Oncofertility Consortium</td>
<td>oncofertility.northwestern.edu</td>
</tr>
<tr>
<td>Live Strong Lance Armstrong Foundation</td>
<td><a href="http://www.livestrong.org">www.livestrong.org</a></td>
</tr>
<tr>
<td>American Society of Clinical Oncologists</td>
<td><a href="http://www.asco.org">www.asco.org</a></td>
</tr>
<tr>
<td>Guidelines for Fertility Preservation</td>
<td></td>
</tr>
<tr>
<td>American Society of Reproductive Medicine</td>
<td><a href="http://www.asrm.org">www.asrm.org</a></td>
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