OPTIONS FOR FERTILITY PRESERVATION AND FERTILITY CARE IN WOMEN DIAGNOSED WITH CANCER

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Learning Objectives

- To discuss the impact of cancer therapy on future fertility in females
- To learn about the current options for fertility preservation in female patients with cancer
- To learn about fertility strategies in female survivors of cancer
Does cancer therapy affect fertility in women?
Risks to Future Fertility in Women with Cancer

- Chemotherapy
- Radiation
- Surgery
How does cancer therapy affect fertility in women?

- Ovarian follicle reserve is finite
  - Diminishing ovarian reserve is associated with decreased fertility potential
Natural decline in ovarian reserve
How does cancer therapy affect fertility in women?

- Ovarian follicles are remarkably vulnerable to agents that cause DNA damage, including ionizing radiation and chemotherapy
  - Primordial, pre-antral, antral follicles all susceptible
  - Dramatic reduction in follicular and oocyte reserve
Treatment-induced decline in ovarian reserve
Possible Treatment Effects

- Immediate (acute) ovarian failure (AOF)
  - Permanent cessation of periods

- Infertility
  - Despite continued periods
  - Loss of oocytes during treatment mimics age-related loss

- Delayed onset of premature ovarian failure
  - Early menopause (before 40)
  - Shortened reproductive lifespan
Factors influencing degree of fertility impairment

- Type of chemotherapy
- Dose of chemotherapy
- Location and dose of radiation
- Age
Type of chemotherapeutic agent

- High Risk: Cyclophosphamide, melphalan, busulfan, chlorambucil, procarbazine, nitrogen mustard

- Moderate Risk: Cisplatin, doxorubicin, paclitaxel

- Low Risk: Methotrexate, 5-fluorouracil, bleomycin, actinomycin D, vinca alkaloids
Reported ovarian failure rates by age and combination chemotherapy regimen in breast cancer patients

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Age</th>
<th>Reported ovarian failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>&lt;30</td>
<td>0%</td>
</tr>
<tr>
<td>AC</td>
<td>30-39</td>
<td>13%</td>
</tr>
<tr>
<td>AC</td>
<td>&gt;40</td>
<td>57-63%</td>
</tr>
<tr>
<td>FAC</td>
<td>&lt;30</td>
<td>0%</td>
</tr>
<tr>
<td>FAC</td>
<td>30-39</td>
<td>10-25%</td>
</tr>
<tr>
<td>CMF</td>
<td>&lt;30</td>
<td>19%</td>
</tr>
<tr>
<td>CMF</td>
<td>30-39</td>
<td>51-77%</td>
</tr>
<tr>
<td>CMF</td>
<td>&gt;40</td>
<td>83-98%</td>
</tr>
<tr>
<td>+ Taxanes</td>
<td></td>
<td>79% (OR 4.05)</td>
</tr>
</tbody>
</table>

Chung et al. Fertil Steril 2013;99:1534
Irradiation dose

Chemaïtilly W et al. JCEM 2006.
Effective sterilizing dose (ESD)

- Defined as the dose of radiotherapy inducing AOF in 97.5% of patients

- Lower ESD with increasing age
  - At birth the ESD 20.3 Gy
  - At 20 years ESD is 16.5 Gy
  - At 30 years ESD is 14.3 Gy

- Ovarian failure risk is 90% of patients post-total body irradiation (TBI) at doses of 10-15.75 Gy

Chemaitilly W et al. JCEM 2006.
Ms Jones is a 38 year old female with newly diagnosed stage IIA, ER+/PR+ carcinoma of the breast.

Treatment course will include:
- Lumpectomy with lymph node dissection
- Combination chemotherapy (AC plus taxol)
- Local radiation to affected breast
- Adjuvant hormonal therapy (5-10 years)

What is her most concerning risk factor for future infertility and ovarian failure?
Incidence

- Incidence of impaired fertility difficult to predict
  - Not well characterized due to variable definitions (15-90%)
- **AGE** is often the most important risk factor
- Non-elective delay in childbearing in females to allow for treatment and recovery from cancer (standard 2 years)
  - Pregnancy is contraindicated during hormonal treatments for breast cancer (tamoxifen and aromatase inhibitors)
  - Recommended delay 5-10 years
Case #1: Ms. Jones

She has always wanted to have kids but currently has no partner. What is her best option with respect to fertility?

A. Not to worry because her fertility will not be affected by her cancer treatment
B. Embryo freezing
C. Egg freezing
D. Ovarian tissue freezing
E. GnRH analog
F. Not to even think about getting pregnant in the future because of her history of breast cancer
What are the options BEFORE Treatment?
As part of informed consent prior to therapy, health care providers should address the possibility of infertility with patients. Referrals for interested patients to reproductive specialists. Discussion at the earliest possible opportunity. Embryo and oocyte cryopreservation are standard practice; other methods are investigational – only for centers with expertise.

Ovarian stimulation process

1. GnRH antagonist
2. FSH/LH
3. hCG
4. Egg retrieval

Day 1 of menses
<table>
<thead>
<tr>
<th>Peak estradiol levels (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural cycle</td>
</tr>
<tr>
<td>Conventional IVF</td>
</tr>
</tbody>
</table>
Ovarian stimulation for breast cancer patients

- **Concerns:**
  - Conventional ovarian stimulation raises estrogen levels
  - Estrogen potentially stimulates malignant cells\(^1,2\)
  - It is not known what peak level is safe in patients with breast cancer

- **Tamoxifen:** Estrogen receptor antagonist

- **Aromatase inhibitors:** suppresses estrogen production

Breast cancer recurrence after IVF compared to matched controls

- 3/42 (7.1%) IVF patients
  - 2 in Tamoxifen-IVF
  - 1 in Tamoxifen + FSH-IVF
  - None in Letrozole + FSH patients
- 4/44 (9%) in Control patients

## Pregnancy rates using frozen embryos

<table>
<thead>
<tr>
<th>Age at time of egg retrieval</th>
<th>Fresh</th>
<th>Frozen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>35-39</td>
<td>45%</td>
<td>30%</td>
</tr>
<tr>
<td>40+</td>
<td>30%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Numbers represent percent pregnancy per attempt when transferring multiple embryos at a time
## Pregnancy rates using frozen eggs

<table>
<thead>
<tr>
<th>Age at time of egg retrieval</th>
<th>Frozen embryos</th>
<th>Frozen eggs</th>
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<tbody>
<tr>
<td>&lt; 35</td>
<td>40%</td>
<td>30-40%</td>
</tr>
<tr>
<td>35-39</td>
<td>30%</td>
<td>20-30%</td>
</tr>
<tr>
<td>40+</td>
<td>20%</td>
<td>15-20%</td>
</tr>
</tbody>
</table>

Numbers represent percent pregnancy per attempt when thawing 6 eggs at a time

Cil et al. Fertil Steril 2013:100:492
Current Consensus among REI experts

Efficacy of frozen embryos vs frozen eggs is believed to be about the SAME!
Case #1: Ms. Jones

She has always wanted to have kids but currently has no partner. What is her best option with respect to fertility?

A. Not to worry because her fertility will not be affected by her cancer treatment

B. Embryo freezing

C. Egg freezing

D. Ovarian tissue freezing

E. GnRH analog

F. Not to even think about getting pregnant in the future because of her history of breast cancer
Timing considerations

**Traditional approach**
- Initial consultation
  - AMH, ultrasound
- Await menses
  - Day 3 FSH, E2
- Initiate ovarian stimulation in early follicular phase
- Time required: 2-6 weeks

**Random start**
- Initial consultation
  - AMH, ultrasound
- Initiate ovarian stimulation immediately regardless of phase of cycle
“Random Start”

- Retrospective cohort of cancer patients (mostly breast cancer) undergoing ovarian stimulation for egg or embryo freezing
- Average age 34
- Random start (n=35) vs Conventional/Early follicular start (n=93)
- Random start required more days of stimulation (mean 10.9) than conventional (mean 9.3)
- No differences in outcome of cycle (number of eggs, embryos)

Cakmak et al. Fertil Steril 2013;100:1673
“Random Start”

- Though random start required 1-2 more days of injections, no need to wait for beginning of menses to start the process
- Allows us to expedite fertility preservation process without compromising outcome

Cakmak et al. Fertil Steril 2013;100:1673
## Timing considerations

### Traditional approach
- Initial consultation
  - AMH, ultrasound
- Await menses
  - Day 3 FSH, E2
- Initiate ovarian stimulation in early follicular phase
- Time required: 2-6 weeks

### Random start
- Initial consultation
  - AMH, ultrasound
- Initiate ovarian stimulation immediately regardless of phase of cycle
- Time required: 2-2.5 weeks
Embryo and egg banking procedures require approximately 2 weeks from start to finish.
Timing of embryo and egg freezing

- Embryo and egg banking procedures should be completed prior to initiation of cancer therapies.
  - Previous chemotherapy is likely to decrease the number of retrievable eggs
  - If attempted within 2-3 months of exposure, no eggs retrieved at the time of egg retrieval
  - Concerns that follicles recently exposed to chemotherapy may yield abnormal oocytes (animal studies)
What are the options DURING Treatment?

Experimental
Ovarian Tissue Freezing

- Ovary(s) removed laparoscopically, divided into small strips, frozen and stored
- Females, before and after puberty
- Can be done after initiation of chemo
- Outpatient surgical procedure
- Experimental, few live births to date (15 reported)
- Re-implantation can restore hormone function
Transplantation of cryopreserved ovarian tissue

- Potential reintroduction of malignant cells into a patient in remission is a theoretical concern
- Testing of tissue for tumor cells is possible by RT-PCR for certain tumor types
- Option is reserved for patients who have no time for ovarian stimulation and are high risk for ovarian failure after cancer treatment
GnRH-Analog Treatment

- Administered during chemo to create a “prepubertal state”
  - May reduce damage to immature eggs, reducing the chance of infertility
- Monthly injection
  - First dose should be given at least 1 week prior to chemo if possible
- Experimental, research varies, most human studies show no effect
Recent RCT of 281 premenopausal women with breast cancer (ages 18-45)

Randomized to chemo alone versus chemo plus 3.75 mg Triptorelin q 4 weeks

12 months follow up post-chemo

Strict definition of menopause (12 mos amenorrhea)

Significant reduction in chemo-induced menopause in Triptorelin group

25.9% versus 8.9% (OR 0.28, 95% CI 0.14-0.59)

Del Mastro et al. JAMA 2011;306:269
What are the options AFTER Treatment?
Evaluating impact on fertility

- Many women resume menstruation, but cannot assume normal fertility

- Ovarian reserve testing
  - Follicle Stimulating Hormone (FSH) and estradiol levels on cycle day 3
  - Ultrasound for ovarian volume and antral follicle count
  - Anti-mullerian Hormone levels
Ovarian reserve testing

- Any of the available tests are most predictive when they are abnormal.
- When the tests are normal, age is the best predictor but should always suspect shortened reproductive lifespan.
- Predictive value of tests have not been validated in cancer population (most data on AMH).
Case #2: A. G.

- 23 y/o with history of Hodgkin’s Lymphoma treated with combination chemo (BEACOPP) at age 11
- Normal menarche at age 13, regular periods
- Strongly desires children of her own genetics but not in the near future
- Currently has a partner and has copper IUD for contraception
- What do you do? Is she at risk for infertility or premature ovarian failure?
# Reported ovarian failure rates by age and chemotherapy regimen in patients with Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Combination Chemotherapy Regimen</th>
<th>Reported rates of ovarian failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVPP</td>
<td>61%</td>
</tr>
<tr>
<td>ChlVPP</td>
<td>53%</td>
</tr>
<tr>
<td>COPP/ABVD</td>
<td>78%</td>
</tr>
<tr>
<td>BEA/COPP</td>
<td>OR 3.55</td>
</tr>
<tr>
<td>ABVD</td>
<td>Unlikely to cause ovarian failure</td>
</tr>
<tr>
<td>BMT</td>
<td>72-100%</td>
</tr>
</tbody>
</table>

Chung et al. *Fertil Steril* 2013;99:1534
A. G.

- **Ovarian reserve testing:**
  - Day 3 FSH: 3.8 mIU/mL
  - Day 3 Estradiol: 42 pg/mL
  - Follicle count: 18
  - AMH 1.02 ng/mL

- AMH and follicle count indicate relative diminished ovarian reserve
AG - Counseling

- Normal FSH but for her age group AMH and AFC low

- Indicates that ovarian reserve is lower than most women in her age group
  - Most likely secondary to her history of chemotherapy

- May be able to conceive on own if wishing to achieve pregnancy in next year or so

- Recommend egg or embryo freezing if desires more than one child or wishes to delay child bearing more than 1-2 years
AG – Oocyte Cryopreservation

- Chose to undergo oocyte cryopreservation
- 12 day stimulation cycle including egg retrieval
- 2 days prior to egg retrieval 18 visible follicles

Diagram:
- GnRH antagonist
- FSH
- hCG
- Egg retrieval

1 8 1 2
AG – Oocyte Cryopreservation

- 16 oocytes retrieved
- 14 oocytes suitable for freezing
- 14 oocytes successfully frozen
  - 80% chance of live birth from these eggs
Delayed fertility preservation

- Ovarian stimulation for egg or embryo freezing can be successful after completion of cancer treatment
  - Ideal interval post-chemotherapy: > 6 months
  - Indicated when risk or evidence of diminished ovarian reserve present
  - Indicated for impending premature ovarian failure
Indicators of ovarian failure

- FSH > 20 mIU/mL
- AMH undetectable (<0.1 ng/mL)
- Follicles absent on ultrasound
- Persistent amenorrhea (>12 months post-treatment)
Options for patients with premature ovarian failure

- Donor eggs
- Donor embryos
- Adoption
Surgical causes of infertility

- Hysterectomy (Endometrial cancer, hyperplasia)
  - Ovarian conservation allows for pregnancy with gestational carrier
- Oophoropexy (GI tumors, sarcoma)
  - Requires abdominal ultrasound-guided oocyte retrieval
- Bilateral salpingo-oophorectomy (BRCA carriers)
  - May consider series of egg freeze cycles prior to BSO
- +/- Trachelectomy (Cervical cancer)
Case #3: L.W.

- 35 y/o G1P0010 Stage IB1 cervical adenocarcinoma underwent vaginal radical trachelectomy, with laparoscopic lymphadenectomy
  - Approximately 1 cm cervical stump, cerclage placed
  - Complicated by severe recurrent cervical stenosis, recurrent bilateral hematosalpinges
  - Required bilateral salpingectomy, trans-hysterotomy laparoscopic identification of cervical os, placement of cervical stent
L. W.
L.W.

- Underwent IVF
  - 17 embryos
  - Transfer of 2 embryos via cervical stent – no pregnancy
- Evaluation of uterine cavity by pipelle biopsy
  - Lymphoplasmacytic infiltrates suggesting endometritis
  - Removal of stent
  - Treatment with doxycycline x 10 days
Frozen embryo transfer

- Unidentifiable cervical os
- Difficult and prolonged procedure under anesthesia
- A few years off my life
- Two embryos transferred — pregnancy achieved!
- Bedrest at 30 weeks due to cervical shortening
- Delivered via C-section at 36 weeks after confirming fetal lung maturity — healthy male infant, 2551 g.
Risks to Future Fertility in Women with Cancer

- Chemotherapy
- Radiation
- Surgery

- Improvements in overall survival $\rightarrow$ Focus on quality of life after cancer
- For many women, fertility is one of the MOST important survivorship issues.
Thank You!
Your Questions

karine.chung@med.usc.edu
## Average Treatment Costs:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo Freezing</td>
<td>$10,000</td>
</tr>
<tr>
<td>Egg Freezing</td>
<td>$8,000</td>
</tr>
<tr>
<td>Ovarian Tissue Freezing</td>
<td>$12,000</td>
</tr>
<tr>
<td>GnRH Analog Treatments</td>
<td>$500/mo.</td>
</tr>
<tr>
<td>In Vitro Fertilization</td>
<td>$7,800/cycle</td>
</tr>
<tr>
<td>Donor eggs</td>
<td>$20,000 - 30,000</td>
</tr>
<tr>
<td>Adoption (domestic, international, public, private)</td>
<td>$2,500 - 35,000</td>
</tr>
<tr>
<td>Surrogacy</td>
<td>$20,000 - 100,000</td>
</tr>
</tbody>
</table>

Financial assistance available through Fertile Action, Livestrong. Some centers will discount rates for women with cancer.
<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Cost Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGG FREEZING</strong></td>
<td>$4,952.00</td>
</tr>
<tr>
<td><strong>EMBRYO FREEZING</strong></td>
<td>$5,342.00 (or $6,092.00 if ICSI is needed)</td>
</tr>
<tr>
<td>Frozen egg or embryo storage fees (per year starting year 2)</td>
<td>$365.00</td>
</tr>
<tr>
<td>Ovarian Stimulation Medications</td>
<td>$1500-5000 (usually able to get for free through various programs)</td>
</tr>
<tr>
<td><strong>OVARIAN TISSUE FREEZING</strong></td>
<td>TBD</td>
</tr>
<tr>
<td>GnRH AGONIST (Monthly injection throughout chemotherapy)</td>
<td>$900-1500 per injection (may be covered by insurance)</td>
</tr>
</tbody>
</table>