Female Fertility Preservation: Options and How We Got Here

George T Koulianos
Program Director
The Center for Reproductive Medicine
Mobile Infirmary Medical Center
Mobile, AL
Learning Objectives

• Describe the most common fertility preservation options
• Understand rationale and evidence for applying specific fertility preservation strategies
• Discuss timing and practical considerations
How big an issue is fertility preservation

• By age 39, 1/51 women will have been diagnosed with invasive cancer
• Women are delaying childbearing 25.2 yo (all time high) with 25% of first births occurring between the ages of 30 & 40
• Improved cancer survival: 77% Dx’d @ <45 yo live >5 years
• Population based studies demonstrate a consistent 30% - 50% reduction in probability of having a live birth in Ca survivors

As part of informed consent *prior* to therapy, oncologists should address the possibility of infertility with patients as early in treatment planning as possible.

ASCO 2013 Guidelines

*Discuss fertility preservation with all patients of reproductive age if infertility is a potential risk of therapy.*

• **Females**
  • Present both embryo and egg freezing as established methods
  • Ovarian tissue freezing is still experimental

• **Males**
  • Sperm banking (council on higher risk of genetic damage in sperm collected after beginning chemo)
WHO NEEDS TO CONSIDER PRESERVATION OF FERTILITY?

- **Cancer patients** before gonadotoxic treatment
- **Other diseases before gonadotoxic treatment** (Systemic lupus, rheumatoid arthritis...)
- Individuals exposed to accelerated loss of oocytes due to **genetic disease** (Turner syndrome, Fragile X premutation (FMR 1), Galactosemia)
- **Fertility extension**. Women delaying pregnancy for career or social reasons
Protection
Preservation
Pregnancy

Fertility
Infertility and Cancer

• 7 - 15% of women are infertile
• About 25% of cancer survivors are infertile
• Resumption of menses is not a good indicator of reproductive potential

Lee SJ. J Clin Oncol 2006
Letourneau JM. Cancer 2011
How Often Do You Refer Patients to RE or Ob-Gyn who Specializes in Fertility

![Bar chart showing the reported frequency of referring patients to RE or Ob-Gyn who specializes in fertility. The categories are Never, Rarely, Usually, and Always. The chart indicates a higher percentage of physicians rarely refer patients compared to other categories.]

Forman EJ et al., Fertil Steril 2010
Effect of Cancer Treatment on Fertility

- Varies based on many factors
- Chemo used and dose
- Size and location of radiation field
- Patient age
- Preexisting egg reserve
- Effect may manifest later via diminished egg reserve or primary ovarian insufficiency
Reproductive Compromise & Cancer

Acute Ovarian Failure After Chemo
Infertility Despite Menses Returning Post Chemo

Adapted from Letourneau JM et al, Cancer 2011
Reported Ovarian Failure Rates by Age and Combination Chemotherapy Regimen in Breast Cancer and Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Chemo Regimen</th>
<th>Age, y</th>
<th>Reported Ovarian Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>&lt;30</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>&gt;40</td>
<td>57-63%</td>
</tr>
<tr>
<td>FAC</td>
<td>&lt;30</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>10-25%</td>
</tr>
<tr>
<td>CMF</td>
<td>&lt;30</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>51-77%</td>
</tr>
<tr>
<td></td>
<td>&gt;40</td>
<td>83-98%</td>
</tr>
<tr>
<td>+ Taxanes</td>
<td></td>
<td>79% (OR 4.05)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPP</td>
<td></td>
<td>61%</td>
</tr>
<tr>
<td>ChIVPP</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td>COPP/ABVD</td>
<td></td>
<td>78%</td>
</tr>
<tr>
<td>BEA/COPP</td>
<td></td>
<td>OR 3.55</td>
</tr>
<tr>
<td>ABVD</td>
<td></td>
<td>Unlikely to cause</td>
</tr>
<tr>
<td>BMT</td>
<td></td>
<td>72-100%</td>
</tr>
</tbody>
</table>

Chung. IVF vs. OTCP in cancer patients. Fertil Steril 2013
Know the Risks

Risk of Amenorrhea from common chemotherapy and radiation treatments

ASCO Guidelines
Fertile Hope, Fast Facts for Oncology Professionals, 2007

Savemyfertility.org

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, melphalan) 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, CHLVPP, CNVPP/EVA, BEACOPP, MOPP/ABVD, COPP/ABVD

Intermediate Risk
- Whole abdominal 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
- AC in women 30–39 years
- CMF, CEF, or CAF x 6 cycles in women <30 years
- Nonalkylating chemotherapy: ABVD, CHOP, COP
- AC
- Radioactive iodine
- MF
- Vincristine

Low Risk
- Paclitaxel, docetaxel (taxanes used in AC protocols)
- Oxaliplatin
- Vinorelbine
- Bevacizumab
- Cetuximab
- Trastuzumab
- Erlotinib
- Imatinib

Unknown Risk
Effect of Cyclophosphamide on Ovarian Reserve

• 2.4 – 3 g/m² over 10 – 12 weeks adds 10 years to ovarian reproductive age
• Or 1.5 – 3 years per treatment cycle

Kim SS. Fertil Steril 2011
Fertility Preservation: where does it fit in?

1. Diagnosis
2. Develop Treatment plan
3. Assess fertility risk
4. Discuss impact of cancer and treatment on reproductive health
5. Patient interested in fertility preservation
   - Yes: Refer to reproductive specialist
   - No: Proceed with treatment
6. Discuss fertility preservation options
Options for Fertility Preservation

• Pelvic shielding
• In vitro maturation (experimental)
• Ovarian tissue preservation (experimental, approx 60 reported live births worldwide)

• Embryo Preservation
  • Must be married or willing to use donor sperm
  • Requires ovarian hyperstimulation

• GnRHa
  • Uncertain benefit

• Oocyte cryopreservation
  • Requires ovarian hyperstimulation and 14-20 days

• Ovarian transposition
  • Preservation of menstrual function is only 50%
    • Due to scatter radiation and/or compromised ovarian blood supply
    • Egg retrieval more difficult requiring 2nd surgery
• **GnRha** may prevent follicles from reaching the cytotoxic threshold by decreasing mitotic activity in the granulosa cells

American Society of Clinical Oncology (ASCO) Guideline 2013

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>GnRH Events</th>
<th>Control Events</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Badawy 2008</td>
<td>35</td>
<td>13</td>
<td>14.54 [4.62, 45.78]</td>
<td></td>
</tr>
<tr>
<td>Gilani 2007</td>
<td>15</td>
<td>10</td>
<td>16.24 [0.81, 325.88]</td>
<td></td>
</tr>
<tr>
<td>Guiseppe 2007</td>
<td>14</td>
<td>8</td>
<td>25.59 [1.29, 506.45]</td>
<td></td>
</tr>
<tr>
<td>Sverrisdottir 2009a</td>
<td>8</td>
<td>2</td>
<td>4.95 [0.95, 25.86]</td>
<td></td>
</tr>
<tr>
<td>Sverrisdottir 2009b</td>
<td>2</td>
<td>3</td>
<td>0.50 [0.08, 3.18]</td>
<td></td>
</tr>
<tr>
<td>Waxman 1987</td>
<td>4</td>
<td>6</td>
<td>0.67 [0.10, 4.35]</td>
<td></td>
</tr>
<tr>
<td>ZORO 2009</td>
<td>21</td>
<td>30</td>
<td>1.78 [0.62, 5.17]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>173</strong></td>
<td><strong>167</strong></td>
<td><strong>3.46 [1.13, 10.57]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events 99, 59

Heterogeneity: $\chi^2 = 13.88$, $\text{df} = 6$ ($P = 0.007$); $I^2 = 66$

Test for overall effect: $Z = 2.17$ ($P = 0.03$)

Oktay K. Fertility preservation in female patients, Human Reproduction Update, Vol.10, No.3 pp. 251±266, 2004
The ovarian dose is reduced by transposition to 5–10%. Behind the uterus.

Medial transposition

Medial transposition up to the pelvic side wall at least 3cm from the upper border of the radiation field.

Lateral transposition

89% spontaneous pregnancy with 75% occurring without repositioning. 11% conceived with IVF. However:

- Fallopian tube infarction.
- Chronic ovarian pain.
- Ovarian cyst formation.
- Migration of ovaries back to their original position.

American Society of Clinical Oncology (ASCO) Guideline 2013
### Ovarian Tissue Cryopreservation

<table>
<thead>
<tr>
<th>Embryo / oocyte cryopreservation</th>
<th>Ovarian tissue cryopreservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women willing to conceive</td>
<td>girls</td>
</tr>
<tr>
<td>Oncologist approval for stimulation</td>
<td>Contraindication for stimulation</td>
</tr>
</tbody>
</table>

**Advantages**
- Successful rate similar to fresh cycles
- Established technique

**Advantages**
- Numerous cycles (up to two years)
- Maintain hormonal function

**Restrictions**
- Limited IVF cycles
- Does not guarantee pregnancy
- Delay CT treatment

**Restrictions**
- Experimental
- Need surgery
- Harboring cancer cells
Eleven MZ twin pairs presented with discordant ovarian function, one sibling normal and the other having POF.
- All frozen cortical tissues was done by the slow freezing technique

All transplants (fresh & frozen) had a return of ovulatory menstrual cycles within 4 months.
The duration of function was 6 years for the fresh and less than 2 years for the slow frozen grafts. With the classical slow freeze technique, the in vitro viability testing showed only 41% of oocytes survived (Newton et al., 1996; Gook et al., 1999; Kagawa et al., 2009; Silber et al., 2010). However, with vitrification of the ovarian tissue there was no difference between fresh unfrozen controls and frozen tissue. (S.J. Silber, Molecular Human Reproduction, Vol.18, No.2, 2012)

It seems likely, therefore, that vitrified ovarian tissue would give better results after transplantation than tissue cryopreserved by slow freeze, but it is too early to state that with any certainty.

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The IVF Process

Approximately 9 weeks from start to pregnancy test

- Ovarian Stimulation
- Egg Retrieval
- Fertilization
- Embryo Transfer
- Oral Contraceptives
Ovarian Stimulation Protocol in Cancer Patients

*Stimulation can begin at any time except during periovulatory period + 2 days*

1. **GnRH Antagonist**
2. **Gonadotrophin Stimulation with Monitoring** (Regular vaginal ultrasounds and estradiol)
3. **Aromatase inhibitor (optional)**
4. **Aromatase inhibitor**
5. **GnRHa Trigger**
6. Retrieval day 11 – 16, 35 hours after trigger immediately followed by oocyte freezing
Ovaries Stimulated with Fertility Drugs
EGG EVALUATION
DAY 0

- **Cumulus Oocyte Complex**
- Starburst Appearance
- Mature Egg MII

- **No Polar Body Present**
- MI Stage Oocyte
- Intermediate Egg

- **Germinal Vesicle Present**
- GV Stage Oocyte
- Immature Egg
Rationale for Oocyte Freezing

- Fertility preservation
  - Prior to cancer treatment
  - Economic & Personal
- A family history of premature menopause
- Religious
- Ethical
  - Young girls requiring medical treatment
  - Women without a partner prior to medical treatment

Factors Affecting Cryopreservation of Oocytes...

- Oocyte Size
- Water Content of Oocyte
- Ice Crystal Formation
- Nuclear Stage of Development
- Cytoplasmic Characteristics
- Freeze time post retrieval (38 to 40 hrs)
- Membrane Permeability
- Cryoprotectant Used and Its Concentration
- Temperature (Slow Freeze and Quick Thaw)
- Oocyte Structural Damage
Cryopreservation – Effect of Freezing on the Cell

Freezing cells below their freeze point

1-Slow  2-Fast  3-Very Fast (Vitrification)
Cryopreservation - Oocytes

Why freeze unfertilized eggs?

1. Formation of donor “egg banks” analogous to “sperm banks” would allow women the same advantages that men now enjoy with regards to preserving their gametes.
2. Establish frozen egg donation, making eggs more available, reducing costs and increasing safety.
3. Allow egg cryostorage for women wishing to retain their reproductive choices despite disease, aging, social or work-related choices.
Glass formation during vitrification

Liquid nitrogen (LN2) -196°C

Pure DPBS

Ice crystal formation

20% EG/DMSO plus 0.4M sucrose

Glass formation

Slow Freezing  Vitrification

Before cooling
- Physiological solution
- Cryoprotectant solution
- Vitrification solution

After cooling
- Ice seeding
- Slow cooling
- Rapid cooling

In LN$_2$

Vitrification Carriers

Cryoloop

- Based upon method developed by Lane et al. *Fertil Steril* 72: 1073; 1999

- Oocytes are placed on a film of vitrification solution

- Dipped into LN$_2$

Primary Benefits of Vitrification

• No ice crystallization
• Higher cryoprotectant concentration/short exposure time
• Rapid vitrification/warming
• Small volume increases cooling rate (15,000 – 30,000 Degrees/minute)
• Minimizes osmotic injuries
• Reduces to freeze from 2 hrs to 10 min
• Very simple protocols without expensive equipment
# Summary of Randomized Trials Fresh vs. Frozen Oocytes

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Oocyte Donors (Cobo 2010)</th>
<th>Infertile Pts &lt;43 yo with &gt;6 oocytes (Rienzi 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitrification (# Pts)</td>
<td>295</td>
<td>40</td>
</tr>
<tr>
<td>Fresh (# Pts)</td>
<td>289</td>
<td>40</td>
</tr>
<tr>
<td># Oocytes Vitrified</td>
<td>3286</td>
<td>124</td>
</tr>
<tr>
<td># Oocytes Fresh</td>
<td>3185</td>
<td>120</td>
</tr>
<tr>
<td>Survival</td>
<td>92.5</td>
<td>96.8</td>
</tr>
<tr>
<td>Fertilization (%) Vitrified</td>
<td>74</td>
<td>79.2</td>
</tr>
<tr>
<td>Fertilization (%) Fresh</td>
<td>73</td>
<td>83.3</td>
</tr>
<tr>
<td>CPR/transfer Vitrified</td>
<td>55.4</td>
<td>38.5</td>
</tr>
<tr>
<td>CPR/transfer Fresh</td>
<td>55.6</td>
<td>43.5</td>
</tr>
<tr>
<td>CPR, Oocyte thawed (%)</td>
<td>4.5</td>
<td>12</td>
</tr>
</tbody>
</table>

Fertility Preservation in Patients Undergoing Gonadotoxic Therapy. ASRM Practice Committee 2013
Aneuploidy risk increases with age


Rate of occurrence (per thousand births)

- Trisomy 21
- Trisomy 18
- Trisomy 13
Embryo Aneuploidy Rates

• < 35 yo 70% of embryos are normal
• > 40 yo 70% of embryos are abnormal
The Odds that any one Embryo will Implant by Age

Figure 34
Percentages of Embryos Transferred That Resulted in Implantation Among Women Using Fresh Nondonor Eggs or Embryos, by Age Group, 2009
## Ovarian Reserve Measures in Cancer Survivors vs. Unexposed Participants Adjusted for Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exposed (n=71)</th>
<th>Unexposed (n=67)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/mL)</td>
<td>11.12</td>
<td>7.25</td>
<td>.001</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>24.21</td>
<td>29.41</td>
<td>.084</td>
</tr>
<tr>
<td>Inhibin B (pg/mL)</td>
<td>27.03</td>
<td>29.59</td>
<td>.582</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td><strong>0.81</strong></td>
<td><strong>2.85</strong></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ovarian volume (mL)</td>
<td>7.42</td>
<td>9.29</td>
<td>.056</td>
</tr>
<tr>
<td>Antral Follicle Count</td>
<td><strong>14.55</strong></td>
<td><strong>27.20</strong></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data from 2013 SART National ART Registry
174,962 cycles

<table>
<thead>
<tr>
<th></th>
<th>Banked Oocyte Donors</th>
<th>&lt; 35</th>
<th>35-37</th>
<th>38-40</th>
<th>41-42</th>
<th>&gt;42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth/ET</td>
<td>43.2</td>
<td>47.7</td>
<td>39.2</td>
<td>28.5</td>
<td>16.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Thawed cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth/ET</td>
<td>37.5</td>
<td>44.4</td>
<td>40.6</td>
<td>36.1</td>
<td>31.6</td>
<td>21.2</td>
</tr>
<tr>
<td>Average number of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>1.7</td>
<td>1.7</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

The goal of fertility preservation is to preserve fertility and not infertility!

SART.org
Timing of Diagnosis to Definitive Treatment

<table>
<thead>
<tr>
<th>Interval from surgery to chemo (weeks)</th>
<th>Overall survival hazards ratio Upper and lower CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 4</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1.021 (0.903 – 1.155)</td>
</tr>
<tr>
<td>5</td>
<td>0.890 (0.782 – 1.012)</td>
</tr>
<tr>
<td>6 – 13</td>
<td>1.002 (0.884 – 1.136)</td>
</tr>
<tr>
<td>P - value</td>
<td>0.14</td>
</tr>
</tbody>
</table>

No evidence for a survival benefit due to early initiation of adjuvant chemo within 2 – 3 months after surgery

Cold S. Br J Cancer 2005
### Timing of Diagnosis to Definitive Treatment

<table>
<thead>
<tr>
<th>Interval from chemo (weeks)</th>
<th>5 year relapse free survival</th>
<th>95% CI</th>
<th>5 year overall survival</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4</td>
<td>73.9</td>
<td>71 – 76.5</td>
<td>83.5</td>
<td>81.1 – 85.7</td>
</tr>
<tr>
<td>&gt; 4 – 8</td>
<td>78.7</td>
<td>76.3 – 80.9</td>
<td>85.1</td>
<td>82.9 – 86.9</td>
</tr>
<tr>
<td>&gt; 8 – 12</td>
<td>82.4</td>
<td>76.5 – 86.9</td>
<td>88.7</td>
<td>83.6 – 83.6</td>
</tr>
<tr>
<td>&gt; 12 – 24</td>
<td>69.3</td>
<td>59.7 – 77</td>
<td>78.4</td>
<td>69.5 - 85</td>
</tr>
<tr>
<td>P</td>
<td>0.004</td>
<td></td>
<td>0.013</td>
<td></td>
</tr>
</tbody>
</table>

Chemotherapy is equally effective up to 12 weeks after definitive surgery.

Overall survival is compromised by a delay of more than 12 weeks after definitive surgery.

Lohrisch C. J Clin Oncol 2006
Fertility Preservation: Special Considerations

• If hyperestrogenemia is a concern aromatase inhibitors can be used to minimize circulating estrogen levels
• BRCA mutation carriers should not have ovarian tissue cryopreservation
• Patients with hematologic malignancies may be too ill for oocyte retrieval and are at higher risk for operative complications
• Theoretical risk of reseeding cancer in patients with hematologic cancers and ovarian tissue transplantation
Fertility Preservation Program Requirements

• Single identifiable contact point
• Interdisciplinary team (Onc, REI, Urol, Repro Surgeons, Anesthesia)
• Fully equipped and readily available IVF lab
• Counselors (Mental health, Genetic, Financial, Legal)
• Interdisciplinary communication among providers is critical
• Medical considerations (Patients health, safety of future pregnancy)

Fertility Preservation Practice Guidelines, ASRM. Fertil Steril 2013
Fertility Preservation
Counseling

- Patients are overwhelmed with recent cancer diagnosis and impending treatment
- Have limited time and many other appointments
- May be sick
- Patients generally not infertile
  - Not familiar with fertility treatments and jargon
  - Multiple conversations and close/frequent contact with patients required
Respective Roles: REI & Oncology

- Discuss infertility as a potential risk of therapy
- Patients with an interest in fertility preservation should be promptly referred to an experienced program
- REI should see patient promptly and council patients on their current fertility potential and potential treatment options and success rates
- REI should be able to provide year round care
- REI should review what happens when patient returns
State of ART

- Controlled Ovarian Stimulation
- Follicular Aspiration
- Egg Freezing
- Ovarian Tissue Banking
- In vitro Maturation
- IVF Or ICSI
- Embryo Cleavage
- Embryo Transfer
- Embryo Cryopreservation PGD Screening
- Pregnancy Diagnosis

Adapted from Oehninger. J Gynecol Invest 12: 222, 2005
Questions