Fertility Preservation:
Who, What, Why, When and How
Glenn L. Schattman, MD
Associate Professor
The Center for Reproductive Medicine and Infertility
Weill Medical College of Cornell University

Disclosure Information
• Has no relationships to disclose
• Will be discussing or referring to unapproved therapeutic strategies and will clearly state that when being discussed

Educational Objectives
• Review guidelines regarding fertility preservation
• Review the effect of treatments on ovarian reserve
• Discuss current fertility preservation options
• Review success rates for:
  ~ Oocyte cryopreservation
  ~ Embryo cryopreservation
  ~ Ovarian tissue cryopreservation
• Novel protocols for random start stimulations
• The Alliance for Fertility Preservation/Fertility Scout

Improved Survival Rates
• 2/3 of children/adolescents survive malignancies
• Survival rates for acute lymphoblastic leukemias are approximately 75%
• Survival rates after lymphoma treatment are approximately 85-90%
• Survival rates for early stage invasive breast cancers >80%

Cancer Statistics
• If current trends continue, there will be ≥22 million new cases of cancer worldwide each year by 2030.1
  1 in 10 cancer cases occur in adults of reproductive age (25-49 yrs)2
  2.2 million new cases yearly in adults of reproductive age by 2030
  Almost 32.5 million people diagnosed with cancer within the past five years were alive at the end of 20122
• US projected survivorship for 2020 is 18.1 million patients3
  5-year survival rate for patients < 45 years is 81.1%4

Fertility Preservation is Important to Patients
• 76% of young cancer survivors (≤ 35 years at time of diagnosis) without children indicate they want to have children in the future1
• 31% of survivors with ≥ 1 child indicate they would like to have another child in the future1

Web-Based Survey: Young Breast Cancer Survivors

- 657 Respondents
- Mean age at diagnosis: 32.9 years
- 72% discussed fertility concerns with MD prior to starting treatment
- Only 51% felt their concerns were adequately addressed
- Future fertility affected treatment decision for 29% of respondents


Guidelines for Fertility Preservation

- ASCO 2006, 2013
  - All oncologists should be prepared to discuss infertility as a risk of treatment
  - Discussion should occur as soon as diagnosis is made and before treatment starts
  - Refer patients who express interest in FP, even ambivalent, to a reproductive specialist
  - Oocyte/embryo cryopreservation recommended for patients facing infertility due to chemotherapy
  - Should “no longer be considered experimental”

Lee SJ, et al. JCO 2006
Loren A, et al. ASCO guidelines JCO 2013
ASRM Practice Committee

Clinical Guidelines, Recommendations, Policy Statements & Opinions

- Association of Pediatric Hematology/Oncology Nurses (APHON) Evidence-Based Policy Statements & Opinions 2014
  - Appropriate fertility preservation options should be made available prior to initiation of cancer treatment
- American Society of Clinical Oncology 2006
  - Oncologists should address the possibility of infertility and be prepared to discuss FP options with reproductive endocrinologists as early as possible
  - Oncologists have a responsibility to inform parents and age-appropriate patients about the likelihood that cancer treatment will permanently affect their fertility.
- Heme, med onc, radiation onc

Ovarian tissue cryopreservation: a committee opinion American Society for Reproductive Medicine (ASRM) 2014
- Ovarian tissue cryopreservation may be the only option available to prepubertal girls, who still considered to be experimental
- ASRM Ethics Committee Opinion 2013
  - Decision should be made at a joint consultation between patient, physician and reproductive specialist
- International Society for Fertility Preservation 2012
  - Fertility issues should be addressed in all patients of reproductive age before cancer treatment

Fertility issues should be addressed to all patients of reproductive age before cancer treatment.


Are We Getting Better?

- 344 survey responses (32%)
  - Heme onc, med onc, radiation onc
  - 50% confident in their knowledge of FP options
  - Most received their information from scientific literature
  - <25% reported knowledge of new IVF protocols
  - Only 24% knew about mature oocyte cryopreservation
  - 18% aware of ovarian tissue cryopreservation
  - “Fellowships in oncology should include training on education and counselling for young cancer patients on fertility related to treatment”

Are we getting better? National Survey Data

- 44% familiar with ASCO guidelines
  - All patients should be offered a fertility consultation
  - 85% refer pubertal male patients for sperm banking
  - >50% of the time
  - 12% referred female pubertal patients >50% of the time
  - 45% not aware of ICSI
  - Not aware of time required for IVF cycle
  - No real change in practice patterns


Oncofertility Guideline Adherence - National Survey Data

- Only 47% of oncologists routinely refer patients to a reproductive endocrinologist

- notable reasons for not referring:
  - perception that patients were too ill to delay transplant (63%)
  - patients were already infertile from prior therapy (92%)
  - time constraints (41%)

Lee SJ, et al. JCO 2006
Loren A, et al. JCO 2013
### Alliance for Fertility Preservation

- 501c3 charitable organization
- Professionals in oncology, reproductive endocrinology, research, bioethics, research, reproductive endocrinology
- Leaders in sub-speciality of fertility preservation

Our Mission: To increase information, resources and access to fertility preservation for cancer patients and the healthcare professionals who treat them.

---

### ASCO: New Guidelines?

- 61 publications identified
  - None prompted a significant change from 2013 guidelines
- When proven fertility preservation methods are not feasible, in young women with breast cancer, GnRH may be offered
- Ovarian tissue cryo is advancing and may evolve to become SOC
  - Safety in leukemia patients needs further study

---

### Strategies to Preserve Fertility

**Before Cancer Therapy**
- Ovarian stimulation
- Oocyte retrieval
- Embryo freezing
- Oocyte freezing

**After Cancer Therapy**
- Ivf (cds)
- Embryo freezing
- Oocyte freezing
- Ovarian cortex freezing
- Whole ovary freezing

- Thawing (when needed)
- In vitro culture
- Natural conception or ivf & et

---

### Age & Fertility

---

### Ovarian Reserve

- GnRH
- FSH
- Estradiol
- Inhibin B
- AMH

---

### Chemotherapy: Cytotoxic agents according to gonadotoxicity

- Most severe
  - Cyclophosphamide
  - Chlorambucil
  - Melphalan
  - Busulfan
  - Nitrogen mustard
  - Procarbazine

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

---

---
Ovarian Effects of Chemotherapy: Burn Out theory

- Destruction of primordial follicles
  - Granulosa cell apoptosis
- Decrease in factors inhibiting PF recruitment (i.e. AMH, etc)
- Increased recruitment and depletion of PF pool
- Increase in developing:PF ratio

- Philouze-Kienle L et al ESHRE 2009
- Rosendahl M et al Fertil Steril 2010;94:156

Ovarian Failure Post Lymphoma Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hodgkin Lymphoma (HL)</th>
<th>Non Hodgkin Lymphoma (NHL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>BEACOPP</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>MOPP</td>
<td>20-50%</td>
<td>6-10%</td>
</tr>
<tr>
<td>CHOP</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Hyper-CVAD</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>HSCT</td>
<td>70-100%</td>
<td>70-100%</td>
</tr>
</tbody>
</table>

Breast cancer: chemotherapy-associated amenorrhea rate (A = doxorubicin; C = cyclophosphamide; E = epirubicin; F = 5-fluorouracil; M = methotrexate (modified according to [39])

- Insufficient data: taxanes, monoclonal antibodies, avastin® (bevacizumab), lapatinib, herceptin® (trastuzumab), and gemzar® (gemcitabine)

Ovarian Reserve after Chemo

- FSH declined at 9M, but still remained elevated (~24IU/L)
- Alkylating agents associated with lowest AMH values post Rx
- Pre-Rx AMH predicted post-Rx values

- Rosendahl M Fertil Steril 2010;94:156

Gonadotoxic Therapy Accelerates Oocyte Loss and Potentially Compromises Quality

- Two potential scenarios with gonadotoxic therapy
  - Near complete primordial follicle depletion, resulting in acute ovarian failure
    - Fertility preservation must be undertaken prior to treatment
  - Moderate primordial follicle depletion resulting in reduced fertility/premature menopause
    - Fertility preservation may be warranted before treatment; fertility is preserved for some time after treatment


Figure 1. Probability of menopause during the first year after diagnosis


Risk of gonadal damage related to age of patient, type of chemotherapeutic agent and total dose.
Female Gonadotoxicity

Diminished Reserve with Low Gonadotoxic Treatments

- patients stratified by gonadotoxicity of therapy and time elapsed - even low gonadotoxic therapies significantly impact reserve years after treatment
- anti-Müllerian hormone and AFC more sensitive markers of ovarian reserve
- FSH, unless markedly elevated, not sensitive

<table>
<thead>
<tr>
<th>Hormonal parameters and antral follicle count in relation to gonadotoxicity of the therapeutic regimen and the time since therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Age at chemo (yrs)</td>
</tr>
<tr>
<td>Age at stimulation (yrs)</td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Lymphomas</td>
</tr>
<tr>
<td>Leukemias</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
</tbody>
</table>

Chemotherapy

- Alkylating agents | 16 | N/A |
- Nonalkylating agents | 6 | N/A |

T = p < 0.0001; x± SEM Azim et al. ASRM 2006

Post-chemotherapy Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Post-chemotherapy Group (n=22)</th>
<th>Pre-chemotherapy Group (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at chemo (yrs)</td>
<td>28.4 ± 1.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Age at stimulation (yrs)</td>
<td>35.7 ± 9.9</td>
<td>36.5 ± 0.8</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Leukemias</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Alkylating agents</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Nonalkylating agents</td>
<td>6</td>
</tr>
</tbody>
</table>

**p < 0.0001; x± SEM Azim et al. ASRM 2006**

Post-chemotherapy Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Post-chemotherapy Group (38 cycles)</th>
<th>Pre-chemotherapy Group (38 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2 FSH (mIU/ml)</td>
<td>8.3 ± 0.7</td>
<td>8.1 ± 0.7</td>
</tr>
<tr>
<td>Day 2 LH (mIU/ml)</td>
<td>5.1 ± 10.6</td>
<td>4.1 ± 4.7</td>
</tr>
<tr>
<td>Day 2 AMH (ng/ml)</td>
<td>0.27 ± 0.88</td>
<td>0.84 ± 0.3</td>
</tr>
<tr>
<td>Total FSH dose (U)</td>
<td>239 ± 237</td>
<td>1659 ± 108</td>
</tr>
<tr>
<td>E2 (pg/ml) on hCG day</td>
<td>546 ± 98</td>
<td>735 ± 106</td>
</tr>
</tbody>
</table>

Stimulation Protocol

- Aromatase Inhibitor-FSH 21
- FSH/GnRH Antagonist 8
- Tamoxifen-FSH 2
- GnRH Agonist FSH 1
- Natural Cycle 4

**p < 0.0001; x± SEM Azim et al. ASRM 2006**

Embryo Biopsy
**Pediatric Grand Rounds - UT Health SA 09/14/2018**

---

**Random Start Ovarian Stimulation**

- FSH
- HMG
- GnRH Ant.
- or hCG
- GnRH Ant.
- or HCG
- Ret/Cryo

**Gonadotropin Dependent (Exponential) Growth Phase**

- Letrozole - sliding scale
  - 2.5 - 7.5 mg/d

**Current Trial: Titrated Letrozole Protocol**

- Ovidrel
- Random start
- E2
- Antagonist
- Serial ultrasounds

**Relapse Free Survival: Ovarian Stimulation and Control Groups**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Letrozole group (L)</th>
<th>Control group (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>79</td>
<td>136</td>
</tr>
<tr>
<td>12</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>24</td>
<td>37</td>
<td>56</td>
</tr>
<tr>
<td>36</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>48</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>

**Letrozole Protocol vs. Elective Oocyte Cryopreservation Lateal Starts**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Letrozole &amp; Endometrial (n=66)</th>
<th>Elective (n=65)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34 (34.38)</td>
<td>37 (34.38)</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.6 (5.99)</td>
<td>21.1 (5.53)</td>
<td>0.81</td>
</tr>
<tr>
<td>Total stimulation days</td>
<td>11.8 (±2.41)</td>
<td>10.4 (±3.69)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total antagonist days</td>
<td>5.26 (±2.26)</td>
<td>4.09 (±2.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total gonadotropins administered</td>
<td>354.4 (±166.9)</td>
<td>360.8 (±184.6)</td>
<td>0.85</td>
</tr>
<tr>
<td>E2 on day of trigger (pg/mL)</td>
<td>445.4 (±235.2)</td>
<td>180.1 (±160.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E2 after day of trigger (pg/mL)</td>
<td>687.4 (±472.3)</td>
<td>243.8 (±952.4)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Peak endometrial stripe (mm)</td>
<td>10.9 (±2.46)</td>
<td>10.1 (±2.52)</td>
<td>0.11</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td>12.6 (±6.23)</td>
<td>10.9 (±3.86)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mature oocytes (%)</td>
<td>86.9%</td>
<td>72.8%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Pereira N et al 2015**
Ovarian Suppression for Chemotherapy Induced POF
Meta-analysis (2014)

- highly significant reduction in the risk of POF when patients receive GnRHa
  (OR = 0.43; CI: 0.22–0.84; p = 0.013)
- significant heterogeneity across included studies (I² = 55.8%; p = 0.012)

Ovarian Cortical Freezing

- 41 women, 53 transplantation procedures
- 32 desired pregnancy, 42 transplant procedures
- Mean age at time of harvest- 29.8
- One ovary removed
  - Risk of ovarian failure >50%
  - Age < 35
  - >50% 5 year survival

Jensen AK, et al Human Reprod 2015;30:2838

Ovarian Tissue Transplantation

- 41 women, 53 transplantation procedures
- 32 desired pregnancy, 42 transplant procedures
- Mean age at time of harvest- 29.8
- One ovary removed
  - Risk of ovarian failure >50%
  - Age < 35
  - >50% 5 year survival

Jensen AK, et al Human Reprod 2015;30:2838

Demographics

- Mean age at transplant- 32.9
- ~1/3 breast cancer
- ~45% of tissue transplanted 1st procedure (9.5 pieces)
  - More tissue transplanted due to low AMH
- Orthotopic transplant - 15
- Orthotopic and heterotopic – 14
- Mixed sites

Jensen AK, et al Human Reprod 2015;30:2838

Outcomes

- 24 clinical pregnancies
- 14 children to 10 women
- 8 pregnancies- Natural conceptions
- 6 pregnancies – IVF
- PR/patient- 31%
Risk of Ovarian Metastasis

- ASCO and ASRM considers ovarian tissue cryopreservation/transplantation investigational1,2

<table>
<thead>
<tr>
<th>Low risk (&lt;1%)</th>
<th>Intermediate</th>
<th>High risk (&gt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilms tumor</td>
<td>Stage I-II breast CA Lobular</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Hodgkin disease</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Squamous cancer of cervix</td>
<td>Cervical adenocarcinoma</td>
</tr>
<tr>
<td>Ewings sarcoma</td>
<td>Pelvic sarcoma</td>
<td>Stage III-IV breast cancer</td>
</tr>
<tr>
<td>Non-genital rhabdomyosarcoma</td>
<td></td>
<td>Genital rhabdomyosarcoma</td>
</tr>
</tbody>
</table>


Future Options

- Pregnancy Outcomes in Cancer Survivors
  - No increased risks of congenital malformations, genetic diseases, malignant neoplasms in children born to cancer survivors remote from therapy1-3
  - Safe interval between chemo and oocyte/embryo cryopreservation unknown:
    - Growing eggs and sperm may be damaged by chemo and radiation, but appear to repair within six months to two years4
    - Human pregnancy outcomes for more recent exposures unknown, animal data suggest increased risk of SAB/birth defects5
  - Guidelines for attempting pregnancy
    - Optimal time unknown
    - Two year wait time after treatment recommended6


ASCO Guidelines: Summary

- People with cancer are interested in discussing fertility preservation
- Oncologic HCP should be prepared to discuss infertility or refer
- HCP’s should refer patients as early as possible
- Encourage patients to participate in registries and studies
- Refer patients to psychosocial providers if distressed about infertility

- Embryo and oocyte cryopreservation are proven methods
- Flexible stimulation approaches reduce delay to treatment
- Ovarian transposition for pelvic RT
- Fertility sparing surgeries when applicable (Trachelectomy)
- "Ovarian suppression may be offered when proven methods are not feasible- should NOT be used in place of proven methods
- "Ovarian tissue cryo still experimental- emerging data may prompt reconsideration of this designation
- Need to confirm if safe for leukemia patients