OVARIAN FUNCTION AFTER CHILDHOOD CANCER

Practicing through Controversy

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Leslie Coker Appiah MD

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Objectives

• Review use and limitations of risk stratification.

• Understand fertility preservation options for adolescents and young adults.

• Navigate controversies in ovarian reserve testing.
US Incidence and Survival

- 1.7 million new cases in 2017
- 10,270 between ages 0 and 14
- 70,000 between ages 15 and 39
- 500,000 childhood cancer survivors estimated by 2020
Clinical Ascertainment of Health Outcomes Among Adults Treated for Childhood Cancer
Melissa M Hudson et.al., JAMA. 2013;309(22):2371-2381

<table>
<thead>
<tr>
<th>Potential Late Effect</th>
<th>Screening test</th>
<th>Exposure Status</th>
<th>Number at risk</th>
<th>Diagnosis before SJLIFE</th>
<th>Diagnosis related to SJLIFE</th>
<th>Diagnosis after SJLIFE</th>
<th>Overall Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>(%)</td>
<td>95% CI</td>
<td>N</td>
</tr>
<tr>
<td>Primary ovarian failure</td>
<td>Menstrual history, FSH, Estradiol</td>
<td>Alkylating agents</td>
<td>Radiation to female reproductive system</td>
<td>553</td>
<td>44</td>
<td>(8.0)</td>
<td>20</td>
</tr>
<tr>
<td>Male germ cell dysfunction</td>
<td>Semen sample analysis</td>
<td>Alkylating agents</td>
<td>Radiation to male reproductive system</td>
<td>328</td>
<td>9</td>
<td>(2.7)</td>
<td>209</td>
</tr>
<tr>
<td>Leydig cell failure</td>
<td>Morning testosterone, LH</td>
<td>Alkylating agents</td>
<td>Radiation to male reproductive system</td>
<td>574</td>
<td>23</td>
<td>(4.4)</td>
<td>37</td>
</tr>
</tbody>
</table>

- 1,713 at risk survivors median age 32 yrs (18-60 yrs)
- Prevalence of primary ovarian failure 12%
"Fertility is a long-term issue influenced by short-term decisions"

- Survivors have concerns about potential infertility.
- Fertility is an important quality of life issue.
- Young adult female cancer survivors regret not pursuing fertility preservation.
- Many report that the inability to have biological children is one of the most distressing aspects of survivorship.

Taylor et al. JPAG 2016;29(6):585-98
Late Effects

Oktem, et al. The Oncologist 2018; 23:214-224
RADIATION
- Pelvic
- Spinal
- Abdominal
- Total-body irradiation

Cranial irradiation
Total body irradiation

Hypothalamus

Adenohypophysis

Neurohypophysis

Damage to HPO Axis
- Infertility
- Miscarriage
- Abnormal timing of puberty
- Hypogonadotropic hypogonadism

Ovarian Damage
- Menstrual irregularity
- Acute ovarian failure
- Diminished ovarian reserve
- Infertility
- Miscarriage
- Premature menopause
- Delayed puberty

Uterine Damage
- Infertility
- Miscarriage
- Preterm birth
- Low-birth-weight infant
- Abnormal placentation
- Fetal growth restriction
- Fetal malposition
- Stillbirth
- Neonatal death
2013 ASCO Recommendations
Endorsed by ASRM, AAP, ACOG, APHON

- Applies to all patients of childbearing age, including adolescents.
- Discussion of fertility risk at the earliest possibility.
- Prompt referral to a qualified specialist if patient interested.
- Promote clinical trials to advance state of knowledge.

Lee et. al. J Clin Oncol. 2006; 24:2917-2931
Loren et. al. J Clin Oncol. 2013
How do we best quantify risk?
## Alkylating Agent Dose (AAD)

### Table 4. Relative Risk of Pregnancy Among Female Childhood Cancer Survivors in Two Separate Multivariate Models

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Individual Chemotherapy Agent</th>
<th>Summed AAD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Summed AAD score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.90</td>
<td>0.69 to 1.18</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
<td>0.72 to 1.16</td>
</tr>
<tr>
<td>3</td>
<td>0.72</td>
<td>0.58 to 0.90</td>
</tr>
<tr>
<td>4</td>
<td>0.65</td>
<td>0.45 to 0.96</td>
</tr>
<tr>
<td>5</td>
<td>0.82</td>
<td>0.55 to 1.24</td>
</tr>
<tr>
<td>6-11</td>
<td>0.76</td>
<td>0.49 to 1.19</td>
</tr>
</tbody>
</table>

Green. J Clin Oncol. 27:2677-2685
### Estimating Risk - CED

**TABLE IV. Rate Ratios for Non-Surgical Premature Menopause: Multiple Poisson Regression Model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CED</th>
<th>AAD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.14</td>
<td>1.09–1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum ovarian dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–99 cGy</td>
<td>2.96</td>
<td>0.92–9.50</td>
<td>0.069</td>
</tr>
<tr>
<td>≥100 cGy</td>
<td>11.68</td>
<td>3.59–38.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13.86</td>
<td>4.04–47.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–99 cGy</td>
<td>10.04</td>
<td>3.40–29.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥100 cGy</td>
<td>10.76</td>
<td>3.32–34.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CED (mg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0–&lt;4,000</td>
<td>0.56</td>
<td>0.07–4.27</td>
<td>0.578</td>
</tr>
<tr>
<td>≥4,000–&lt;8,000</td>
<td>2.74</td>
<td>1.13–6.61</td>
<td>0.025</td>
</tr>
<tr>
<td>&gt;8,000</td>
<td>4.19</td>
<td>2.18–8.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AAD tertile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CED, Cyclophosphamide Equivalent Dose; AAD, Alkylating Agent Dose score; RR, rate ratio; CI, confidence interval; values shown in bold are statistically significant.
Cyclophosphamide Equivalent Dose Calculation. The CED is calculated using the following equation: CED \( (mg/m^2) = 1.0 \) (cumulative cyclophosphamide dose \( (mg/m^2) \)) + 0.244 (cumulative ifosfamide dose \( (mg/m^2) \)) + 0.857 (cumulative procarbazine dose \( (mg/m^2) \)) + 14.286 (cumulative chlorambucil dose \( (mg/m^2) \)) + 15.0 (cumulative BCNU dose \( (mg/m^2) \)) + 16.0 (cumulative CCNU dose \( (mg/m^2) \)) + 40 (cumulative melphalan dose \( (mg/m^2) \)) + 50 (cumulative Thio-TEPA dose \( (mg/m^2) \)) + 100 (cumulative nitrogen mustard dose \( (mg/m^2) \)) + 8.823 (cumulative busulfan dose \( (mg/m^2) \)).

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Alkylation agent</td>
<td>Cumulative dose ( (mg/m^2) )</td>
<td>101000</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ifosfamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Procarbazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Chlorambucil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>BCNU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CCNU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Melphalan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Thiopeta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Nitrogen Mustard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Busulfan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Cyclophosphamide</td>
<td>Equivalent Dose Score =</td>
<td>24644 mg/m2</td>
<td></td>
</tr>
</tbody>
</table>

http://oncofertility.northwestern.edu/sites/oncofertility.northwestern.edu/files/ced_calculator.xlsx
High Gonadotoxic Risk:
>80% risk of loss of reproductive potential

- Alkylating-intensive chemotherapy
  - any treatment regimen containing procarbazine
  - busulfan cumulative dose >600 mg/m2
  - cyclophosphamide equivalent dose (CED) ≥ 7,500 mg/m2
  - alkylating chemotherapy conditioning prior to SCT
- Whole abdomen/pelvic irradiation to ovaries
  - ≥15 Gy pre-pubertal, >10 Gy post-pubertal, >6 Gy adult
- Whole abdomen/pelvic irradiation to uterus ≥30 Gy
- Total body irradiation and cranial radiation ≥30 Gy

Metzger ML. J Clin Oncol; 31(9), 2013
Hematopoietic cell transplantation (HCT)

- Stem cell transplant includes high dose alkylating chemotherapy agents.
- Total Body Irradiation (TBI) is often used concomitantly.
- For pre-pubertal females, incomplete pubertal development or pubertal failure in approximately 57% of females following HCT.
- In post-pubertal females, ovarian failure observed in 65-84% of pediatric patients.
- In young adult females, ovarian failure observed in > 90% of patients.
<table>
<thead>
<tr>
<th>Subfertility/Infertility Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk &gt; 80%</strong></td>
</tr>
<tr>
<td>Conditioning for BMT</td>
</tr>
<tr>
<td>Hodgkin’s: w/ alkylating agents</td>
</tr>
<tr>
<td>Soft-tissue sarcoma: metastatic</td>
</tr>
<tr>
<td>Ewing’s sarcoma: metastatic</td>
</tr>
<tr>
<td><strong>Medium Risk 30 – 70 %</strong></td>
</tr>
<tr>
<td>AML</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Ewing’s sarcoma: non-metastatic</td>
</tr>
<tr>
<td>Soft-tissue sarcoma: stage II/III</td>
</tr>
<tr>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Hodgkin’s: alternating alkylator tx</td>
</tr>
<tr>
<td><strong>Low Risk &lt; 20%</strong></td>
</tr>
<tr>
<td>ALL</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
</tr>
<tr>
<td>Soft-tissue sarcoma: stage I</td>
</tr>
<tr>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>Germ-cell tumors (fertility sparing)</td>
</tr>
</tbody>
</table>
Gonadotoxicity of Newer Agents

- Paclitaxel, docetaxel (taxanes used in AC protocols)
- Oxaliplatin
- Irinotecan
- Bevacizumab
- Cetuximab
- Trastuzumab
- Erlotinib
- Imatinib
Diane, I want to find a more descriptive slide on these newer agents regarding what we know about toxicity.

Appiah, Leslie A, 3/18/2018
Practice Pearl

• The risk of acute ovarian failure after cancer treatments is 12%.

• Fertility is an important quality of life indicator and should be addressed prior to cancer treatments.

• The cyclophosphamide equivalent dose scoring system is the best tool for comparing alkylator therapies.

• Highest risk and low risk categories for ovarian failure are more well-defined than moderate risk categories.
Which Fertility Preservation Options are Available?
<table>
<thead>
<tr>
<th>Fertility Preservation Methods</th>
<th>Success rates</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mature oocyte cryopreservation</td>
<td>35 - 50%</td>
<td>No partner needed; 10 – 14 days stimulation; surgical procedure; costs; no ovarian function preserved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulation may occur at any phase of the cycle</td>
</tr>
<tr>
<td>Embryo cryopreservation</td>
<td>40%</td>
<td>Partner or sperm donor needed; 10 – 14 days stimulation; surgical procedure; costs; no preservation of ovarian function; embryo ownership concerns</td>
</tr>
<tr>
<td>Ovarian transposition</td>
<td>88-90%</td>
<td>Underutilized</td>
</tr>
<tr>
<td>Ovarian shielding</td>
<td>75-80%</td>
<td>Scatter effect; consider concomitant chemotherapy</td>
</tr>
<tr>
<td>Fertility Preservation Methods</td>
<td>Investigational Methods</td>
<td>Considerations</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Immature oocyte cryopreservation</td>
<td>No partner needed; no stimulation; surgical procedure; costs; no ovarian function preserved</td>
<td></td>
</tr>
<tr>
<td>Ovarian tissue freezing</td>
<td>Surgical procedure; costs; transplantation not suitable with high gonadal involvement; preservation of gonadal function</td>
<td></td>
</tr>
<tr>
<td>GnRHa ovarian suppression</td>
<td>Conflicting data; recent data in breast cancer patients more reassuring</td>
<td></td>
</tr>
</tbody>
</table>
Indications for Ovarian Tissue Cryopreservation

- Edinburgh criteria for malignant disorders (modified):
  - High risk of gonadal failure (> 50%) after cancer treatment
  - Absence of previous high gonadotoxic chemotherapy
  - Absence of surgical contraindication
  - Negative serologies

- Nonmalignant disorders treated with immunosuppression or SCT

- Individuals with gender and sex diversity

- Genetic predisposition to accelerated follicular loss

86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children.

- 95 total children worldwide
- Age range from adolescence to mid 30’s
- Spontaneous and assisted conception
- 32% delivery rate - suggest OTC no longer be experimental
- Transplanted tissue shown to be viable for up to 10 years

<table>
<thead>
<tr>
<th>Pediatric and Teen Ovarian Tissue Removed for Cryopreservation Contains Follicles Irrespective of Age, Disease Diagnosis, Treatment History, and Specimen Processing Methods.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duncan FE¹, Pavone ME¹, Gunn AH¹, Badawy S², Gracia C³, Ginsberg JP⁴, Lockar B⁴, Gosiengfiao Y⁵, Woodruff TK¹</td>
</tr>
</tbody>
</table>

- 24 patients s/p ovarian tissue cryopreservation
- No previous treatment and low and high risk treatment
- Oncologic and non-oncologic diagnoses
- 10/24 underwent removal of cortical strips vs oophorectomy
- Primordial and/or early-activated primary follicles in all samples
- Small pre-antral follicles identified in patients who had not received oncologic treatments

Duncan et al. J Adolesc Young Adult Oncol. 2015 Dec 1; 4(4): 174–183
Heterotopic Transplantation

First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy.

Stern CJ, Cook D, Hale LG, Agresta F, Oldham J, Rozen G, Jobling T

- 21 yo s/p bilateral oophorectomy for granulosa cell tumor
- OTC prior to the second surgery with histological analysis
- Grafts to pelvic sidewalls and anterior abdominal wall under peritoneum 7 years later without pregnancy after transfer
- Second graft to anterior abdominal wall 2 years later
- Stimulation, retrieval, ICSI, embryo transfer and twin delivery

In Vitro Maturation

First pregnancy and live birth resulting from cryopreserved embryos obtained from in vitro matured oocytes after oophorectomy in an ovarian cancer patient.

Prasath EB¹, Chan ML, Wong WH, Lim CJ, Tharmalingam MD, Hendricks M, Loh SF, Chia YN.

- 21 yo s/p interval bilateral oophorectomy for ovarian serous carcinomas
- OTC at second surgery followed by aspiration of all visible follicles
- ICSI followed by 2 embryo transfer and delivery of healthy infant
- 20-35% live birth rate after IVM of growing follicles

- Pre-pubertal ovaries
  - Presence of abnormal non-growing follicles with slow in vitro growth and maturation
  - Ability to grow and acquire maturation complex with transplantation

Prasath et al. 2014 Hum Reprod
In Vitro Activation

Activation of dormant follicles: a new treatment for premature ovarian failure?

Kazuhiro Kawamura, Nanami Kawamura, and Aaron J.W. Hsueh

- Women diagnosed with POI
- OTC followed by fragmentation of ovarian strips into cubes
- PI3K signaling stimulation of ovarian cubes
- Auto-transplantation followed by ovarian stimulation, retrieval and IVF
- Embryo transfer has led to 4 births to date

• Transabdominal monitoring with transvaginal retrieval.

• Higher gonadotropin doses may be required in early pubertal patients.

• Efficiency in adolescents needs to be confirmed\textsuperscript{Cil and Oktay}.
  
  • 28.1% probability of live-birth at age 25 for 2 oocytes thawed after vitrification
  
  • Probability increased to 31.3% with 6 oocytes

\textsuperscript{Cil and Oktay et al. Fertil Steril 2013;100:492-9}
GnRHa and Ovarian Protection:
Premature Ovarian Failure – Breast Cancer

OR for premature ovarian failure: LHRHa versus chemotherapy alone

Lambertini et al. Annals of Oncology; 2015
GnRHa and Ovarian Protection: Pregnancy – Breast cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Odds ratio (95% CI)</th>
<th>Events, treated</th>
<th>Events, controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamberti (2014)</td>
<td>2.48 (0.64, 9.53)</td>
<td>8/148</td>
<td>3/133</td>
</tr>
<tr>
<td>Gerber (2011)</td>
<td>1.00 (0.06, 16.76)</td>
<td>1/30</td>
<td>1/30</td>
</tr>
<tr>
<td>Munster (2012)</td>
<td>0.15 (0.01, 3.24)</td>
<td>0/26</td>
<td>2/21</td>
</tr>
<tr>
<td>Elgindy 1 (2013)</td>
<td>1.00 (0.06, 16.93)</td>
<td>1/25</td>
<td>1/25</td>
</tr>
<tr>
<td>Elgindy 2 (2013)</td>
<td>3.12 (0.12, 80.39)</td>
<td>1/25</td>
<td>0/25</td>
</tr>
<tr>
<td>Moore (2015)</td>
<td>2.23 (1.04, 4.77)</td>
<td>22/105</td>
<td>12/113</td>
</tr>
<tr>
<td>Fixed effect ($I^2 = 0.0%$, $P_{heterogeneity} = 0.629$)</td>
<td>1.83 (1.02, 3.28)</td>
<td>33/359</td>
<td>19/347</td>
</tr>
<tr>
<td>Random effect</td>
<td>1.93 (1.05, 3.53)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR for pregnancy: LHRHa versus chemotherapy alone
GnRHa and Ovarian Protection

Hickman, Falcone et al. J Reprod Gen. 2017
Practice Pearl

- Ovarian stimulation in older adolescents may be offered where expertise is available.

- Ovarian tissue cryopreservation combined with aspiration and *in vitro maturation* of follicles when present should be considered.

- *In vitro* activation is an emerging investigational option for patients with POI due to any cause.

- GnRHa has been shown to have a protective effect against the development of POI primarily in breast cancer. Studies in other populations are less definitive and not yet standard of care.
How do we Optimize Conception?
Fertility in Childhood Cancer Survivor Cohorts

- Childhood cancer survivors with spontaneous menses more than 5 years after diagnosis had a 13-fold higher risk of premature menopause.

- Survivors had a significantly decreased pregnancy rate with overall 38% (30% for male and 46% of female) reporting having a pregnancy compared to 62% in controls.

- 13% of survivors required more than 12 months of attempts to achieve pregnancy compared to 8.3% of sibling controls.

Sklar et al. CCSS J Natl Cancer Inst. 2006;98:890-6
Chow et al. The Lancet Oncol 2016;17:567-76
• Growth span from primordial to pre-ovulatory follicle: 6 months
• Risk of mutagenesis maximal during this maturation phase
• Recommendation: delay conception for 6 months after completion of treatment
Antral Follicle Count

- The mean of the number of follicles measuring 2-10 mm in both ovaries
- AFC < 5 considered diminished ovarian reserve
- Not optimal in adolescents who cannot tolerate a transvaginal U/S
Anti-Mullerian Hormone

Serum AMH (picomoles per liter) in 926 healthy infants, girls, adolescents, and adult women.

# Ovarian Reserve Testing

<table>
<thead>
<tr>
<th>AMH ng/ml</th>
<th>Clinical Situation</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low (&lt;0.5)</td>
<td>Impending onset of premature menopause</td>
<td>Predicts low ovarian response to stimulation</td>
</tr>
<tr>
<td>Low (0.5 - 1.0)</td>
<td>Limited egg supply</td>
<td>Shortened reproductive window</td>
</tr>
<tr>
<td></td>
<td>Diminished reserve</td>
<td></td>
</tr>
<tr>
<td>Mid-range (&gt; 1-3.5)</td>
<td>Normal testing</td>
<td>Consider preservation if high risk treatment</td>
</tr>
<tr>
<td>Elevated (&gt;3.5)</td>
<td>Polycystic ovaries</td>
<td>Risk of OHSS</td>
</tr>
<tr>
<td>Age</td>
<td>5th %ile</td>
<td>50th %ile</td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>10-12</td>
<td>0.15</td>
<td>1.62</td>
</tr>
<tr>
<td>13-15</td>
<td>0.44</td>
<td>2.11</td>
</tr>
<tr>
<td>16-18</td>
<td>1.29</td>
<td>0.61</td>
</tr>
<tr>
<td>19-21</td>
<td>0.71</td>
<td>3.72</td>
</tr>
</tbody>
</table>
AMH

- Participants with pretreatment AMH level > 2 ng/ml recovered their AMH level at a rate of 11.9% per month after chemotherapy\(^{Dillon et al.}\).

- Participants with pretreatment AMH < 2 ng/ml recovered at a rate of 2.6% per month.

- AMH shown to decrease before the onset of irregular cycles and before the rise of FSH levels\(^{Grynnerup et al.}\).

Limitations of AMH

- Fluctuations can be observed over the course of year(s)
- Cannot compare between assays
- Does not reliably predict pregnancy rates
Monitoring Ovarian Reserve

Who to refer to Gynecology and/or Endocrinology:

- All post-pubertal patients treated with a potential gonadotoxic regimen without any signs or symptoms of POI,
- Who desire assessment about potential for future fertility
- Patients with POI who require HRT for pubertal induction

What to order:

- Baseline FSH, LH and Estradiol at age 13
- FSH, LH and Estradiol with abnormal menses and signs of estrogen deficiency

COG LTFU 2013; Van Dorp et al., 2016
Monitoring Ovarian Reserve

How to Use AMH:
• AMH not yet considered standard of care
  • Reasonable to measure in survivors ≥ 25

Consider:
• Baseline AMH to assess ovarian reserve prior to cancer treatment
• Serial AMH yearly to follow rate of decline
• Refer to REI for fertility treatment when levels fall below norms for age or if patient desires preservation

Guzy and Demeestere. Minerva Ginecologica 2017 Feb;69(1):57-67
Van Dorp et al., 2016
Practice Pearl

• Currently no guidelines to recommend fertility preservation based on pre-treatment FSH, AMH or AFC.

• Currently no standard of care regarding post-treatment monitoring in the absence of clinical signs of ovarian insufficiency.

• Consider: Yearly monitoring if AMH within reference range for age and FSH < 10.

• Consider: Referral to REI if AMH less than reference range for age or FSH > 10.
Future Directions

• Identify targeted agents that minimize gonadal injury.

• Improve risk stratification to better identify candidates for fertility preservation pre-treatment.

• Streamline counseling and implementation of fertility preservation therapies.

• Collaborate with regional REI centers and basic science researchers to provide multiple approaches to fertility preservation.
Case 1

- 18 yo diagnosed with h/o high-grade soft tissue sarcoma at age 13
- 14 cycles of vinc/doxo/cyclophos alternating with ifos/etoposide after resection
- Recurrence treated with salvage cyclophosphamide and topotecan
- Received Lupron for menstrual suppression with return of menses post treatment
- Prior to salvage therapy: AMH 2.62 ng/ml FSH 3.1 mIU/ml
- 3 years post treatment: AMH 0.35 ng/ml FSH 6.21 mIU/ml
- 4 years post treatment: AMH 0.04 ng/ml
- Referred to REI for oocyte cryopreservation
Case 2

- 20 yo G0 with Hodgkin lymphoma s/p ABV treatment without Dacarbazine
- Surveillance scan showed recurrence 3 months post-treatment
- Plan for chemotherapy with ICE or R-ICE followed by stem cell transplant
- Nexplanon placed prior to treatment
- Chemotherapy induced amenorrhea with return of menses 2-3 weeks post tx
- Desires future fertility
- AMH 0.93 ng/ml, FSH 1.69 mIU/ml and E2 182 pg/ml
- Underwent OTC with 8 vials frozen, no immature follicles identified for vitrification
What Cancer Cannot Do

Cancer is so limited...
It cannot corrode Faith,
It cannot shatter Hope,
It cannot cripple Love,
It cannot destroy Peace,
It cannot kill Friendship,
It cannot suppress Memories,
It cannot silence Courage,
It cannot conquer the spirit,
It cannot invade the Soul,
It cannot steal Eternal Life.