ONCOFERTILITY BEST PRACTICES: OPTIMIZING REPRODUCTIVE OUTCOMES IN CANCER

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Objectives

• Explain the effects of cancer treatments on fertility and limits of risk stratification.

• Discuss standard and novel fertility preservation therapies for patients with cancer.

• Identify and manage reproductive late effects in survivorship.

The impact of cancer on subsequent chance of pregnancy: a population-based analysis.

• Young adult survivors ages 18 – 39 years 38% less likely to conceive compared to controls

• Chance of achieving pregnancy greater than 5 years after diagnosis HR 0.57
How is Risk Quantified?

Estimating Risk

Subfertility/Infertility Risk

<table>
<thead>
<tr>
<th>High Risk &gt; 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning for BMT</td>
</tr>
<tr>
<td>Hodgkin: w/ alkylators</td>
</tr>
<tr>
<td>Soft-tissue sarcoma: metastatic</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
</tr>
<tr>
<td>Localized pelvic radiation</td>
</tr>
<tr>
<td>Total body irradiation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medium Risk 30 – 70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Soft-tissue sarcoma: stage II/III</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Hodgkin: alternating alkylators</td>
</tr>
<tr>
<td>Craniopinal radiation &gt; 24Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Risk = 20%</th>
</tr>
</thead>
<tbody>
<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

• Oxaliplatin
• Irinotecan
• Bevacizumab – 30% rate of primary ovarian insufficiency
• Cetuximab
• Trastuzumab
• Erlotinib
• Imatinib

Loren et al. J Clin Oncol 2013;31:2500-2510

Expert Consensus Position Statements

• American Society of Clinical Oncology (ASCO) 2006, 2013
• American Society for Reproductive Medicine (ASRM) 2010
• Association of Pediatric Hematology/Oncology Nurses (APHON)

- “Physicians should inform cancer patients about options for fertility preservation and future reproduction prior to treatment…”
- “…regardless of the patient’s age, gender, culture, socioeconomic status, or healthcare team bias…”
- “…and continue throughout treatment and survivorship in a manner appropriate to the patient’s developmental stage at that time.”

Statements supported by American College of Obstetricians and Gynecologists (ACOG) and American Academy of Pediatrics (AAP).

Gap

Less than 30% receive fertility preservation therapies.
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
### Which Fertility Preservation Options are Available?

#### Fertility Preservation Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Success Rate</th>
<th>Partner</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Methods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mature oocyte cryopreservation</td>
<td>35-50%</td>
<td>No</td>
<td>10-14 days stimulation; surgical procedure; no ovarian function preserved; stimulation may occur at any phase of the cycle</td>
</tr>
<tr>
<td>Sperm cryopreservation</td>
<td>57%</td>
<td>No</td>
<td>At least two samples recommended prior to exposure</td>
</tr>
<tr>
<td>Embryo cryopreservation</td>
<td>60-70%</td>
<td>Yes or donor</td>
<td>10-14 days stimulation; surgical procedure; no preservation of ovarian function; embryo ownership concerns</td>
</tr>
<tr>
<td>Ovarian transposition</td>
<td>60-90%</td>
<td>N/A</td>
<td>Underutilized</td>
</tr>
<tr>
<td>Ovarian shielding</td>
<td>75-80%</td>
<td>N/A</td>
<td>Scatter effect; consider concomitant chemotherapy</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td><strong>Investigational Methods</strong></td>
<td></td>
<td></td>
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<tr>
<td>Immature oocyte cryopreservation</td>
<td>No</td>
<td>No</td>
<td>No stimulation; surgical procedure; costs; no ovarian function preserved</td>
</tr>
<tr>
<td>Ovarian tissue freezing (no longer investigative)</td>
<td>No</td>
<td>Surgical procedure; costs; transplantation not suitable with high gonadal involvement or hormone sensitive tumor; preservation of gonadal function</td>
<td></td>
</tr>
<tr>
<td>Testicular tissue freezing</td>
<td>No</td>
<td>Similar to OTC</td>
<td></td>
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<tr>
<td>GnRH ovarian suppression</td>
<td>No</td>
<td>Conflicting data; recent Cochrane study clearer evidence</td>
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Ovarian Tissue Cryopreservation

• 130 children born worldwide
• 4700+ cryopreserved tissues with 360 transplantations
• Age range pre-pubertal* to mid 30’s
• 29 - 32% delivery rate with half of singletons conceived naturally
• Recommend no longer consider experimental for post-pubertal patients
• Hormone function up to 10 years

OTC and Orthotopic Transplantation

Methodologies to Optimize the Potential of Cryopreserved Tissue

In Vitro Growth of Primordial Follicles

Artificial Ovary

AMH
VEGF
S1P
Anti-oxidants
Stem Cells
Additives

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.

- 21 yo s/p interval bilateral oophorectomy for ovarian 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

Fertility preservation using controlled ovarian hyperstimulation and oocyte cryopreservation in a premenarcheal female with myelodysplastic syndrome

- Potentially higher gonadotropin doses in early puberty
- Transabdominal monitoring with sedated transvaginal retrieval
- Efficiency in adolescents needs to be confirmed Cil and Oktay
- 28.1% live-birth at age 25 for 2 oocytes thawed after vitrification
- Probability increased to 31.3% with 6 oocytes
Fertility Preservation Methods

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<td>GnRHa ovarian suppression</td>
<td>N/A</td>
<td>Conflicting data; recent Cochrane study supports use</td>
</tr>
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GnRHa and Ovarian Protection

Cochrane Review 2019

<table>
<thead>
<tr>
<th>GnRHa and Ovarian Protection</th>
<th>GnRHa</th>
<th>Control</th>
<th>Relative Effect</th>
<th>p value</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstruation recovery</td>
<td></td>
<td></td>
<td>RR 1.60 (1.14 to 2.24)</td>
<td>0.006</td>
<td>Low-certainty</td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td></td>
<td></td>
<td>RR 0.44 (0.31 to 0.61)</td>
<td>&lt; 0.00001</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ovulation</td>
<td></td>
<td></td>
<td>RR 2.47 (1.43 to 4.26)</td>
<td>0.001</td>
<td>Low-certainty</td>
</tr>
</tbody>
</table>
Cochrane Review 2019

GnRH agonist appears to be effective in protecting the ovaries during chemotherapy, in terms of maintenance and resumption of menstruation, treatment-related premature ovarian failure and ovulation. Evidence for protection of fertility was insufficient and needs further investigation.

<table>
<thead>
<tr>
<th>Condition</th>
<th>GnRHa</th>
<th>Control</th>
<th>Relative Effect</th>
<th>p value</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>32 of 356 (9%)</td>
<td>22 of 347 (6.3%)</td>
<td>RR 1.49 (0.93 to 2.7)</td>
<td>0.09</td>
<td>Low-certainty</td>
</tr>
</tbody>
</table>

How to Screen for Reproductive Late Effects?

Cancer Care Paradigm Shift

- Survival
  - Clinical trials
  - Aggressive therapy
- Quality of Life
  - Symptoms
  - Prevention
  - Treatment
- Eradicate
  - Targeted therapy
  - Gene therapy
Reproductive Late Effects

- Decreased libido
- Diminished self-esteem
- Dyspareunia/Lost intimacy
- Vaginal stenosis
- Hematocolpos
- Diminished uterine volume
- Fetal loss
- Low birthweight
- Vaginal stenosis
- Hypoestrogenism
- Vasomotor/GSM/bone loss
- Delayed puberty
- Infertility
- Infertility
- Hormonal Insufficiency
- Genital Graft Versus Host Disease
- Sexual Dysfunction
- Decreased libido
- Diminished self esteem
- Dyspareunia/Lost intimacy

Monitoring Ovarian Reserve

- AMH not yet considered standard of care for ovarian monitoring

- Baseline AMH and FSH
- Post-treatment AMH and FSH

- AMH ≤ reference range for age:
  - FSH < 10 mIU/ml:
    - Continue yearly monitoring**
  - FSH ≥ 10 mIU/ml:
    - Refer to REI

- ** Perform one year post-treatment completion
- ** Consider every six months depending on the value

Gougeon et al., Endocr Rev. 1996 Apr;17(2):121-55
Meirow et al., J Natl Cancer Inst Monogr. 2005;34:21–5
Chung et al., Fertil Steril 2013;99:1534-42

AMH: anti-Müllerian hormone
FSH: follicle-stimulating hormone

Monitoring Ovarian Reserve

- AMH not yet considered standard of care for ovarian monitoring

- Baseline AMH and FSH
- Post-treatment AMH and FSH

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Female Genital Tract Graft-Versus-Host Disease

GVHD | Genital Atrophy
--- | ---
Redness of vulva | Pale pink vaginal walls
Erosions, sores, fissures | Vaginal tissue bleeds easily with contact
Tenderness of vulvar glands | Labia thinner, sometimes fuse
Scarring | 

Clinical guidelines for gynecologic care after hematopoietic SCT. Report from the international consensus project on clinical practice in chronic GVHD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduce mechanical or chemical irritation</td>
<td>AIIIb</td>
</tr>
<tr>
<td>Avoid perfumed emollients and soaps</td>
<td></td>
</tr>
<tr>
<td>2. Topical class IV corticosteroids to rapidly control inflammation</td>
<td>BIib</td>
</tr>
<tr>
<td>Mometasone furoate ointment, betamethasone ointment, triamcinolone acetonide ointment</td>
<td></td>
</tr>
<tr>
<td>3. Topical calcineurin inhibitors for long-term treatment</td>
<td>CIIb</td>
</tr>
<tr>
<td>Tacrolimus or pimecrolimus</td>
<td></td>
</tr>
<tr>
<td>4. Topical estrogen as supportive therapy to increase epithelial thickness and improve resilience</td>
<td>BIib</td>
</tr>
<tr>
<td>Estradiol valerate gel</td>
<td></td>
</tr>
<tr>
<td>5. Regular intercourse or use of dilators to prevent narrowing and stenosis</td>
<td>CIIla</td>
</tr>
<tr>
<td>6. Manual lysis of adhesions under anesthesia if refractory to therapy</td>
<td>CIIla</td>
</tr>
</tbody>
</table>
Hormone Replacement Therapy:
Estrogen Effects on Physiology

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Oral</th>
<th>Transdermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>First pass through liver</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Estrogen delivery to tissues</td>
<td>High to liver</td>
<td>Similar in all tissues</td>
</tr>
<tr>
<td>Dosing</td>
<td>Supra-physiologic</td>
<td>Physiologic</td>
</tr>
<tr>
<td>Mimics normal physiology</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>Hepatic protein alterations</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Risk of VTE</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Increased TG</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Increased HDL/LDL ratio</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Uterine growth</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Decreases</td>
<td>No effect</td>
</tr>
</tbody>
</table>

Lobo, R. Obstetrics and Gynecology Clinics of North America 1987; 14,1:143-167

Transdermal 17b-estradiol no increased VTE risk (OR 0.9)

WHI findings cannot be extrapolated to pediatric and adult population less than age 60 years
Kmietowicz et al. BMJ 2019;364:l157

GUSM: Non-Estrogen Therapies

- Hyaluronic acid – biopolymer that releases water molecules
- Compared to estrogen - 84% and 89% response respectively
- DHEA 6.5 mg vaginal suppository x 12 weeks for dyspareunia
- Osapemifine (SERM): (FDA) menopause related dyspareunia
- CO2 laser – need comparison studies and long-term safety data
- Intravaginal oxytocin 400 IU qhs x 7 weeks; inhibits cancer cells

Sexual Dysfunction

- Adolescent survivors engage in risky health behaviors at rates generally equivalent to their siblings
- 77% of adult survivors of childhood cancer reported sexual dysfunction irrespective of gender or age

Existing paradigm

Emerging paradigm

Adapted from material by: University of Michigan School of Medicine, Office of Undergraduate Medical Education.
Practice Pearls

• Acute ovarian and testicular gamete failure 12% and 66%
• Pregnancy rates decreased to 38% for young adults
• OTC is clinical care and combined with IVM when feasible
• Ovarian stimulation may be offered in post-pubertal adolescents
• Evaluation of reproductive late effects is more than just fertility
• Contraception and sexual function management vitally important

Future Directions

• Identify targeted agents that minimize gonadal injury
• Improve risk stratification to better identify candidates for fertility preservation pre-treatment
• Standardize assessment and management of reproductive late effects in survivorship
• Optimize ovarian tissue transplantation procedures

Patient Experiences

"75% of cancer survivors without children stated they wanted to have children in the future." 1

"Women counseled about their risk of infertility by an oncologist and a fertility specialist had significantly less regret about their decision to preserve fertility that those counseled only by an oncology team." 2

"Patients experience less regret and have improved quality of life when counseled about fertility preservation options even if no option is pursued." 3
Save the Date!
Fertility Preservation and Reproductive Late Effects Conference

University of Colorado Cancer Center, Children's Hospital Colorado
Friday May 21st and Saturday May 22nd, 2021
Denver, Colorado, USA

Chair: Leslie Coker Appiah, MD and Co-chair: Anna Franklin, MD