Fertility Preservation: Beyond Oncology

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No financial disclosures or conflicts of interest
Learning Objectives

• Explain oncologic and non-oncologic conditions that benefit from fertility preservation therapies

• Describe standard and novel fertility preservation options in special populations

• Discuss the process of incorporating a fertility preservation program into practice

Cancer and Fertility
Case 1

21 yo G2P1011 with Hodgkin Lymphoma s/p 6 cycles of (ABVD) adriamycin, bleomycin, vinblastine and dacarbazine 2 years prior now with recurrence. Receiving ifosfamide, carboplatin and etoposide. Using OCPs and amenorrheic.

Does not recall fertility preservation consultation prior to initial chemotherapy.

Recommend ovarian reserve testing at completion of therapy and intrauterine device for contraception.

High Risk Therapy

Alkylating-intensive chemotherapy
• cyclophosphamide cumulative dose ≥7,500 mg/m2
• cyclophosphamide equivalent dose (CED) ≥ 7,500 mg/m2
• any treatment regimen containing procarbazine
• busulfan cumulative dose >600 mg/m2
• alkylating chemotherapy conditioning prior to SCT
• whole abdomen/pelvic irradiation ≥15Gy in pre-pubertal girls
• total body irradiation
• combination of any alkylating agent with total body irradiation or whole abdomen or pelvic radiation
• cranial radiation ≥30 Gy
Estimating Risk - CED

TABLE IV: Rate Ratios for Non-Surgical Premature Menopause: Multile Poisson Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>CED</th>
<th>AAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.14</td>
<td>1.09-1.20</td>
</tr>
<tr>
<td>Minimum ovarian dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphomas</td>
<td>1.60</td>
<td>0.92-2.89</td>
</tr>
<tr>
<td>&gt;100 Gy</td>
<td>1.68</td>
<td>1.54-1.84</td>
</tr>
<tr>
<td>Hodgkin lymphomas</td>
<td>13.65</td>
<td>6.01-31.77</td>
</tr>
<tr>
<td>Non-Hodgkin lymphomas</td>
<td>10.63</td>
<td>5.46-20.67</td>
</tr>
<tr>
<td>&gt;100 Gy</td>
<td>10.75</td>
<td>3.22-31.91</td>
</tr>
<tr>
<td>CED (mg/m²)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0-9000</td>
<td>0.95</td>
<td>0.09-9.47</td>
</tr>
<tr>
<td>&gt;9000-&lt;3000</td>
<td>2.74</td>
<td>1.13-6.61</td>
</tr>
<tr>
<td>&gt;3000</td>
<td>4.12</td>
<td>2.18-8.08</td>
</tr>
</tbody>
</table>

CED: Cyclophosphamide Equivalent Dose; AAD: Alkylation Agent Dose score; RR, rate ratio; CI, confidence interval; values shown in bold are statistically significant.


Chemotherapy and Fertility

Ovarian Failure

Testicular Failure

Howell. J Natl Cancer Inst Monogr 2005;34:12-17
Estimating Risk: Radiation in Females

<table>
<thead>
<tr>
<th>Radiation dose, Gy</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p value</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (all levels)</td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2.50</td>
<td>0.80</td>
<td>0.67 to 1.11</td>
<td>.15</td>
<td>0.82</td>
<td>0.58 to 1.17</td>
<td>.27</td>
</tr>
<tr>
<td>2.50-5.00</td>
<td>0.56</td>
<td>0.37 to 0.85</td>
<td>.007</td>
<td>0.67</td>
<td>0.43 to 1.04</td>
<td>.075</td>
</tr>
<tr>
<td>&gt; 5.00</td>
<td>0.18</td>
<td>0.13 to 0.25</td>
<td>&lt; .001</td>
<td>0.20</td>
<td>0.14 to 0.29</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hypothalamic</td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10.00</td>
<td>0.85</td>
<td>0.72 to 1.01</td>
<td>.067</td>
<td>0.86</td>
<td>0.72 to 1.02</td>
<td>.088</td>
</tr>
<tr>
<td>&gt; 10.00</td>
<td>0.61</td>
<td>0.44 to 0.83</td>
<td>.002</td>
<td>0.61</td>
<td>0.44 to 0.85</td>
<td>.003</td>
</tr>
</tbody>
</table>

Green, J Clin Oncol. 2009;27(16):2677-2685

Estimating Risk: Radiation in Males

Spermatogenesis Following Single Dose Radiation

Howell, J Natl Cancer Inst Monogr 2005;34:12-17
Minimizing Risk

<table>
<thead>
<tr>
<th>Protective Agent</th>
<th>Mechanism of action</th>
<th>Treatment interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH analog</td>
<td>Suppresses HPO axis; unclear</td>
<td>No interference</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Inhibit c-Abl kinase apoptosis pathway</td>
<td>May interfere w/ apoptosis</td>
</tr>
<tr>
<td>Sphingosine-1-Phosphate</td>
<td>Inhibit sphingomyelin apoptosis pathway</td>
<td>May interfere w/ apoptosis</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Anti-apoptotic activity; Antioxidant activity via IGF-1 axis; Possible HPO axis suppression</td>
<td>No interference</td>
</tr>
<tr>
<td>AS101</td>
<td>Inhibits P13K/PTEN Akt follicle activation pathway; anti-apoptosis</td>
<td>No interference; may have additive/synergistic interaction</td>
</tr>
<tr>
<td>Bone marrow mesenchymal stem cells</td>
<td>Tissue differentiation, angiogenesis, anti-apoptosis</td>
<td>May cause drug resistance with Cisplatin</td>
</tr>
<tr>
<td>Granulocyte-Colony Stimulating Factor (G-CSF)</td>
<td>Unclear: possibly angiogenesis; anti-apoptosis</td>
<td>No interference</td>
</tr>
</tbody>
</table>

Expert Consensus Position Statements

- American Society of Clinical Oncology (ASCO)
- American Society for Reproductive Medicine (ASRM)
- Association of Pediatric Hematology/Oncology Nurses (APHON)

- “As part of education and informed consent before cancer therapy”…physicians should inform cancer patients about options for fertility preservation and future reproduction … “or refer to reproductive specialists…”

- “…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 50% of patients recall discussing fertility risks with a healthcare provider.


Fertility Preservation Barriers

“the only fertility preservation method most oncologists felt knowledgeable about was sperm cryopreservation (64%)” Adams 2013, BJC

“referrals to reproductive endocrinologists made approximately 39% of the time” Forman 2010, Fertil Steril

“patient is too ill to delay treatment” - 50% of respondents in national survey of pediatric nephrologists Miller 2014 J Renal Care

“lack of patient interest in fertility preservation (38%)”
Patient Experiences

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

A third of survivors who already had at least one child wanted another”

Patients experience less regret and have improved quality of life when counseled about fertility preservation options even if no option is pursued”


Non-oncologic conditions
Case 2

11 yo female with sickle cell anemia refractory to first-line therapy. Plan for hematopoietic stem cell transplantation (HSCT). Received fertility preservation counseling.

Ovarian reserve testing at baseline: AMH: 1.1 ng/ml, FSH 5 mIU/ml, Estradiol 7.6 pg/mL

Given high risk of ovarian failure, family elected OTC. Procedure was performed in conjunction with central line placement without complication.
Stem cell transplant: 
Non-oncologic conditions

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Autoimmune conditions</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>Multiple sclerosis</td>
<td>Severe combined immuno-deficiency</td>
</tr>
<tr>
<td>Fanconi’s Diamond Blackfan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>Systemic sclerosis</td>
<td>Wiskott-Aldrich disease</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Systemic lupus erythematosus</td>
<td>Metabolic storage defects</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>Mucopolysaccaridoses Amyloidosis Gaucher’s disease</td>
</tr>
</tbody>
</table>

Case 3

15 yo with immune complex mediated membranous glomerulonephritis s/p therapy with 3 g/m² cyclophosphamide. Treated with GnRHa for menstrual suppression. Currently on cyclosporine and steroids. Treatment course complicated by VTE on anticoagulation.

Ovarian reserve testing 12 months post-completion of therapy: AMH 1.98 ng/ml.

Given anticoagulation and persistent renal disease with menorrhagia, continued on GnRHa. Dose increased to 22.5 mg due to continued bleeding and incomplete HPO axis suppression.
Renal disease and fertility

• Classic regimen: 0.75 – 1 g/m² cyclophosphamide per month for up to 6 months then every 3 months for up to 2 years (cumulative dose > 7500 mg/m²)

• Mycophenolate mofetil (CellCept) preferred induction agent for patients desiring fertility; Cytoxan continues to be important during induction in severe renal disease or relapsed pediatric patients

• Newer regimens: 0.75 – 1 g/m² cyclophosphamide for 3 to 6 months with conversion to mycophenolate or tapering to low dose cyclophosphamide or azathioprine


Case 4

19 yo G0 diagnosed with primary ovarian insufficiency at age 14. Received HRT with adequate breast development and switched to OCPs for ease of use.

Labs at consultation: FSH 67.3 mIU/ml, Estradiol 30 pg/ml, AMH <0.03 ng/ml; 46 XX, FMR1, anti-thyroid and anti-adrenal antibody testing negative

Counseled on attempt at oocyte freezing - declined
• 37 infertile women with POI
• N=31
  • > 1 year amenorrhea with FSH levels > 40 mIU/ml
• N=6
  • > 4 months amenorrhea with FSH levels > 35 mIU/ml
• Oophorectomy, vitrification and transplantation
• Gonadotropin injections
• Monitoring with U/S and serum estrogen levels


<table>
<thead>
<tr>
<th>Residual follicles at histology and growth after transplantation (n)</th>
<th>Age at ovariectomy (y)</th>
<th>Time (y) from diagnosis of POI to ovariectomy</th>
<th>Number of patients with AMH before ovariectomy (pg/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (17)</td>
<td>37 ± 4.7 (28–43)</td>
<td>7.5 (2.5–12.1)†</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Present but no growth (11)</td>
<td>37 ± 4.9 (31–48)</td>
<td>5.0 (3.0–5.5)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Present and growth (9)</td>
<td>39 ± 4.4 (29–42)</td>
<td>1.0 (0.5–4.7)†</td>
<td>3 (30%)</td>
</tr>
</tbody>
</table>

- ICSI and embryo cryopreservation
- Uterine priming and embryo transfer
- 3 pregnancies
  - 1 miscarriage and 2 successful live births
- Greater follicular growth with earlier intervention
Case 5

5 year old female with 45XO,46XY Turner mosaicism for gonadectomy. Negative ultrasound and tumor markers.

Family interested in fertility preservation. Oophorectomy performed after pre-operative discussion with pathology.

Frozen section revealed no oocytes; ovarian stromal tissue present; suspect gonadoblastoma therefore no tissue was frozen. Final pathology revealed bilateral gonadoblastomas.

Disorders of Sexual Differences

Individually rare but in aggregate not uncommon – 1/4600

- Previous classification - conditions associated with:
  - Gonadal dysgenesis
  - Undervirilization of 46 XY individuals
  - Prenatal virilization of 46 XX individuals

- Current classification of DSDs
  - Sex chromosome DSDs
  - 46 XX DSDs
  - 46 XY DSDs

Lawson Wilkins Pediatric Endocrine Society and European Society for Paediatric Endocrinology
Oocyte Cryopreservation for Fertility Preservation in Postpubertal Female Children at Risk for Premature Ovarian Failure Due to Accelerated Follicle Loss in Turner Syndrome or Cancer Treatments

K. Oktay MD 1,2,*, G. Bedoschi MD 1,2

- 5 cases of premature ovarian failure
  - 3 Turner syndrome; 1 germ-cell tumor; 1 leukemia
- Ages 11-15
- Standard ovarian stimulation protocol
- Transabdominal U/S for monitoring
- Transvaginal U/S under anesthesia for retrieval
- 4-11 mature oocytes cryopreserved; in vitro maturation performed on retrieved germinal vesicles

Ovarian stimulation in adolescents

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

David E. Ehrlichman, M.D., Owen K. Davis, M.D., Nikola Zulinovic, M.D., Zen Rosenwaks, M.D., and Dan L. Schalkwyk, M.D.

- No large studies of stimulation in adolescents
- Adolescent females are able to participate in informed assent
- Gonadotropin doses similar to adult patients
- Consider GnRHa trigger instead of hCG to minimize OHSS risk
Gonadal dysgenesis, hypoplastic uterus, normal fallopian tubes

Uterine priming and hormone replacement

Oocyte donation with GIFT and semen insemination

Full term male infant delivered by cesarean

Reported pregnancies in 46 XY females have all been secondary to oocyte or embryo donation

**Mixed gonadal dysgenesis**

- Few case reports of successful paternity in phenotypic males

- No reports on extraction of immature oocytes for IVM in phenotypic females

- No reports on stimulation of ovarian follicles

*Sugawara 2012;25(4):96-9
Flannigan 2014;8(1-2):e108-10*
Case 6

- 20 yo MTF transgender patient planning to undergo gender affirming hormone therapy
- Fully identified as female for 1 year with good family support
- High desire for future biological children
- Counseled on fertility preservation options
- Underwent sperm cryopreservation
  - 2 collections (5 vials/collection) to ensure “at least 3 kids”

The Desire to have Children and the Preservation of Fertility in Transsexual Women: A Survey
P. De Sutter, M.D., Ph.D., K. Kira, M.Sc., A. Verschoor and A. Hotamisly

Reproductive wish in transsexual men.

- Approximately half of MTF and FTM transgender persons express a wish for future children
- Transgender persons with children score higher on mental & vitality scores than those without
- Parenting noted as a suicide protective factor in transgender women
Fertility options in transgender people.
De Roo C¹, Tilleman K¹, TSjoen G², De Sutter P¹.

- Majority of transgender persons believe fertility preservation should be discussed & offered
  - urgency for a rapid transition may prevent fertility preservation

- Discussion of fertility options with patients prior to treatment or medical intervention is recommended

World Professional Association for Transgender Health Standards of Care 7th version

### Gender Reassignment Therapy & Fertility

- Estrogen ⇒ decreased testicular volume, poor semen quality and azoospermia with possible reversal
- Testosterone ⇒ reversible amenorrhea without follicle depletion; pregnancies reported in FTM individuals on/after T
- Genital reconstructive surgery ⇒ irreversible infertility
Transgender: Fertility Preservation Options

- Standard and experimental options

- Special Considerations
  - FTM patient
    - Vaginal examination & procedures
  - MTF patient
    - Need for masturbation, semen production & storage
    - Testicular sperm extraction/aspiration (TESE/TESA)

- Ovarian & Testicular Tissue Cryopreservation
  - Removed at time of genital reconstructive surgery

Fertility Preservation Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperm cryopreservation</td>
<td>Standard; no partner needed; specimen may be suboptimal due to malignancy and HRT</td>
</tr>
<tr>
<td>Mature oocyte cryopreservation</td>
<td>Standard; no partner needed; 10 – 14 days stimulation; surgical procedure; costs; no ovarian function preserved</td>
</tr>
<tr>
<td></td>
<td>Stimulation may occur at any phase of the cycle</td>
</tr>
<tr>
<td>Embryo cryopreservation</td>
<td>Standard; partner or sperm donor needed; 10 – 14 days stimulation; surgical procedure; costs;</td>
</tr>
<tr>
<td>(40% success rate)</td>
<td>no preservation of ovarian function; embryo ownership concerns</td>
</tr>
<tr>
<td>Ovarian transposition</td>
<td>Standard; underutilized</td>
</tr>
<tr>
<td>(Success rates of 88-90%)</td>
<td></td>
</tr>
</tbody>
</table>
## Fertility Preservation Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature oocyte cryopreservation</td>
<td>Investigational; no partner needed; no stimulation; surgical procedure; costs; no ovarian function preserved</td>
</tr>
<tr>
<td>Ovarian and testicular freezing</td>
<td>Investigational; surgical procedure; costs; transplantation not suitable with high gonadal involvement; preservation of gonadal function</td>
</tr>
<tr>
<td>GnRHa ovarian suppression</td>
<td>Investigational; conflicting data; limited data on reproductive outcomes</td>
</tr>
</tbody>
</table>

## Ovarian Tissue Cryopreservation

**Livebirth after orthotopic transplantation of cryopreserved ovarian tissue**


**Pregnancy after Transplantation of Cryopreserved Ovarian Tissue in a Patient with Ovarian Failure after Chemotherapy**

**Live birth after autograft of ovarian tissue cryopreserved during childhood**

Isabelle Demestere, Philippe Simon, Laurence Dedeken, Federica Moffa, Sophie Tsépédidis, Cecile Brachet, Anne Delbaere, Fabienne Devreker, and Alina Ferster.
Ovarian Tissue Cryopreservation

Cortex Dissected from Medulla

Thickness = 1 mm


Orthotopic Transplantation: Ovarian Fossa

Donnez et al. Frontiers in Bioscience 2012
Orthotopic Transplantation: Contralateral Ovary

Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of women</th>
<th>Age (years) (mean, range)</th>
<th>Tissue transported online prior to freezing</th>
<th>Cryopreservation</th>
<th>1st transplant</th>
<th>2nd transplant</th>
<th>3rd transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>12/3</td>
<td>33.9 (26.0–48.7)</td>
<td>16.5 (20.7–24.2)</td>
<td>31.0 (28.0–37.8)</td>
<td>32.3 (29.4–34.7)</td>
<td>34.0 (36.7–38.4)</td>
<td></td>
</tr>
<tr>
<td>Mediastinal Hodgkin</td>
<td>3/4</td>
<td>29.4 (23.4–34.1)</td>
<td>31.0 (28.0–37.8)</td>
<td>32.3 (29.4–34.7)</td>
<td>34.0 (36.7–38.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>5/3/1</td>
<td>31.0 (25.9–37.1)</td>
<td>33.8 (29.6–37.1)</td>
<td>34.0 (36.7–38.4)</td>
<td>35.6 (38.4–39.1)</td>
<td>37.7 (39.6–39.1)</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>3/1</td>
<td>31.2 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>2</td>
<td>31.3 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
<tr>
<td>Endometrial sarcoma</td>
<td>2</td>
<td>31.3 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
<tr>
<td>Primary testicular tumors</td>
<td>1</td>
<td>31.3 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
<tr>
<td>Non-secretory tumors</td>
<td>2</td>
<td>31.3 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
<tr>
<td>Nephrogenic rests</td>
<td>2</td>
<td>31.3 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td>2</td>
<td>31.3 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>31.3 (21.1–41.7)</td>
<td>31.3 (21.1–41.7)</td>
<td>33.3 (23.3–43.3)</td>
<td>35.3 (35.9–39.6)</td>
<td>37.8 (39.3–39.6)</td>
<td></td>
</tr>
</tbody>
</table>


Jensen et al. Hum. Reprod. 2015;0(0):1-8
Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark

- Ovarian tissue cryopreservation initiated in Denmark in 2000
- 800 patients have undergone ovarian tissue cryopreservation
- Annual activity of 13-14 cases per million inhabitants per year
- 53 transplantations to 41 patients over 10 years
- Among 32 women with a pregnancy-wish, 24 clinical pregnancies and 10(31%) had a child/children
- Transplanted ovarian tissue may last 10 years

Jensen et al. Hum. Reprod. 2015;0(0):1-8

Restoration of Hormonal Function

Silber. Ovarian cryopreservation and transplantation for fertility preservation. MHR 2012
Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG IBCSG, ECOG, and CALGB (Alliance).

- 218 premenopausal patients age < 50
- Stage IIA ER/PR-negative breast cancer
- Randomized to cyclophosphamide w/ or w/o Goserein (GN) 3.6 mg SQ 1 week before tx
- Primary: 2-year amenorrhea + elevated FSH

<table>
<thead>
<tr>
<th>Primary ovarian insufficiency</th>
<th>Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 22% standard group</td>
<td>- 12 standard group</td>
</tr>
<tr>
<td>- 8% Goserein group</td>
<td>- 22 Goserein group</td>
</tr>
<tr>
<td>P = 0.04</td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>

**Fertility Preservation Costs**

<table>
<thead>
<tr>
<th>Method</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperm cryopreservation</td>
<td>$400 + $175 for semen analysis</td>
</tr>
<tr>
<td>Oocyte cryopreservation</td>
<td>$8000 plus meds, $4000 - $6000 (reduced costs through Livestrong) plus meds</td>
</tr>
<tr>
<td>Embryo cryopreservation IVF</td>
<td>$5500 - $13000, $7800 - $12000 plus meds</td>
</tr>
<tr>
<td>Long term storage</td>
<td>$275, $75 reduced costs</td>
</tr>
<tr>
<td>Ovarian tissue cryopreservation</td>
<td>$10000 - $30000 for oophorectomy (funding), $500 for tissue processing (funding)</td>
</tr>
</tbody>
</table>
Family Building Options

<table>
<thead>
<tr>
<th>Donor Embryos</th>
<th>Donor Oocytes</th>
<th>Gestational Surrogate</th>
<th>Adoption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryos donated</td>
<td>Oocytes donated</td>
<td>Pregnancy carried for patient</td>
<td>Legal parent-child relationship created</td>
</tr>
<tr>
<td>Success rate &gt; frozen embryo/IVF transfers</td>
<td>40-50% success rate</td>
<td>Success rate similar to fresh cycle IVF</td>
<td>$2500-$35000</td>
</tr>
<tr>
<td>$5,000-$7,000 + IVF costs</td>
<td>$5,000-$15,000 + IVF costs</td>
<td>$10,000-$100,000</td>
<td></td>
</tr>
</tbody>
</table>


Preimplantation Genetic Diagnosis

- Pregnancy success rates: 27 – 39% per embryo transfer
- No increased risk of perinatal deaths or congenital malformations

Ovarian reserve testing

Baseline testing and 12 months after completion of therapy


Anti-Müllerian Hormone

La Marca A. Et al. Anti-mullerian hormone (AMH) as a predictive marker in assisted reproductive technologies ART. Hum Reprod Update 2010;16(2):113-130.
Anti-Mullerian Hormone

Serum AMH (picomoles per liter) in 926 healthy infants, girls, adolescents, and adult women. La Marca A. et al. Anti-mullerian hormone (AMH) as a predictive marker in assisted reproductive technologies ART. Hum Reprod Update 2010;16(2):113-130.

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</td>
<td>Impending onset of premature menopause</td>
<td>Predicts low ovarian response to stimulation</td>
</tr>
<tr>
<td>(0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Limited egg supply</td>
<td>Shortened reproductive window</td>
</tr>
<tr>
<td>(&lt;1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-range</td>
<td>Normal testing</td>
<td>Consider preservation if high risk chemotherapy</td>
</tr>
<tr>
<td>(1-3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>PCO or PCO-like</td>
<td>Risk of OHSS</td>
</tr>
<tr>
<td>(&gt;3.5)</td>
<td>ovaries</td>
<td></td>
</tr>
</tbody>
</table>

- Fluctuations can be observed over the course of year(s)
- Does not reliably predict pregnancy rates

1Modified, Toner. Fertil Steril 2013
Implementing a fertility preservation program

Oncofertility Program Website: www.ukhealthcare.uky.edu/fertility-preservation

Team Members
Charity Rogers, RN - Gynecology
Diana Holtzhaeur, RN - Oncology
Leslee Bertram, DNP - Oncology
Christina Conley, APN - Oncology
The Oncofertility Program at UK HealthCare provides a comprehensive approach to fertility preservation for patients undergoing cancer treatment. This program offers a variety of methods to maintain fertility, including assisted reproductive technologies and other options. The program's goal is to help patients retain their ability to have children even if it is not their current desire.

*New patient presents to oncology, and an oncology treatment plan is developed.*

**Patient Navigator or Clinical Research Nurse** serves as the central point of contact for patients.

**Prepubertal Patients**
- Male: Testicular tissue freezing
- Female: Ovarian tissue freezing

**Pubertal Patients**
- Male: Sperm/Testicular tissue freezing
- Female: Egg/Embryo Ovarian freezing

**Work-flow**

- When the patient is treated, a fertility preservation consultation is scheduled before the patient is discharged.
- The consultation consists of a discussion about the options for fertility preservation and how these options can be integrated into the patient's overall treatment plan.
- The patient is provided with information about the risks and benefits of each option and is encouraged to make an informed decision about which option is best for them.

**Fertility Consult**

- **Prepubertal**
  - Male: Testicular tissue freezing
  - Female: Ovarian tissue freezing

- **Pubertal**
  - Male: Sperm/Testicular tissue freezing
  - Female: Egg/Embryo Ovarian freezing
Fertility Preservation Process

- Sperm freezing
- Embryo/Oocyte freezing
- Ovarian tissue freezing

Referral to IVF office for semen collection and drop-off x2 samples

Proceed with therapy

Referral to IVF office for stimulation, retrieval and freezing

Proceed with therapy

Coordinate laparoscopic oophorectomy with C-line or port placement

Ovarian tissue processed

20% research - tissue transported to Oncofertility Consortium/Chicago
80% patient use - tissue stored in long term site in Minnesota @ Repotech Ltd.

Proceed with therapy

FERTILITY CONSULTATION WORKFLOW

Fertility Navigator
- Provide initial contact information
- Arrange an appointment for the patient
- Coordinate between the patient and the fertility team
- Ensure the patient’s understanding of the process
- Schedule follow-up appointments as needed

Obstetrician On Call
- Ensure patient’s readiness for pregnancy
- Schedule an appointment for the patient
- Coordinate with the Fertility Navigator

Gynecologist and Urologist On Call
- Schedule an appointment for the patient
- Coordinate with the Fertility Navigator
- Provide initial consultation

Fertility Navigator
- Provide initial contact for any patient requesting reproductive treatment
- Schedule an appointment with the appropriate specialist
- Ensure patient’s understanding of the process
- Schedule follow-up appointments as needed

Research Coordinator
- Coordinate with research institutions
- Ensure patient’s understanding of the process
- Schedule follow-up appointments as needed

Oncofertility Referral

Electronic Medical Record

- Physician note
- Nursing systems assessment
EMR Data Management

EPIC Fertility Synopsis (Testing Phase)

Collaboration

Oncology/Endocrinology  
Gynecology/Surgery/REI  
PCP  
Care Managers  
Social Work  
Ethics  
Patient/Family  
Optimize Outcome
Future Directions

• Identify agents that minimize risk prior to and during gonadotoxic therapy

• Advance reproductive technologies such as in-vitro maturation of immature ovarian follicles and spermatogonial stem cells

• Standardize and streamline counseling and implementation of fertility preservation therapies

Challenging Cases - Audience
References


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