Overview

- Fertility impacting diseases
- Chemotherapy and Radiation
- Fertility Preservation
  - Pre-treatment counseling
  - Fertility preservation methods
  - IVF safety
  - Practical Information

Introduction

- Women have a 42% lifetime risk (1 in 2.4) of cancer
  - 5.7% under age 40
  - 0.7% under age 20
- ASMR declined 30-40% in women of reproductive age 1986-2010

Risk of infertility among cancer survivors

- Depends on:
  - Type of stage of cancer
  - Drug class and cumulative dose
  - Radiation field, number of treatments, and cumulative dose
  - Extent of surgical therapy
  - Age (eg, prepubertal, postpubertal, near menopause)
  - Gender
  - Genetic Factors
  - Development of post-treatment hypothyroidism
Up To Date (2018): Fertility Preservation in Patients Undergoing Gonadotoxic Treatment or Gonadal Resection

Chemotherapy and Radiation

Chemo and Fertility

Definitely associated with ovarian damage

<table>
<thead>
<tr>
<th>Nitrogen mustard</th>
<th>Methotrexate (alkylating agent)</th>
<th>Taxol (taxane)</th>
<th>Paclitaxel (taxane)</th>
<th>Bleomycin</th>
<th>Doxorubicin</th>
<th>VINCA alkaloids</th>
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<tbody>
<tr>
<td>Venetoclax</td>
<td>Valrubicin</td>
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(a) Diagrammatic view of an ovary section to reveal the follicles in its interior.
Multiple drug regimens

- Hodgkin lymphoma
  - ABVD
    - Low incidence of chemo-induced ovarian failure
    - 90% normal spermatogenesis at 1 year
  - BEACOPP
    - Approx. 50% ovarian failure
    - 3+ cycle of MOPP
    - Azoospermia in ~90% at 1 year (likely from procarbazine)

- Early stage breast cancer
  - Two commonly used adjuvant chemo regimens:
    - CMF (cyclophosphamide, MTX, and 5-FU)
    - AC (doxorubicin plus cyclophosphamide)
  - Ovarian failure CMF>AC

Radiation Therapy

- XRT more damaging to ovarian tissue than chemo
- Transient amenorrhea
  - resolves after 6-18 months
- Wallace et al. (2005) estimated radiosensitivity of oocyte to be <2 Gy
  - Calculated dose = immediate/permanent ovarian failure
    - Birth: 20.3 Gy
    - 10 yo: 18.4 Gy
    - 20 yo: 16.5 Gy
    - 30 yo: 14.3 Gy
    - 40 yo: 6.0 Gy

Assessment of fertility potential after cancer therapy

- Females:
  - Amenorrhea/oligomenorrhea
  - Evaluate for FSH
  - Diagnosis problematic: ovarian dysfunction may not be permanent
  - Regular menstrual cycles
  - Assessment of ovarian reserve: AMH or AFC

- Males:
  - Semen analysis
    - If repeated analyses demonstrate severe oligospermia/azoospermia - > FSH/LH and testosterone

Pretreatment Counseling

- Risk of treatment-induced infertility
- Possible interventions to preserve fertility
- Only 26% of women 40 years and younger with breast cancer had a documented fertility discussion with their physician
- 90% of these women pursued further consultation for fertility preservation
- Initiate conversation early - fertility interventions can take time and delay start of treatment

McCray et al. (2016)
Disclosure

• No large RCTs evaluating majority of the following interventions

• No long-term follow-up studies assessing the possible impacts of fertility treatment on cancer survivors

• Oncologists remain cautious about use of traditional assisted reproductive technology (ART) in women with estrogen-dependent malignancies

Fertility Preservation

Fertility Risk Reduction

• Preservation:

• Fertility “Preservation”:

Fertility Preservation Methods

• Cryopreservation
• Protecting native ovarian function
• Alternatives
• Safety Concerns
• Practical Information (i.e. cost, contact info)

Cryopreservation

• Embryo
• Oocyte
  • Mature
  • Immature
• Ovarian tissue
• Whole ovary
What is in vitro fertilization (IVF)?

IVF Protocols

- Ovarian stimulation with gonadotropins (FSH +/- LH) takes advantage of that month’s developing follicular pool
- Ovulation must be prevented (GnRH agonists or antagonists) during ovarian stimulation
- Letrozole to keep estrogen levels low in breast cancer patients
- At the end of stimulation, final stage of oocyte maturation with injection of HCG
- Egg retrieval
- Embryos cultured (“grown”) in lab
- Freezing of embryos

IVF - Stimulation Phase

- Daily subcutaneous injections of FSH +/- LH
- Monitoring with transvaginal U/S and bloodwork q 2-3 days (follicle growth, estradiol level)
- Stimulation phase typically lasts 9-12 days
- When oocytes are “ready,” patient stops gonadotropins and GnRHα, takes HCG 36 hours before egg retrieval

IVF - Egg Retrieval (OPU)

IVF - Fertilization

Standard IVF

- Intracytoplasmic Sperm Injection

IVF - Embryo Culture

- Day 1: Fertilization
- Day 2: 4-cell
- Day 3: 8-cell
- Day 4: Morula
- Day 5: Blastocyst
Embryo Cryopreservation

- Fresh eggs fertilized with sperm +/- ICSI then frozen
  - No known time limit for the duration of embryo storage
  - Live birth from 20 year old embryo!
- Live birth rates from frozen-thawed embryos depends on the age of the woman at the time of egg-retrieval
- Obstetrical outcomes equal for fresh vs frozen embryos

Up to Date: Fertility preserving options for women of advancing age

IVF Success Rates

- 1986: First human birth after oocyte cryopreservation
- 2012: ASRM lifted ‘experimental’ label
- Limitations
  - Lower survival, fertilization rate, pregnancy rate
  - Mature oocyte fragile during thaw
  - Large size
  - High water content
  - Ice formation, chilling injury and osmotic damage all detrimental to mitotic spindle
  - May delay start of cancer treatment
  - High estradiol levels
  - Not an option for prepubertal patients

Oocytes – Mature Oocytes

- Good option for patients:
  - No long-term partner
  - Religious or ethical objection to embryo freezing
  - Young age/good ovarian reserve
Oocyte cryopreservation - outcomes

Elective oocyte freezing

<table>
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<tr>
<th>Number of mature eggs</th>
<th>Fertilized</th>
<th>Derived from 50%20%</th>
<th>Derived from 50%20%</th>
<th>Derived from 50%20%</th>
<th>Derived from 50%20%</th>
<th>20%20%</th>
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<tr>
<td>15 eggs</td>
<td>23.5%</td>
<td>23.5%</td>
<td>17.0%</td>
<td>17.0%</td>
<td>5.0%</td>
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<tr>
<td>50-14 eggs</td>
<td>45.0%</td>
<td>38.7%</td>
<td>32.4%</td>
<td>28.6%</td>
<td>28.6%</td>
<td>51.4%</td>
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<tr>
<td>20-14 eggs</td>
<td>48.8%</td>
<td>45.3%</td>
<td>41.9%</td>
<td>31.8%</td>
<td>21.8%</td>
<td>28.6%</td>
</tr>
<tr>
<td>39-14 eggs</td>
<td>47.8%</td>
<td>51.4%</td>
<td>45.3%</td>
<td>32.1%</td>
<td>32.1%</td>
<td>38.3%</td>
</tr>
<tr>
<td>Total</td>
<td>58.8%</td>
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Ovarian tissue cryopreservation

Posthumous use of reproductive tissue

- Consent form, advance directive to be completed at time of cryopreservation
- Consent could allow use of the gametes by a partner, donation to others, research, or destruction/discarding of the tissue
- Children born after posthumous conception are the legal children of the deceased

Fertility Preservation Methods

- Cryopreservation
- Protecting native ovarian function
- Alternatives
- Safety Concerns
- Practical Information (i.e. cost)
Protecting Native Ovarian Function

- Radiation Therapy
  - Transposition (oophoropexy)
  - Shielding
  - Auto-transplantation

- Chemotherapy
  - GnRH agonist treatment

Women receiving radiation

- **Transposition** (oophoropexy)
  - Once radiation field is planned, move ovary to position to best protect it from exposure
    - Non-pelvic tumors and narrow midline radiation field
      - Simple oophoropexy
    - Broad pelvic radiation (absence of chemo)
      - Consider transposing ovaries out of radiation field

Women receiving chemotherapy

- Option #1: proven cryopreservation techniques
- GnRH agonist treatment: not recommended as primary treatment for fertility preservation
  - Not shown to be equivalent or superior to embryo or oocyte cryopreservation
  - Ideally: fertility preservation AND restoration of cycles
  - Should be considered if cryopreservation is not an option
- Alternative use: reduction of HMB in women at risk for severe chemotherapy-induced thrombocytopenia.
GnRH agonist suppression

CFAS, ASCO differ on their support for this method of FP

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Egg donation

- No fresh/frozen oocytes/ovarian tissue available
- Intact uterus
- Consider fresh/frozen donor oocytes and partner's sperm for IVF
- Success rates >50-60% per embryo transfer

Embryo Donation

- Couples in IVF programs sometimes donate excess cryopreserved embryos
- Can implant these embryos in a woman with a uterus, even if no ovarian function is present
Adoption • Another option for parenthood

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Women with Breast Cancer • Ovarian stimulation
• 4-6 week hiatus between breast ca surgery and initiation of chemo
  • Yield = extremely low
  • IVF
  • Estradiol levels 10 x natural cycle
  • Concern: breast tumors contain estrogen receptor-positive cells
  • Even ER-negative can be estrogen responsive
  • Approach: minimize estrogen exposure during fertility preservation procedures
    • Letrozole
    • Tamoxifen

Women who cannot undergo ovarian stimulation • Large/locally advanced (inflammatory) breast ca
• Neoadjuvant chemo is begun immediately after diagnosis and before surgical treatment
• Consider harvesting immature oocytes
• BRCA carriers and other women with hereditary breast-ovarian cancer syndromes
  • Risk of developing ovarian cancer
  • Relatively high incidence of occult ovarian cancer
  • Future avenues: possible to culture frozen-thawed ovarian tissue strips to achieve oocyte maturation and perform IVF

Women with Breast Cancer • Letrozole (aromatase inhibitor)
• Advantage: peak estradiol levels are close to those observed in natural cycles
• Recommended: letrozole-FSH protocol
  • Low estradiol exposure
  • High oocyte recovery
• Additional concerns:
  • BRCA1 mutation carriers: lower ovarian response rate to letrozole-FSH than BRCA mutation-negative patients, and produce fewer eggs
  • These patients may be more vulnerable to gonadotoxic effects of cancer treatments.

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IVF – treatment delay

Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG)

- 7501 Danish patients with early stage breast cancer between 1977-99
- Three different chemotherapy regimens, as treatment changed during the study period
- Chemo treatment start after surgery divided into 4 groups – weeks 1-3, week 4, week 5, or week 6-12

Impact on Survival of Time From Definitive Surgery to Initiation of Adjuvant Chemotherapy for Early-Stage Breast Cancer

Caroline Lefebvre, Charles Pezard, Karen Galanor, Caroline Spinn, Suzanne Taylor, Jeff Barnett, and Jan A. Ollivier

- 2594 Canadian patients with stage I or II breast cancer between 1989-98.
- Chemo treatment start after surgery divided into 4 groups – < 4 weeks, 5-8 weeks, 8-12 weeks, and > 12 weeks

Safety of IVF in breast cancer

Kim J et al J Clin Endocrinol Metab. 2016 Jan 11

- Prospective study of 337 women with stage 1-3 breast CA, all saw FP specialist
- 120 underwent FP (gonadotropins + letrozole), 217 didn’t (controls)
- Followed for avg of 5 years
- No difference in recurrence or survival
- No effect of BRCA status, ER status of tumor, or timing of ovarian stim (pre- or post-surgery)

Fertility Preservation Methods

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Components of Fertility Preservation Program

- Rapid access
- Multidisciplinary team – physicians, nurses, pharmacists, embryologists, administration
- Experienced lab – embryo, oocyte, sperm cryopreservation protocols, +/- IRB-approved protocols for testicular/ovarian tissue cryo
- Counsellors – mental health, genetic, financial
- Interdisciplinary collaboration

Current Status of IVF Funding in Canada

Quebec:
- Funding started August 2010 but cancelled in 2014, now income-based assistance sliding scale

Ontario:
- One lifetime IVF cycle funded for patients since January 2016
- Cap on number of provincially funded cycles/year; each clinic has a maximum number of funded cycles/year based on clinic size and volume

Manitoba:
- Fertility Treatment Tax Credit – 40% of up to $20000 fertility treatment fees + drug expenses (max $8000 per year)

New Brunswick:
- The Special Assistance Fund for Infertility Treatment
- One-time grant for 50% of fertility treatment fees + drugs, up to maximum of $5000

Financial Assistance

- Partnership with Fertile Future helps reduce cost of FP treatments for patients
- Fertile Future is a Canadian non-profit organization that provides fertility preservation information and support services to cancer patients and oncology professionals
- Power of Hope is a financial assistance program for Canadian cancer patients wishing to pursue fertility preservation prior to beginning fertility threatening treatment

Cost of treatments:
- IVF:
  - Embryo cryopreservation: $4600 (SG) or $3600 (standard IVF)
  - Oocyte cryopreservation: $4667
- Sperm cryopreservation: $0
- Storage of embryos/oocytes: $900, then $300/yr
- Leuprolide acetate 3.75mg: $500/month
Ethical Considerations

- Risk to future fertility of cancer treatments
- Fertility preservation treatment options
- Any investigational/experimental aspects of fertility treatments
- Risks of delaying cancer treatments
- Likelihood of success of FP options
- Potential risks of FP treatments
- Treatment costs
- Disposition of human reproductive material / posthumous use
- Alternative fertility options (oocyte donation, gestational carriers, surrogacy, adoption)

Conclusions

- Embryo or oocyte cryopreservation are good options for female oncology patients who wish to preserve fertility prior to cancer treatments
- Cryopreservation does not guarantee that patients will be able to have children after their treatment
- Cryopreservation is unaffordable or impractical for some patients
- Further studies are needed to gather better long-term data on outcomes and safety, although current research is reassuring

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