Fertility Preservation Options for Cancer Patients

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In compliance with accreditation, we require the following disclosures to the session audience:

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• Provincial programs
  • Provincial contracts (Ontario)
  • Provincial medical services (Quebec)
  • Tax credit (Manitoba)

• Fertile Future ($3000 female $350 male)

• IVF clinic discounts

• Pharmaceutical support (compassionate medications)

• Funding initiatives
  • The Walking Egg (2010)  www.thewalkingegg.com  (Collaboration with ESHRE and WHO)
  • Friends of Lo-Cost IVF (2011)  www.freindsoflcivf.org
Overview

- Male cancer patient
- Female cancer patients
  - Assessment of fertility
  - Impact of cancer treatments
  - Fertility preservation options
Number of Cancer Survivors Increasing

Canadian Cancer Statistics 2019 – Canadian Cancer Society
Overview

- Male cancer patient
- Female cancer patients
  - Assessment of fertility
  - Impact of cancer treatments
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Chemotherapy in Male

- Common for patients to present with oligo/azospermia (fever-related, or direct effect)

- Gonadal dysfunction 70-98% depending on follow-up period\(^1-5\)
  - Azoospermia and oligospermia – epithelial effect
  - Loss of Leydig cell function will result in hypogonadism but uncommon

- Azospermia from HL and NHL can regain spermatogenic capacity at varying times (keep testing)

References:
Chemotherapy in Male

- Compared with siblings, cancer survivors are approximately 50% more likely to be infertile > 5 years following treatment (CCSS studies)\(^6\)

- Over 60% survivors achieve fatherhood without IVF/ICSI\(^9\)

- Elevated risk of fetal malformation for up to 2 years following chemotherapy\(^{10}\)

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Most established fertility preservation technique for men supported by large cohort studies

ASCO recommends sperm cryopreservation prior to initiating cancer treatment

- Recommend 3 samples separated by 48 hours of abstinence, with each ejaculate in multiple straws

Loren AW et al. *J Clin Oncol*;epub

Overview

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Infertility distress can affect overall mood and PTSD\textsuperscript{1}

- Psychological stress level of infertility ranks with that of cancer\textsuperscript{2}
- Lack of knowledge about their own reproduction and existing reproductive technologies
- 75% of childless cancer patients want children in the future\textsuperscript{3,4}

Goals of Fertility Preservation

▷ Hope for motherhood

▷ Increased probability of pregnancy in future

▷ In terms of the cancer
  • NOT affect cure
  • Positive distraction
Overview

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Fresh Own Egg IVF Success by Age

CDC/SART Assisted Reproduction Technologies 2015 National Summary Report

Pregnancies
Live births
Single-infant live births
Impact of chemotherapy

**Graph 1:**
- X-axis: Age (years)
- Y-axis: Follicle Number
- Key events:
  - Birth
  - Optimal fertility
  - Decreased fertility
  - End of fertility
  - Irregular cycles
  - Menopause

**Graph 2:**
- Pre-chemotherapy follicle number curve
- Post-chemotherapy follicle number curve
- Key events:
  - Chemotherapy intervention
  - End of fertility
  - Menopause
Ovarian Reserve Testing

- Estimate risk of ovarian failure from cancer treatment
- Counseling on the impact of treatment on reproductive lifespan
- Estimation of the yield of eggs with ovarian stimulation/IVF
- Determine gonadotropin dose required to achieve an optimal egg yield
- Determine accessibility of ovaries for egg retrieval procedure (ultrasound)
• Pituitary gonadotropin closely linked to ovarian reserve and egg quality

• MSP-insured

• Low in the early follicular phase

• Often used for predicting IVF success rates
  - Pregnancy OR 0.58 when ≥ 10 IU/L\(^1\)
  - Sensitivity 7% and PPV 90+%\(^2\)

• Performed early follicular phase by transvaginal ultrasound

  Antral follicle = 2-9 mm

  Normal values: 4-10 per ovary

• Declines with age

  Before age of 37: 4.8% per year
  After age of 37: 11.7% per year

• Valuable screening tool for IVF

Testing Ovarian Reserve - Antimullerian Hormone (AMH)

- Secreted from granulosa cells of growing follicles
- AMH is the “follicular gatekeeper” that limits the size of the cohort available to respond to pituitary gonadotropins each month\(^1\)\(^-\)\(^2\)
- Cycle day independent – dominant follicle and corpus luteum do not secrete
- Best screening test for ovarian response for predicting ovarian response and monitoring of reserve after treatments and over time

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Gonadotoxicity of Chemotherapy

- **Ovarian Failure** (10-30%)
- **Temporary Amenorrhea** (60%)

Key Points:
- **S phase specific**
  - Antimetabolites, Topoisomerase II inhibitors
- **M phase specific**
  - Antimicrotubule agents, Topoisomerase II inhibitors

**Chemotherapeutic Agents**
- Alkylating Agents
- Antitumor Antibiotics

**Cell Cycle Phases**
- $G_1$, $S$, $G_2$, M

**Pathways**
- Primordial follicle pool
- Small Preantral
- Large Preantral
- Small Antral
- Large Antral
- Preovulatory

**Markers**
- AMH
- FS (Follicular Stimulant)
Overt ovarian insufficiency

Immediate Premature Ovarian Failure (prior to age 40)

Occult ovarian insufficiency

Regular cycles

Infertility

Early ovarian failure (prior to age 40)

Menopause = no period >12 months = Sterility

Ovarian Failure Risk by Cytotoxic Agent

Highest risk with alkylating agents
- Cyclophosphamide $>4000\,\text{mg/m}^2$
- Ifosfamide $>16,000\,\text{mg/m}^2$
- Nitrosoureas (CCNU, BCNU) $>300\,\text{mg/m}^2$
- Melphalan $>40\,\text{mg/m}^2$
- Busulphan $>300\,\text{mg/m}^2$
- Procarbazine $>4000\,\text{g/m}^2$

Damario et al, 2001
Dose-Dependent Effect of Cyclophosphamide

Meirow et al. (1999)
Ovarian Failure in Childhood Cancer Survivor Studies (CCSS) Survivors vs Siblings

• Multicenter study
• 20,000 pediatric oncology patients treated between 1970 - 1986
• Survived at least 5 years
• Retrospective questionnaire-based study looking at incidence and severity of chronic health conditions in survivors compared to siblings

13-fold increase in rate of POF

Green et al. JCO 2009;27(14):2374
• International Breast Cancer Study Group

• $n = 1407$ premenopausal women randomized to no/low or high intensity chemotherapy

• Assessed at 5 and 10 yr

• OR for temporary amenorrhea 1.96 $p<0.0001$

• OR for premature menopause 2.03 $p<0.0001$
Unique large study of adult survivors

Retrospective cohort study

Cancer diagnosis between 1981 and 2012 in Scotland

Aged 39 or less at diagnosis

n = 23,201 total

n = 10,271 not pregnant prior to diagnosis compared to matched control group from general population

Anderson et al. Hum Reprod 2018;33(7)1281-1290
Impact of Cancer – Population-based analysis

- 38% less likely to conceive (SIR 0.62 for pregnancy 95% CI: 0.60-0.63)

- Consistent across all ages and cancer types

- Marked reduction with breast, cervical, CNS and leukemia

- No increased risk of:
  - SAB
  - Stillbirth
  - TAB

Anderson et al. Hum Reprod 2018;33(7)1281-1290
Fertility after ABVD for Lymphoma

N = 30
Age 24 ± 4.7 years
• n=250 breast cancer patients
• Aged 18-39 years
• Adjuvant/neoadjuvant chemotherapy
• Slow recovery AMH in 45%
• 92.4% rate amenorrhea
Predictive Model for Ovarian Failure

98% sensitivity for amenorrhea/ovarian failure
80% specificity

Anderson et al. JCEM 2011;96(5):1336-1343
Radiation Effects on the Ovary

• Causes widespread DNA damage via free radical production within field
  
  Necrosis, apoptosis, DNA damage, mutations, carcinogenesis

• Ovaries can be damaged by direct or indirect radiation through abdominal, pelvic, TBI or craniospinal radiotherapy

• Ovarian follicle very sensitive to ionizing radiation

• Over 80% of women receiving pelvic radiation or BMT experience amenorrhea

• Effect on fertility varies according to:
  
  Dose received by ovaries
  Number of follicles present at the time of treatment
Radiation Effect on Ovary - CCSS

Survivors With AOF (%)

- 0-12 yr
- 13-20 yr

Minimum Dose of Radiotherapy to the Ovaries (Gy)

(909) (373) 0
(858) (343) 0.01-0.99
(187) (11) 1.00-9.99
(69) (24) 10.00-19.99
(64) (33) ≥ 20.00

AOF = Acute Ovarian Failure

Green et al, J Clin Onc 2009, 27, 14, 2374
ESD: dose of fractionated radiotherapy [Gy] at which premature ovarian failure occurs immediately after treatment in 97.5% of patients

Predicting age of menopause after TBI

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Radiation Effect on the Uterus

Uterus affected by doses as low as 5 Gy

• Decreased uterine volume and uterine vasculature
• Lower likelihood pregnancy
• Increased risk pre-term labour, low birth weight and positional abnormalities for fetus
• Effects more pronounced with prepubertal exposure

Overview

- Male cancer patient
- Female cancer patients
  - Assessment of fertility
  - Impact of cancer treatments
  - Fertility preservation options
Fertility Preservation Options

Optimize future natural fertility

- Surveillance - ovarian reserve testing
- Interval pregnancies
- GnRH/LHRH agonist

Optimize future fertility treatment outcomes

- Oocyte cryopreservation
- Embryo cryopreservation
- Ovarian tissue cryopreservation
GnRH/LHRH agonists

Reduction in amenorrhea rates noted in patients using as adjuvant therapy

▷ Hypogonadotrophic hypogonadal state and ovarian quiesance¹

▷ Reduction of ovarian blood flow²

▷ Direct effects via ovarian GnRH receptors³,⁴

GnRH agonist for Ovarian Function Preservation
Meta-analysis

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<td>Del Mastro et al, 2011</td>
<td>88</td>
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<td>Munster et al, 2012</td>
<td>23</td>
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<td>Song et al, 2013</td>
<td>53</td>
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<td>Elgindy et al, 2013</td>
<td>41</td>
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<td>Moore et al, 2015</td>
<td>61</td>
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<td>Total</td>
<td>435</td>
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Heterogeneity: $\tau^2 = 0.28$, $X^2 = 14.13$, $df = 6$ ($P = .03$); $I^2 = 58\%$

Test for overall effect: $Z = 3.16$ ($P = .002$)

Assisted Reproductive Technologies
Oocyte Retrieval
Requires ovarian stimulation

Most established fertility preservation technique for women with cancer

Requires sperm

Millions of babies born world-wide
Birth outcome rates

ART cycles using FET – own oocytes, 2015

- Ongoing clinical pregnancy
- Live birth
- Singleton live birth
- Live birth

Percent per ET cycle (%)

Age at time of oocyte retrieval (years)

- <35
- 35–37
- 38–40
- 41–42
- ≥43

- 84.1% cSET
- 77.1% cSET
- 62.1% cSET
Oocyte Cryopreservation

- Requires ovarian stimulation
- No sperm required
- Lower pregnancy compared to embryo cryopreservation
- Fewer than 100,000 babies born of this technology (mostly DE)
How many eggs should we freeze?

Achieving a 75% LBR
- Age 34 - 10 eggs
- Age 37 - 20 eggs
- Age 42 - 61 eggs

N = 520

Concerns with IVF in Cancer Patients

▶ Estrogen is carcinogenic

▶ Conventional IVF raises estrogen levels 10-fold

▶ VTE not a significant risk with ovarian stimulation but potentially is in hypercoagulable states like cancer

▶ Ovarian Hyperstimulation Syndrome (OHSS)

▶ No increase in breast cancer recurrence in short-term observational studies

3. Love et al. JCO 2008;26:253
Fertility Preservation Protocol for IVF

Consultation
GnRHa
GnRH Antagonist

GnRHa
Antagonist
Retrieval

FSH
LH/hMG

Letrozole 7.5 mg daily

Natural Cycle
IVF Cycle

E2
P4
A RETROSPECTIVE STUDY ON THE USE OF DOSE-DEPENDENT LETROZOLE AIMING TO REDUCE CANCER GROWTH / RECURRENCE AND ADVERSE EVENTS IN PATIENTS UNDERGOING OVARIAN STIMULATION

Breast  77  73.3
Lymphoma  13  12.4
Cervical  5  4.8
Colon  2  1.9
Endometrial  2  1.9
Ovarian  2  1.9
Rectal  1  0.9
Rhabdomyosarcoma  1  0.9
Appendiceal  1  0.9
Brain  1  0.9

# mature eggs  NS
FSH dose  NS
Cycle length  NS

Rahana et al. F&S 2019;111(4):e51-e52
Ovarian Tissue Freezing

- No stimulation required
- Can be done any time during the cycle
- Potential to restore fertility and hormones
- Requires surgery - laparoscopy
Ovarian Transplantation - Outcomes

- 60+ pregnancies reported to date
- One reported BRCA patient
- Largest series in monozygotic twins (7 pregnancies) for POF not cancer and fresh transplants
- No pregnancies to date from whole ovary transplant

Silber et al. Hum Reprod 2008;23(7):1531-1537
Ernst et al. Hum Reprod 2010 Advanced Pub
Sanchez-Serrano et al. Fertil Steril 2010;93(1)
Pregnancy Outcomes in Cancer Survivors

- No increased risks of congenital malformations, genetic diseases, malignant neoplasms in children born to cancer survivors remote from therapy\(^1-3\)

- Limited evidence of increased risk of pregnancy loss after chemotherapy

- Radiotherapy associated with pregnancy complication

- Safe interval between chemo and oocyte/embryo cryopreservation unknown:
  - Human pregnancy outcome for more recent exposures unknown, animal data suggest increased risk of SAB/birth defects\(^5\)

Patient should be made aware of fertility preservation options at diagnosis

All chemotherapy appears to impact ovarian reserve

Consider pre-chemo GnRHa downregulation

Time permitting consider egg and embryo cryopreservation

To achieve a 75% live birth rate with egg freezing:

- Age 34 – 10 eggs
- Age 37 – 20 eggs
- Age 42 – 61 eggs
Take Home Message

- Ovarian tissue transplantation remains experimental
- Ovarian stimulation appears to be safe but aromatase inhibitors should be considered to reduce exposure to estrogen in women with breast cancer
- Pregnancy appears safe for cancer survivors following appropriate medical assessment