Fertility Preservation – Building the Bridges

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McGill University Health Center
Director, REI Division, Dept. of Obstetrics & Gynecology
McGill University
Fertility preservation

• Malignant diseases are common: 2013, 805,500 women diagnosed with cancer in the U.S. (National Cancer Institute: http://seer.cancer.gov/statfacts)
• Survival rates are increasing (Blatt 1999, Armenian et al Pediatr Blood Cancer 2012,)

• Chemotherapy:
  • Destruction of growing follicles
  • Loss of primordial follicles
    • Loss of local regulatory factors
    • Accelerated recruitment of primordial follicles.
    • Decreasing ovarian reserve
Fertility preservation

Indications:

- Cancer patients before gonadotoxic treatment
- Other diseases before gonadotoxic treatment
- Young patients with Turner syndrome, Fragile X pre-mutation (FMR 1), Galactosemia
- Endometriosis?
- Women in mid-thirties without partner
Options for fertility preservation

Should be tailored according to:

• Patient’s age
• Type of disease
• Spread of the disease
• Planned treatment
• Time available
• Whether she has a partner

(Holzer et al Gyn Min 2005)
Options for fertility preservation

• Ovarian protection:
  • Ovarian shielding
  • Ovarian transposition prior to local radiotherapy (Bishara M Tulandi T 2003)

• GnRH analog may have a protective effect
  • Higher rates of resumption of menses and ovulation
  • No improvement of pregnancy rates (Bedaiwy 2010)

• The final conformation is still awaited.
AS101: Immuno-modulatory compound
Fertility preservation?

(Kalich-Philosoph et al Sci Transl Med 2013)
Cryopreservation for Fertility Preservation
Options for fertility preservation: Cryopreservation of ovarian tissue

- Available for pre- and post-puberty patients
- Hundreds to thousands of primordial follicles may be preserved.
- No medical delay, no ovarian stimulation
- Does not require a male partner
- At least 2 surgical procedures (+ IVF)
- Loss of follicles, absence of inhibitory mechanism?
- 24 live births reported (Donnez et al Fertil Steril 2013)
- Theoretic risk of neoplastic cells in transplanted tissue – recurrence (Bittinger 2011, Dolmans 2010, Meirow 2008)
- BRCA 1&2 carriers - potential of developing ovarian cancer (Colgan 2001)
Embryo and oocyte cryopreservation

• **Embryo:**
  - live birth rates 15-38% per embryo transfer, depending on the age at the time of oocytes retrieval.
  - Post pubertal patients.
  - Partner required, donor sperm?

• **Oocyte:**
  - 1st live birth 1986 (Chen et al)
  - 1986-1997: 5 live births
  - Tremendous improvement
  - Oocyte vitrification and warming should no longer be considered experimental. *(ASRM practice committee guidelines 2013)*
Embryo or oocyte cryopreservation after ovarian stimulation

• Pregnancies reported are the result of collection after ovarian stimulation
  • Time interval needed for conventional COH: two weeks, starting during menstruation
  • Ovarian stimulation associated with high estrogen levels.
Random start COH +/- aromatase inhibitor


• Conventional, late follicular, luteal, similar:
  • Oocytes yield
  • Mature oocytes yield
  • Maturation rate
  • Fertilization rate *(Cakmak et al Fertil Steril 2013)*

• Aromatase inhibitor + FSH:
  • Similar oocyte yield
  • Similar fertilization rate
  • No increased risk of relapse *(Oktay et al JCEM 2005, Johnson et al RBM Online 2013,Cakmak et al Fertil Steril 2013)*

• Does not totally avoid stimulation.
• Delay ≈ 10 days
Vitrification of IVM oocytes

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>20</td>
</tr>
<tr>
<td>Mean age</td>
<td>30.7 ± 3.7</td>
</tr>
<tr>
<td>No. of mature oocytes retrieved</td>
<td>7</td>
</tr>
<tr>
<td>No. of immature oocytes retrieved</td>
<td>295</td>
</tr>
<tr>
<td>Mean oocyte maturation rate (%)</td>
<td>67.9 ± 4.1</td>
</tr>
<tr>
<td>No. of oocytes vitrified and thawed</td>
<td>215</td>
</tr>
<tr>
<td>No. of oocytes survived (mean % ± SEM)</td>
<td>148 (67.5 ± 5.8)</td>
</tr>
<tr>
<td>No. of oocytes fertilized (mean % ± SEM)</td>
<td>96 (64.2 ± 4.5)</td>
</tr>
<tr>
<td>No. of embryos transferred (median; range)</td>
<td>64 (3.2; range 1 - 6)</td>
</tr>
<tr>
<td>No. of implantations (mean % ± SEM)</td>
<td>5 (10.3 ± 5.7)</td>
</tr>
<tr>
<td>No. of clinical pregnancies (%)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>No. of live births (%)</td>
<td>4 (20)</td>
</tr>
</tbody>
</table>

Holzer et al ESHRE 2007
Oocyte aspiration from excised ovarian tissue

(Huang, et al Fertil Steril 2007)
Fertility preservation strategies offered at McGill Fertility Preservation Center

Chemotherapy can be delayed and hormonal stimulation not contraindicated

IVF Treatment

Chemotherapy cannot be delayed and/or hormonal stimulation should be avoided

In-vitro maturation of oocytes

Collection of immature oocytes from ovarian tissue

Laparoscopic ovarian tissue resection

Ovarian tissue cryopreservation

Mature oocytes

Male partner

Embryo vitrification

No male partner

Oocyte vitrification
McGill Fertility Preservation Center: Catchment Area

- Greater Montreal
- Quebec
- Other Canadian provinces
- Physicians: Oncology, Haematology, Radiation Oncology, Surgery, Paediatrics.
- Nurses: nursing coordinators.
- Non-medical professionals, self referrals
### Counselling

<table>
<thead>
<tr>
<th>Initial contact designated secretary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
</tr>
<tr>
<td>Schedule</td>
</tr>
</tbody>
</table>

### Appointment at the fertility preservation center

<table>
<thead>
<tr>
<th>History taking (Fellow)</th>
<th>Ultrasound (AFC, cycle stage)</th>
</tr>
</thead>
</table>

### Consultation review of all options, tailored options

<table>
<thead>
<tr>
<th>GnRH analog</th>
<th>Ovarian tissue</th>
<th>Oocyte (IVF/IVM)</th>
<th>Embryo (IVM/IVM)</th>
<th>Do nothing</th>
<th>3rd party</th>
</tr>
</thead>
</table>

### Nursing consultation

<table>
<thead>
<tr>
<th>Discuss and teach planned treatment</th>
<th>Draw blood tests</th>
<th>Feedback to physician</th>
</tr>
</thead>
</table>

### Treatment

<table>
<thead>
<tr>
<th>Oocyte CP</th>
<th>Embryo CP</th>
<th>Ovarian tissue CP</th>
<th>GnRH-a</th>
<th>Follow up</th>
</tr>
</thead>
</table>

### 2nd collection

<table>
<thead>
<tr>
<th>Luteal collection</th>
<th>Additional cycle</th>
</tr>
</thead>
</table>

### Long term follow up

<table>
<thead>
<tr>
<th>US (AFC)</th>
<th>FSH AMH</th>
<th>Consultation</th>
<th>Counselling</th>
</tr>
</thead>
</table>
### Fertility Preservation for Cancer Patients (April 2003 - July 2013)

<table>
<thead>
<tr>
<th>Vitrified</th>
<th>Patients</th>
<th>Cycles</th>
<th>Oocytes</th>
<th>Embryos</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVM oocyte</td>
<td>99</td>
<td>107</td>
<td>757</td>
<td></td>
</tr>
<tr>
<td>IVM embryo</td>
<td>68</td>
<td>79</td>
<td></td>
<td>340</td>
</tr>
<tr>
<td>IVM oocyte/embryo</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>168</strong></td>
<td><strong>187</strong></td>
<td><strong>768</strong></td>
<td><strong>346</strong></td>
</tr>
</tbody>
</table>

**12 patients, 4 live births, 1 ongoing pregnancy**

| IVF oocyte              | 88       | 91     | 1002    |         |
| IVF embryo              | 39       | 41     |         | 248     |
| IVF oocyte/embryo       | 5        | 5      | 34      | 30      |
| **Total**               | **132**  | **137**| **1036**| **278** |
4 patients had oocyte cryopreservation due to Endometriosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age(y)</th>
<th>Stage</th>
<th>AFC</th>
<th>Cycle</th>
<th>Total GT dose(IU)</th>
<th>Collected Oocytes</th>
<th>MII</th>
<th>Total vit</th>
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<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>IV</td>
<td>3</td>
<td>1</td>
<td>4050</td>
<td>8</td>
<td>4</td>
<td>21</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>7200</td>
<td>5</td>
<td>4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>4800</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>IV</td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
<td>28</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>N/A</td>
<td>24</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>3 cm susp. endometrioma</td>
<td>17</td>
<td>1</td>
<td>2400</td>
<td>9</td>
<td>8</td>
<td>26</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>2</td>
<td>2175</td>
<td>22</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>IV</td>
<td>9</td>
<td>1</td>
<td>7050</td>
<td>11</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Patient</td>
<td>Total frozen Oocytes</td>
<td>Thawed oocytes</td>
<td>Oocytes survived</td>
<td>Oocytes fertilized</td>
<td>Embryos cleaved</td>
<td>Embryos transferred</td>
<td>Pregnancy</td>
<td>Live birth</td>
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<td>-------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>P-1</td>
<td>21</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2*</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P-2</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>3**</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>P-2</td>
<td>41</td>
<td>12</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>1***</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P-3</td>
<td>26</td>
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<td>-</td>
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<td>-</td>
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<td>-</td>
</tr>
</tbody>
</table>

*add. embryo from a fresh cycle **cleavage ***blastocyst
Oncofertility in Canada

- 4250 Reproductive age females (20-39) are diagnosed with cancer every year in Canada. Yee et al. JOGC 2012
- A small fraction of these are referred for fertility preservation every month.
- Most fertility clinics: monthly referrals ranged from 0 to 2. Yee et al. Eur J Cancer Care 2013
- Referral for female fertility preservation for young women with cancer in Canada is remarkably low.
Information gap

• Lack of medical team-to-patient information transmission is a significant contributor to patients being unable to make choices regarding fertility preservation. Rosen et al. Semin Oncol Nurs 2009

• Professional organizations: patients often feel oncologists are not attentive to their fertility needs, do not inform them of available options, or do so in a way that is not conducive to information and resource transmission. Ethics committee – ASRM. Fertil Steril 2005
Information gap

- Knowledge deficit with the oncology community
- Unaware of resources available
- Unaware of the increased success rates with fertility preservation techniques
  
  Woodruff et al Nat Rev Clin Oncol. 2010

- Pilot project of patient education and referral system: increased the number of consultations with fertility specialists 9-fold
  
  Quinn et al J Natl Compr Canc Netw. 2011
Assisted Human Reproduction Canada (AHRC): Oncofertility in Canada, an Overview and Action Plan

Ruth Ronn, Hananel Holzer
Oncofertility in Canada
An Overview and Action Plan

Ruth Ronn, Hananel Holzer
Oncofertility in Canada
An Overview and Action Plan

• Build a nation wide on-line referral system to local fertility preservation facilities.
• Establish a national data base reference of fertility preservation referrals.
• Establish concrete resources for both patients and physicians on fertility preservation.
• Build the bridges of communication and resource sharing required to bring translated knowledge together to the patient, physician and fertility clinics.

Ronn & Holzer. Curr Oncol 2013
- CKN: portal at the intersection of key target populations in the Canadian cancer community – patients, medical professionals and caregivers.

- integrative network
- Fertility Preservation referrals
- resource-based collaborative program
- efficient
- time sensitive

KEY STAKEHOLDERS

- Patients, Families
- Fertility Clinics, Fertility Foundations and Advocacy Groups
- Medical Professionals, Researchers, Health Insurance Programs and Health Policy Makers

The OncoFertility Referral Network

www.cancerkn.com
Role of the Scientific Advisory Board:
The Scientific Advisory Board will act as a medical and scientific consulting group to ensure a system of collaboration between the medical professional community and the fertility community is maintained and shares best practices and research.

- **Dr. Hananel Holzer** - *Lead Medical and Scientific Advisor, CKN Oncofertility Referral Network*, Director REI Division Department of Obstetrics and Gynecology McGill University
- **Samantha Yee**, Co-Editor CKN OFRN Content, Social Worker, Centre for Fertility and Reproductive Health (CFRH), Mount Sinai Hospital. University of Toronto.
- **Dr. Aaron Jackson**, Co-Editor CKN OFRN Content, Ottawa Fertility Centre & Dept of OB/GYN, Division of Reproductive Medicine, Assistant Professor – University of Ottawa, President- Fertile Future
- **Dr. Karen Glass**, CReATe Fertility Centre, Assistant Professor at University of Toronto, Immediate Past Chair of the Fertility Preservation Special Interest Group of the ASRM
- **Dr. Janet Takefman**, Director of Psychological Research & Services, McGill University Health Centre Reproductive Centre (MUHCRC)
- **Dr. Jeffrey Roberts**, Co-Director Pacific Centre for Reproductive Medicine
- **Dr. Togas Tulandi**, Academic Vice Chairman of Obstetrics and Gynecology McGill University
- **Dr. Ruth Ronn**, Department of Obstetrics & Gynaecology, Queen’s University
- **Dr. Ronald Barr**, Professor, Pediatrics, Pathology and Medicine McMaster University
- **Dr. Keith Jarvi**, Division of Urology, Mount Sinai Hospital
- **Dr. Peter Chan**, Associate Professor, Urology, McGill University, Montreal, Quebec
- **Dr. Ellen Greenblatt**, Medical Director for the Centre for Fertility and Reproductive Health (CFRH), Mount Sinai Hospital, Associate Professor, University of Toronto
- **Sherry Levitan**, B.Sc., LL.B. Ms Levitan’s current practice is in Toronto, Canada and is focused on third party reproductive technology.
- **Dr. Chantal Seguin**, Assistant Professor, Department of Medicine, Division of Experimental Medicine, McGill Faculty of Medicine
Oncofertility Referral Network (OFRN)
Project development

• CKN will establish the foundations for communication, and creating a collaborative educational platform for patients, physicians and fertility clinics.

• A targeted, campaign to reach patients, physicians, medical professionals providing full access to educational tools and resources that are part of the referral service.

• The data collected and its analysis - valuable to researchers and can assist in policy development and assessment.
Cancer is a journey...we’re with you every step of the way.

Cancer Knowledge Network (CKN) is North America's most widely read cancer education portal, providing valuable, practical resources for people living with cancer, the doctors who treat them, and the loved ones who care for them.

CKN offers a wealth of practical information, research findings, first-hand stories, and advice from those who have lived through the challenges of cancer.
Oncofertility Referral Network

Oncofertility has emerged as a new interdisciplinary approach to address the reproductive future of young men, women, and children facing a life-threatening cancer diagnosis. The CKN Oncofertility Referral Network is a nationwide platform that links patients, physicians and fertility clinics to ensure time-sensitive needs are met in providing fertility options for young cancer patients as they embark on treatment.

This network will create a multidisciplinary dialogue between patients and their medical team about fertility sparing options, offering accessible educational information and resources alongside a timely, efficient referral system to fertility specialists.

<table>
<thead>
<tr>
<th>For Physicians: Make a Referral</th>
<th>For Patients: List of Fertility Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resources for Professionals</strong></td>
<td><strong>Resources for Patients</strong></td>
</tr>
<tr>
<td>Cancer, Fertility and Motherhood</td>
<td>A Primer on Fertility Law in Canada for Cancer Survivors</td>
</tr>
<tr>
<td>CKN OFRN: Scientific Advisory Board Members</td>
<td>Cancer, Chemotherapy, and Children: A Cancer Survivor’s Personal Story Regarding Fertility</td>
</tr>
<tr>
<td>Current Oncology: Oncofertility in Canada Series</td>
<td>Developing a Program for Adolescents and Young Adults (AYA) with Cancer</td>
</tr>
<tr>
<td>Effect of cancer on ovarian function in patients undergoing in vitro fertilization for fertility preservation: a reappraisal</td>
<td>Female Sexuality Issues Post Cancer Treatment</td>
</tr>
</tbody>
</table>
Canadian Fertility Centers

Find a fertility center in Canada by filtering by province or find the closest locations by searching by postal code.

Alberta (1)  British Columbia (3)  New Brunswick (1)
Nova Scotia (1)  Ontario (15)  Quebec (2)
Refer a patient: The Toronto Centre for Advanced Reproductive Technology Ltd. (TCART)

The Toronto Centre for Advanced Reproductive Technology Ltd. (TCART) offers the following services:

- Compassionate Care for Cancer Patients
- Donor Eggs (female)
- Donor Sperm (male)
- Egg Freezing (female)
- Embryo Freezing (female)
- Genetic Testing
- Gestational Surrogacy (female)
- Ovarian Suppression (female)
- Social/Psychological Services
- Sperm Banking (male)
- Testicular Sperm Extraction (male)

The Toronto Centre for Advanced Reproductive Technology is a full-service family treatment centre founded by Dr. Robert Casper, Professor, Division of Reproductive Sciences at the University of Toronto. Dr. Casper’s clinical and research efforts have won him international recognition, enabling him to assemble an exceptional team over the many years he has been working in this field. Since founding the Toronto Centre for Advanced Reproductive Technology, he has helped to conceive thousands of babies. The most advanced diagnostic and therapeutic techniques available in Canada (IVF, ICSI, pre-implantation genetic diagnosis and egg freezing) are available to our patients, sometimes in conjunction with our sister clinics throughout the world. We receive referrals worldwide due to our specific expertise and our long established track record of excellence. At the Toronto Centre for Advanced Reproductive Technology, we promise you will be comfortable and confident throughout your entire treatment experience. From the moment you begin treatment, we tailor our evaluations and services to you. Through our personalized care and cutting-edge fertility technologies, we will help guide you every step of the way. Our close affiliation with the University of Toronto provides services based on the latest research and technology. We have two young and talented naturopathic doctors at TCART who specialize in all aspects of naturopathy including nutritional guidance and acupuncture. We also have a staff clinical psychologist to support patients' emotional needs. The science of reproductive medicine is constantly
Conclusions

• Patients should be consulted regarding the options for Fertility Preservation

• Some of the current options of fertility preservation should be considered as investigational.

• Others are not a guaranty for a future live birth.

• “Tailored made”, interdisciplinary approach.

• Cancer treatments should NOT be compromised.
Conclusions

• Patients are there, taken care of by the oncology community.
• Expertise are there, within the REI community.
• Referral system: quick, efficient, informative – coming.