# Building the bridges

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### McGill University Health Centre Reproductive Center



### 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 )
- Gynecological cancers: nearly 20% of the 1.6 million estimated new cancer cases (Siegel R, 2014. CA Cancer J Clin 2014)
- Survival rates are increasing (Blatt 1999, Armenian et al Pediatr Blood Cancer 2012)



- Destruction of growing follicles
- Loss of primordial follicles
- Ovarian atrophy



#### Chemotherapy : Direct and indirect damage

cortex

Apoptosis



in vivo studies do not show signs of apoptosis in oocytes or granulosa cells of dormant primordial follicles



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(Meirow et al. Hum Reprod 2007)



- Loss of local regulatory factors
- Accelerated recruitment of primordial follicles.
- Decreasing ovarian reserve

# Cyclophosphamide treatment of mice ovaries:



(Kalich-Philosoph et al Sci Transl Med 2013)



- Alkylating agents:
  - Cyclophosphamide, ifosfamide, nitrosoureas, chlorambucil, melphalan, and Busulphan
  - not cell-cycle specific, highest risk of ovarian failure.
- Antimetabolites
  - methotrexate, bleomycin, 5-fluorouracil, actinomycin-D, mercaptopurine, vincristine)
  - impact the cells of the metabolically active ovarian follicles , are considered to be low risk for gonadal dysfunction
- Platin intermediate risk
- Bevacizumab (avastin): potential high risk for POF (FDA warning)



- Direct damage to ovaries
- Damage to hypothalamic-pituitary axis
- Dose dependent; total dose and fractionation schedule
- Age dependent; size of primordial follicle pool
- Radiation field dependent
- Could also affect uterine function:
  - Small uterine volume
  - Impaired blood flow
  - Endometrial damage
  - M/C, low birth weight, premature deliveries. (Green et al Am J Obstet Gynecol 2002)



- For a given dose of radiation, the younger patients are, the later the onset of premature menopause.
- LD50 <2 Gy.
- The effective sterilising dose falls with increasing age:
- Effective sterilising doses : 20·3 Gy at birth, 18·4 Gy at 10 years, 16·5 Gy at 20 years, and 14·3 Gy at 30 years.
- Model to predict the age of ovarian failure after treatment with a known dose of radiotherapy. (W Hamish B Wallace, Lancet 2005, International Journal of Radiation Oncology\*Biology\*Physics 2005)



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



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)
- Goserelin with chemotherapy appeared to protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility (POEMS NEJM 2015)
- The final conformation is still awaited.

•SP-1-P? AS 101?



#### 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 (<u>+</u> IVF)
- Loss of follicles, absence of inhibitory mechanism?
- 60 live births reported 33/111 (29.7%) (Donnez 2015).
- Theoretic risk of neoplastic cells in transplanted tissue recurrence (Bittinger 2011, Dolmans 2010, Meirow 2008)



# Risk of presence of neoplastic cells in the transplanted tissue

- Other organ transplants: donor derived malignancy (Kauffman 2002, Ison 2011 AM J Transplant)
- Extreme caution is warranted before we assume that we understand tumour biology well enough to estimate the risk of transmission of malignant cells in auto-transplanted ovarian cortex.
- BRCA 1&2 carriers potential of developing ovarian cancer (Colgan 2001)
- Prophylactic BSO, transplant ovarian fragments?



- In-vitro growth and IVM of primordial follicles: 2 step culture system: culture of tissue followed by isolation of follicles and culture. Or using 3D supportive matrix. (Abir et al. Histol. Histopatho 2006 Picton et al. Reproduction 2008, Telfer et al. Hum Rep. 2008, Woodruff 2009)
- Major hurdles remain for improving culture systems to promote coordinated development of the cumulus-oocyte complex to achieve oocyte growth and the competence to produce embryos, and to attain live offspring ... (Telfer et al Fertil Stril 2013)

# Embryo and oocyte cryopreservation

#### • Embryo:

- live birth rates 15-40% 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)



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

- Random start : stimulation luteal phase, late follicular phase. (Von Wolff et al Fertil 2009, Sonmezer et al Fertli Steril 2011 2011)
- Conventional, late follicular, luteal similar:
  - Oocytes yield
  - Mature oocytes yield
  - Fertilization rate (Cakmak et al Fertil Steril 2013)
- Survival, implantation, pregnancy, and live birth rates?
- Luteal-phase ovarian stimulation: 55% pregnancy rate in frozen-thawed ET cycles (Kuange et al Fertile Sterile 2014)



# Random start COH +/- aromatase inhibitor

- 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



- IVM may be considered:
- PCOS related infertility
- other indications for ART with PCO
- over responders
- oocyte donation
- poor responders?
- failed IVF?



### Vitrification of IVM oocytes

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

Holzer et al ESHRE 2007



# Oocyte aspiration from excised ovarian tissue



(Huang, et al Fertil Steril 2007)



Fertility preservation:

- time factor
- stimulation contraindicated
- from ovarian tissue

# Fertility preservation in pre-pubertal children

- Childhood Cancer Survivor Study:
  - RR for infertility 1.48 , and 2.92  $\leq$  24
  - TTC: Survivors longer than control, 13% vs. 8% > 1year.
  - Underreporting.

(Barton et al Lancet Oncol 2013)

• Very few treatments benefit younger patients at risk of infertility after treatment

# Fertility preservation in pre-pubertal children; Ovarian tissue cryobanking

- Primary method of fertility preservation for prepubertal girls
- A 13 yo premenarcheal MDS, COS oocyte freezing. (Reichman et al Fertil Steril 2012)
- One ovary removed from 47 patients aged 0.1-14 years
- Ovarian tissue fragments frozen
  - strong inverse correlation found between age and follicular density
  - none of the cases had visible ovarian tumour components (Poirot 2007)
- 58 patients 0.8-15.8 years, underwent ovarian tissue cryopreservation.
  - 1 case of ovarian lymphoma infiltration (Jadoul 2010)

# Fertility preservation in prepubertal children: Ovarian tissue cryobanking

- 2 cases puberty was induced by re-implantation of ovarian tissue cryopreserved before puberty. (Poirot et al Lancet 2013, Ernst et al Eur J Cancer 2013)
- Animal models: puberty and fertility restored (Sauvat et al PIos One 2008)
- Xenotransplantation: High follicle survival, maintained large pool of premordial follicles, responsive to gonadotropins. (Luyckx et al Fertil Steril 2013)
- Antral follicle formation occurred post-xenotransplantation in a single ovarian fragment without exogenous hormone stimulation (Lotz et al. Reproductive Biology and Endocrinology 2014)
- Human : Fertility has not been demonstrated yet.

Number of genital cancers in the world and corresponding rates of patients eligible for fertility preservation each year.

	Number of Gynecologic Cancer in the world	Premenopaus al women (%)	Eligible women for fertility preserving with respect to stage and grade (%)	Number of women eligible for fertility preserving approach
Cervical cancer	529,800	20	48	23,000
Endometrial cancer	287,100	10–5	30–20	5400
Ovarian cancer	225,500	15–10	15	2500

Dursun, Critical Reviews in Oncology/Hematology 2014



- Cervical conization
- Simple trachelectomy
- Radical trachelectomy+laparoscopic pelvic lymphadenectomy
  - Vaginal
  - Abdominal
- Ovarian transposition

Indications for radical trachelectomy for early stage cervical carcinoma

- 1. Strong fertility desire
- 2. Age <40 years
- 3. Proven diagnosis of invasive cervical cancer; ideally, disease located primarily on the ectocervix
- 4. Stage la1 with LVSI, la2, lb1
- 5. Tumor size <2 cm
- 6. Limited endocervical involvement can be exactly determined by colposcopic examination and/or MRI
- 7. No evidence of pelvic lymph node metastasis and/or other distant metastasis
- 8. Exclusion of unfavorable histology (e.g., neuroendocrine carcinoma)
- 9. Gynecologic oncologist who has an experience in laparoscopic and radical vaginal surgery



Conservative options

- Grade I stage IA endometrial cancer
- Endometrial atypical hyperplasia with well differentiated endometrioid pattern
- High-dose oral progestins\* +ART
- No standard recommendations for patients selection, treatment protocols, long-term follow up (Rackow, Obs & Gyn 2006)
- Fertility-sparing management should not be contraindicated in older patients with previous infertility or obesity (Koskas, Fert. Steril. 2014)



- Young women who desire to preserve their fertility
- Fertility saving surgery: early-stage and low-grade disease (Ayhan A, Eur Jo of Gyn Onc. 2003)
- Selection: stage, grade, ploidy state, histological subtypes
- Stage IA Grade 1 (?2)
- TAH BSO vs. UL SO: 5y survival rate similar , recurrence rate 9% and 11.6% respectively.

(Zanetta Brit J of Obs & Gyn 1997, Schilder JM, Gyn On 2002, Colombo N,2006, Dursun, Critical Reviews in Oncology/Hematology 2014)

• Early stage high grade? (Ditto A, Gyn Onc. 2015)

### Border-line ovarian tumors

- Conservative surgery
- Ovarian cystectomy or unilateral oophorectomy
- Risk of relapse after ovarian stimulation is 19.4% (12/62 patients)
- Live birth rate 28%

(Denschlag D, Gyn & Obs Inv. 2010)

• Rate of new lesion/recurrence is relatively high, mortality remains low. Many patients are able to conceive after conservative surgery

(ACOG, Obstet Gynecol. 2000)

- Fertility preservation was not found to be associated with an increased risk of relapse in young patients with advanced disease (Helpman Fert Steril 2015)
- Referrals: new lesion/recurrence
- To puncture or not to puncture?

# malignant ovarian germ cell tumors

- Fertility sparing surgery is the standard treatment with stage I A disease.
- In more advanced disease: fertility sparing surgery is still available.
- With administration of platinium based therapies cure is possible even in advanced stage and fertility is preserved as well

(Gershenson, Clin Obstet Gynecol 2012)



## Fertility preservation strategy McGill Fertility Preservation Center

Chemotherapy can be delayed (10-12 days) and hormonal stimulation is not contra indicated:

- Ovarian stimulation
  - Oocyte cryopreservation
  - Embryo cryopreservation

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

- hCG trigger, IVM of GV oocytes
  - Oocyte cryopreservation
  - Embryo cryopreservation

Ovarian cortex harvesting:

- Follicle aspiration, IVM
  - Oocyte cryopreservation
  - Embryo cryopreservation
- Ovarian tissue cryopreservation





### 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





#### Fertility preservation Embryo and oocyte cryopreservation Stimulated and non-stimulated cycles 2004-2013





Fertility preservation Embryo and oocyte cryopreservation Stimulated and non-stimulated cycles 2004-2013

Type of	No. patients			Age (years)			AFC		
Cancer	IVF	IVM	P Value	IVF	IVM	P Value	IVF	IVM	P Value
Hematologic	60 (40.8%)	35 (19.9%)	P < 0.0001 (1.7 to 4.6)	26.6±5.2	26.7±5.1	NS	15 (10-20)	21 (13- 28) <sup>J</sup>	0.02 (-10 to -1)
Breast	32 (21.8%)	115 (65.3%)	P < 0.0001 (0.09 to 0.24)	31.2±4.6	32.3±5.1	NS	12 (7-17)	17 (10-24)	0.01 (-7 to -1)
Gynecologic	18 (12.2%)	7 (4%)	0.01 (1.18 to 2.09)	29.7±5.2	28.7±7.9	NS	12 (6-15)	8 (6-16)	NS
Others	37 (25.2%)	19 (10.8%)	0.001 (1.24 to 1.99)	29.0±6.4	27.8±5.3	NS	18 (13-24)	18 (15-20)	NS

#### Stimulated cycles returning patients

Patient	Total embryos Transferred	Total ET trials	Clinical Pregnancy (healthy babies)	Gestational age	Gender and birth weight
					Boy 2150 gm
				31 weeks	Girl 1930 gm
1	5	3	2 (3)	41 weeks	Boy 2721 gm
					Girl 3885 gm
2	3	3	1 (1)	39 weeks	
3	4	2	0	-	-
4	2	1	0	-	-
	1	1	1 (1)	39 week	Boy 3630 gm
5					
6	5	2	0	-	-



# Non-stimulated cycles returning patients

Patient	Total embryo transferred	Total ET trials	Clinical Pregnancy- healthy baby	Mode of delivery	Gender and birth weight
1	2	1	0	-	-
2	9	4	1-1	Cesarean delivery	Girl 4100 gm
3	2	1	0	-	-
4	1	1	0	-	-
5	3	1	1-0*	-	-



- 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.



• 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



- 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



Ruth Ronn, Hananel Holzer

Assisted Human Reproduction Canada(AHRC): Oncofertility in Canada, an Overview and Action Plan





### 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.







#### C cancer knowledge network

#### KEY STAKEHOLDERS

Fertility Clinics, Fertility Foundations and Advocacy Groups

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

The OncoFertility Referral Network

Patients, Families

Medical Professionals, Researchers, Health Insurance Programs and Health Policy Makers



#### Concer knowledge network

#### **Scientific Advisory Board**

The Scientific Advisory Board will act as 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, Director, REI Division Department of Obs and Gyn McGill University
- Dr. Keith Jarvi Chief, Division of Urology, Mount Sinai Hospital
- Dr. Jeffrey Roberts, Co-Director Pacific Centre for Reproductive Medicine
- Sherry Levitan, B.Sc., LL.B, Toronto.
- Dr. Ellen Greenblatt, Medical Director. Mount Sinai Centre for Fertility and Reproductive Health.
- Dr. Karen Glass, Sunnybrook Health Science Centre and Women's College
- Dr. Janet Takefman, Director of Psychological Research & Services, McGill University Health Centre Reproductive Centre
- Dr. Togas Tulandi, Academic Vice Chairman of Obs and Gyn McGill University
- Dr. Ruth Ronn, Queen's University
- Dr. Peter Chan, Director of Male Reproductive Medicine McGill University
- Dr. Ronald Barr Professor, Pediatrics, Pathology and Medicine McMaster University
- Dr. Chantal Seguin, Division of Experimental Medicine, McGill University, Hematology/ Oncology, Montreal General Hospital



Project development

- Over a 2-year period the CKN *Oncofertility Referral Network* will establish the foundations for communication, and creating a collaborative educational platform for patients, physicians and fertility clinics.
- Launch of the network -awareness campaign nationwide through multiple channels.
- A targeted, audience-specific campaign to reach patients, physicians, medical professionals and clinics providing full access to educational tools and resources that are part of the referral service.
- The data collection of the CKN *Oncofertility Referral Network* and its analysis will be invaluable to researchers from a broad spectrum of disciplines and can assist in policy development and assessment .



#### **CKN Oncofertility Referral Network Home**



# 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-

#### Enter the Canadian Oncofertility Referral Network Here



Cancer Knowledge Network



#### LANDING PAGE

#### C knowledge network

Home » Oncofertility Referral Network

#### **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-preserving but fertility 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.

#### For Physicians: Make a Referral

**Resources for Professionals** 

Cancer, Fertility and Motherhood

CKN OFRN: Scientific Advisory Board Members

Current Oncology: Oncofertility in Canada Series

Effect of cancer on ovarian function in patients undergoing in vitro fertilization for fertility preservation: a reappraisal

#### For Patients: List of Fertility Clinics

**Resources for Patients** 

A Primer on Fertility Law in Canada for Cancer Survivors

Cancer, Chemotherapy, and Children: A Cancer Survivor's Personal Story Regarding Fertility

Developing a Program for Adolescents and Young Adults (AYA) with Cancer

Female Sexuality Issues Post Cancer Treatment

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Home » Canadian Fertility Centers

# **Canadian Fertility Centers**



Map c Report a map error



Home » Clinics » The Toronto Centre for Advanced Reproductive Technology Ltd. (TCART)

#### 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

#### C knowledge network

#### Sample Intake Form

Physician Info		I authorize the CANCER KNOW and disclose my personal health i Notice of Purposes, provided pur	LEDGE NETWORK (CKN) to collect, use information as outlined in the above suant to s.18(6) of PHIPA:		
lame *	Physician License Number *	Patient Name *			
Department *	Office Number *	Patient Signature (optional)			
mail *	Pager Number				
Patient Information			a		
lame *	Age *	*	Physician Name *	Physician Signature *	
lumber of Children *	Language *	physician, I have been authorized by my patient to sign this consent			
Vork Phone	Cell Phone	on his/her behalf.			
ype of Disease *	Date Diagnosed *				C
Planned Treatment *	Time Frame *	Date *	Print / PDF a copy o	f this form	

Protection Act (PHIPA)

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- Diagnosis
- Planned treatment
- Schedule
- Ovarian stimulation
- Vaginal puncture
- Communication



- 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.



- Fertility preservation is of utmost importance to patients and families of patients undergoing potentially gonadotoxic treatment
- We provide option to try to preserve fertility potential
- This hope alone may help in struggle to overcome the disease
- Patients are there, taken care of by the oncology community.
- Expertise are here , within the REI community.
- Challenge: building the bridges.

