### "Fertility Preservation in Pediatric and Adolescent Oncology"

Chris Fryer with special thanks to: Dr S Pritchard at BC Children's Hospital and Dr A Gupta at Hospital for Sick Kids

### DON'T PUT ALL YOUR EGGS (OR SPERM) IN ONE BASKET!





### Disclosure

I have no conflict of interest
No commercial interests
Nothing to disclose



### **Cures in perspective**

Ref: Ellison L Canadian cancer statistics at a glance: cancer in children CMAJ 2009;180:422-4

- Every year in BC 250+ children and young adults (<24yrs) become 5-yr cancer survivors (80% 5yr S).
- Many will have a normal life expectancy without complications.

#### For some the problem does not end there.

- Some will have recurrence of their cancer.
- Some already have sequelae of cancer and its Rx.
- Others are at risk for future health problems. e.g Fertility
- Many cured patients and their physicians are unaware of treatment related health risks.
- Newer therapies pose potential unknown problems.

### Infertility: The sword of Damocles



Dionysius (II) was a tyrant of Syracuse in 400BC. Damocles used to make comments to the king about his wealth and luxurious life. One day Dionysius turned to Damocles and said, "If you think I'm so lucky, how would you like to try out my life?" Damocles readily agreed, and so Dionysius ordered everything to be prepared for Damocles to experience what life as Dionysius was like. Damocles was enjoying himself immensely... until he noticed a sharp sword hovering over his head, that was suspended from the ceiling by a horse hair. This, the tyrant explained to Damocles, was what life as a ruler was really like. Is this true for fertility issues in the

# Oncofertility

- "Oncofertility" is a relatively new term used to describe the combined goals of curing cancer and preserving fertility.
- Fertility and pubertal development may be adversely affected by cancer treatments
- Most information on fertility in survivors is retrospective, self reported and not easy to measure.

# Estimating the Risk

- Often VERY difficult!!
  - Various cancers with various protocols with multiple agents and variable dosing leads to difficulty in risk assessment
- Gross estimates based on diagnosis, planned therapy and pre-treatment factors
- High risk situations are fairly clear, but grey zone is predominant and makes counseling difficult

## **Fertility issues**

- Infertility from cancer treatment causes more distress than de novo infertility (Schover 2009)
- Some patients choose less efficacious treatment to preserve fertility
- Double jeopardy fear of mortality and loss of genetic continuity



# Learning Objectives

- Be able to understand the mechanisms that can adversely affect fertility in survivors of pediatric and adolescent cancer.
- Describe the currently available and potential future technologies for fertility preservation in this population
- Counsel and implement fertility preservation procedures for pediatric and adolescent cancer patients

### Male and Female Fertility

Normal development and function Effects of radiation Effects of chemotherapy Monitoring function Preservation techniques Effects on pregnancy and lactation Options for the infertile

#### How does Cancer Treatment Affect Fertility?





#### ■Males

Azoospermia

Sperm is produced from puberty to late in life

Younger age more sensitive

Low testosterone

Females
 Acute Ovarian Failure
 •Premature ovarian failure
 •Ocytes fixed and decline
 with age
 •Older age more sensitive
 low hormones

### Female Fertility Normal development and function

Ovarian Functions

To produce mature oocytes (eggs)

- To produce hormones
  - Oestrodiol
  - Progesterone



### **Normal Ovarian Function**

- Females are thought to have a finite number of oocytes
- In early embryonic life- several million non growing follicles. Progressive decline thereafter
- At birth approx 2,000,000 remain
- By puberty 400,000 are left
- Menopause occurs when approx 1000 follicles remain



# Is the Ovarian Reserve still considered Finite?

- Stem cells in mouse ovaries can generate oocytes in vitro.
   When transplanted into chemotherapy conditioned adult mice they matured and could be fertilized.
- 2012- Similar studies with adult human ovarian cortical tissue shows mitotically active cells which are capable of producing human oocytes in vitro and in vivo.
- ??Can this technology be used in the future to create new human oocytes and to "wind the clock back"
   Discussed later

### Hormone production Hypothalamus-Pituitary-Ovary Axis



### Radiation to the Hypothalamic-Pituitary axis but not chemotherapy affects function

- Effect of Radiation is delayed
   18Gy to Pituitary affects inhibition of GnRH
  - Premature release of GnRH and premature puberty
     Treatment – GnRH analogs
    - (Lupron)
- >24Gy to anterior pituitary
  - Often causes gonadotrophin (LH, FSH) deficiency
    - Delayed puberty or absent menses
    - Treatment Hormone replacement (Birth Control pill)



### Radiation Effects on the Ovary



Effect of radiation on ovary may be delayed but is permanent

Radiation to the ovaries can damage hormone production.

Dose and age effect

- Acute ovarian failure (Never menstruated or menses stopped within 5 years of treatment)
- If prepubertal will not go through puberty
- Premature menopause (Cessation of menses before age 40)

Treatment by replacement therapy (birth control pills)

#### Age at menopause (ov failure) relative to dose of pelvic XRT Wallace Int J Rad Oncol Biol Phys 2005 cGy 🔶 5 yr --- 10yr 👈 15 yr 🔆 20 yr 7/22/2014

# Radiation Effects on the Ovary



Radiation to the ovaries can damage oocytes

- Oocytes are very sensitive 200cGy kills 50% of oocytes 1000cGy kills 90%
- Effect on **fertility** varies according to:
  - Increasing dose and fraction size increases risk
  - Increasing age (fewer follicles present at the time of treatment) increases risk

# Radiation Effect on the Uterus

Uterus may be damaged by doses >1000cGy
 Decreased uterine vasculature
 Decreased muscular elasticity (may need C-section)
 Decreased growth (small for gestational age)
 Positional abnormalities for fetus
 Cervical incompetence and pre-term birth

### Surgery Effect on Fertility

- Resection of ovary (primary ovarian tumour)
   Usually unilateral
- Hysterectomy (rhabdomyosarcoma)



Chemotherapy affects ovarian function both hormonal and oocytes dose/age dependant delayed effect recovery possible

- Highest risk
  - Alkylating agents
    - Cyclophosphamide
    - Ifosfamide
    - Nitrosoureas (CCNU, BCNU)
    - Melphalan
    - Busulphan
    - Procarbazine
    - Chlorambucil

  - May develop
     Acute ovarian failure
    - Temporary ovarian failure\* common Premature ovarian failure

Moderate risk

Intensive combination chemotherapy

Unknown

Newer agents

### Myelotoxic dose equivalents of alkylators

#### Green DM. Pediatr Blood Cancer 2014;61:53-67

Agent dose mg/m <sup>2</sup>	Correction factor
Cyclophosphamide	1.0
Ifosphamide	0.244
Procarbazine	0.857
Chlorambucil	14.286
BCNU	15
CCNU	16
Melphelan	40
Thiotepa	50
Nitrogen Mustard	100
Busulphan	8.823

# **Risk of alkylator Infertility**

CTX equivalent

$mg/m^2$	Male	Female
<4000	unlikely	unlikely
4000-8000	40%	30%
8000-20000	60%	50%
>20000	90%	80%

- These figures are very approximate with confidence intervals varying up to +/-15%
- Green DM Pediatr Blood Cancer 2014;61:53-67 (female data)
- Green DM J Clin Oncol 2010;28:332-9 (male data)

# How can we Monitor Ovarian Reserve?

- Menstrual History and FSH not very useful
  - By the time FSH increases ovarian failure is imminent
- Antral follicle count is useful but labour intensive

paid by MSP

Trans vaginal ultrasound



# How should we Monitor Ovarian Reserve?

#### Anti Mullerian Hormone (AMH)

- Produced by granulosa cells of immature ovarian follicles. Independent of menstrual cycle
- Declines within 5 years of menopause
- AMH is decreased in all females during chemotherapy treatment but in those who have not suffered significant ovarian damage it increases again after chemotherapy.

Can be monitored sequentially to give estimate of ovarian reserve.

Not funded by MSP – BC Bio and sent to RepoSource Fertility Diagnostics in USA cost \$150

### Fertility Preservation Females

- Ovarian Shielding prior to XRT
- Ovarian transposition
  - Within the abdomen but outside of the radiation field
- □ GnRH agonists-
  - to suppress ovarian function and possibly decrease cell death

#### Results of clinical trials controversial

- Elgindy EA Obstet Gynecol. 2013 121:78-86. no benefit
- Del Mastro L . JAMA 2011;306:269-76 benefit
- Blumenfeld Z Fertil Steril 2008;89:166-73 benefit
- Sphingosine-1-phosphate suppresses cyclophosphamide induced follicle apoptosis in human fetal ovarian xenografts in nude mice ☆Investigational: <u>Mene Y. Fertil Steril.</u>2014 Jun 30.

# Fertility Preservation - Females

You can preserve before or AFTER treatment

#### Oocyte Cryopreservation

- Historically difficult to freeze oocytes but technology has improved.
- Successful, approx 4000 live births
  - BUT-
    - Must be post pubertal
    - Oocyte stimulation and retrieval can take 4-6 weeks
    - Expensive \$5,000-10,000 per course
  - Consider after treatment if high risk of premature menopause (measure AMH and Antral follicle count).



### Fertility Preservation- Females

#### In Vitro Maturation –

Possible future consideration for prepubertal girls

- Aspiration of immature oocytes followed by maturation in vitro
- Small numbers fertilized and cryopreserved.

# Is the Ovarian Reserve still considered Finite?

studies with adult human ovarian cortical tissue shows mitotically active cells which are capable of producing human oocytes in vitro and in vivo.

- "wind the clock back" Cryopreservation of ovarian tissue Schmidt KT et al, Fertil Steril, 2011,;95:696-701
  - Cortical strips high concentration of primordial follicles
  - Still experimental but OK for pre pubertal girls



#### Human Reproduction, Vol.28, No.4 pp. 1069-1076, 2013

Advanced Access publication on January 29, 2013 doi:10.1093/humrep/des472

human reproduction

**ORIGINAL ARTICLE Reproductive endocrinology** 

#### Genetic variation may modify ovarian reserve in female childhood cancer survivors

#### W. van Dorp<sup>1,2,\*</sup>, M.M. van den Heuvel-Eibrink<sup>1</sup>, L. Stolk<sup>3,4</sup>, R. Pieters<sup>1</sup>, A.G. Uitterlinden<sup>3,4</sup>, J.A. Visser<sup>3</sup>, and J.S.E. Laven<sup>2</sup>

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Submitted on August 17, 2012; resubmitted on November 14, 2012; accepted on December 27, 2012

**STUDY QUESTION:** Are genetic polymorphisms, previously identified as being associated with age at menopause in the healthy population, associated with ovarian reserve and predicted age at menopause in adult long-term survivors of childhood cancer?

**SUMMARY ANSWER:** The CT genotype of rs1172822 in the *BRSK1* gene is associated with lower serum anti-Müllerian hormone (AMH) levels and a younger predicted age at menopause in adult survivors of childhood cancer.

# Pregnancy Outcome

#### ■ For those who do achieve pregnancy

- Previous uterine radiation
  - Increased risk of pregnancy loss, preterm delivery, Small for gestational age.
  - No increase in genetic defects
- Previous hypothalamus/pituitary radiation
  - Increased risk of pregnancy loss
- Previous chemotherapy
  - No increase in risk of pregnancy loss or perinatal problems
  - No increase in genetic defects
- Previous anthracyclines
  - Monitor cardiac function during pregnancy

### Lactation

- 2400cGy Radiation to the whole brain may interfere with normal lactation (inability to breast feed)
- Warning sign- failure of breasts to enlarge during pregnancy

### **Overall Risks to Female Fertility**

#### High Risk

Ovarian irradiation

- Hypothalamic Pituitary Irradiation
- Chemotherapy with high dose alkylators

#### Medium Risk

- Chemotherapy with alkylators at less than high dose
- Intensive combination chemotherapy
- Low risk
  - Non alkylator chemotherapy

## **Normal Testicular Function**

#### • Functions

- To produce spermatazoa
  - Spermatogonial stem cells
  - Sertoli (nurse) cells
- To produce male hormones
  - Leydig cells- produce testosterone
  - Sertoli cells produce Inhibin (regulates sperm production)



## **Male Fertility**



Sg spermatogonia

Sc primary spermatocytes

**Sd** = spermatids





- Pre-pubertal testes contain primordial germ cells that are susceptible to toxicity but do not contain mature spermatocytes
- Post-pubertal males produce 100 to 200 million sperm per day
- Ongoing mitosis allows sperm production to continue well into advanced age

# Hypothalamus- pituitary-Testis axis

- GnRH from ----- Hypothalamus stimulates pituitary to release FSH and LH
- FSH stimulates sertoli cells, sperm production and Inhibin
- LH stimulates Leydig cells to produce testosterone



### Radiation to the Hypothalamic-Pituitary axis but not chemotherapy affects function

#### □ Low dose cranial radiation (<1800cGy)

- less likely to cause precocious puberty in boys than girls
- High dose cranial radiation (2400cGy)
  - At risk for hormonal failure
  - If prepubertal failure to progress through puberty risk increases with dose
  - Treatment testosterone replacement

# RadiationEffect on the testis

#### **Testicular radiation**

Germinal epithelium (Spermatogenesis) is very sensitive to radiation



- 15cGy can impair spermatogenesis
- 350cGy can cause permanent azoospermia
- 750+cGy causes infertility in 90% of patients
- Fractionated radiation is more detrimental (as opposed to ovary since cells are dividing).
- Residual sperm may have increase fragmentation
- May have some recovery over a few years

### Chemotherapy Effects on the Testis

- Germinal epithelium (spermatogenesis) is very sensitive to chemotherapy- especially alkylating agents
  - Recovery after chemotherapy is possible.
- Leydig cells (testosterone production) are more resistant

#### Chemotherapy affects spermatogenesis delayed effect with recovery possible

The cumulative dose determines the magnitude and duration of impaired spermatogenesis

- Alkylating agents are major offending agents
  - Cyclophosphamide
  - Ifosfamide
  - Nitrosoureas (CCNU, BCNU)
  - Melphalan
  - Busulphan
  - Procarbazine
  - Chlorambucil

Combination chemotherapy lowers the dose threshold

### Surgery Adverse effects on Fertility

- Orchiectomy for testicular cancer
- Radical retroperitoneal lymph node dissection
  Dry ejaculation or ED
- Radical prostatectomy
  ED (30-80%)

# **Overall Risks to Male Fertility**

#### High Risk

- Testicular irradiation
- Hypothalamic Pituitary Irradiation
- Chemotherapy with high dose alkylators
- prostatectomy

#### Medium Risk

- Chemotherapy with Platinum Drugs
- Chemotherapy with alkylators at less than high dose
- Low risk
  - Non alkylator chemotherapy

### Investigation of Testicular Function

- Physical assessment of pubertal status
  - Development of normal secondary sexual characteristics reflects Leydig cell function
  - Testicular size reflects spermatogenesis
- Measurement of plasma hormones
  - FSH, LH, Testosterone, Inhibin B
  - High LH, Low testosterone = Leydig cell dysfunction
  - High FSH, Low Inhibin B = Impaired spermatogenesis
- Semen analysis the gold standard
  - Sperm concentration, motility, morphology, volume, fructose level, pH,

# Fertility Preservation males



- Testicular shielding or transposition during radiation
- Sperm Banking
  - Well established, successful
  - Must be Tanner 4- 5 (pubertal)
  - Often low sperm count at diagnosis
  - Should be offered to all male patients > Tanner stage 3 (especially if treatment includes alkylators or testicular radiation)
  - Consider sperm banking after completion of chemotherapy for patients at high risk of relapse

### Sperm Cryopreservation

 Human sperm has been successfully cryopreserved since the early 1950's First pregnancy: 1953

 Sperm cryopreservation can potentially preserve fertility for many patients if done prior to their undergoing cancer treatment

Very few sperm are needed to use ART – ICSI
Sperm can be stored for many years and be viable

Acts as "insurance" which may never be needed

#### Fees Sperm freezing/banking \$ 300 Subsequent samples \$ 150 Annual storage fees \$ 240 Intrauterine Insemination (IUI) Sperm Preparation \$ 300



# **Roadblocks to Sperm banking**

#### Patient factors

- Patient too unwell at diagnosis to provide sample
- Patient embarrassed or upset
- Time may need to start treatment immediately

#### Family/ Caregiver Factors

- Biases
- Caregiver education

#### System Factors

- Access to cryopreservation
- Facilities that are child/teen friendly
- Need a team approach
- Cost



### Methods of obtaining sperm

- Ejaculation
- Sperm can also be collected by vibratory stimulation, electoejaculation, needle aspiration, or open biopsy with tissue freezing



# Surgical methods

#### Surgical sperm retrieval

- For patients who are not able to produce a semen
- Involves a small incision in the scrotum and extraction of sperm from the epididymis or testis
- Sperm can be obtained pre pubertal
- Roadblocks to surgical sperm retrieval
  - Organization
    - Need to do before start chemotherapy
    - Co-ordination with cryopreservation, during day time hours
    - Must be free of radionucleotide
    - Need results of transmissable disease testing
  - <sup>•</sup> Cost -\$2000

# Surgical methods

- Testicular tissue cryopreservation (Experimental)
  - Remove a small part of the testis and cryopreserve, and, hopefully, later re-implant
  - In vitro differentiation mice only
  - Risk of transplanting malignant tissue
  - No reports of success so far
  - Not available in BC
- Not viable for pre pubertal boys

Experimental fertility preservation interventions in pre-pubertal boys: A report on preferences of teenage cancer survivors, parents, and oncologists

Principal Investigator: Armando Lorenzo Co-Principal Investigator: Abha Gupta Co-Investigators: Lillian Sung, Katherine Boydell, Kirk Lo Sub-site Investigators: Carol Portwine, Sheila Pritchard Project Coordinator: Rachel Donen



### Study on Perception of testicular biopsy

- Multicentre study of attitudes of patients, parents and health care providers towards testicular biopsy at diagnosis
  - Research
  - Possible future fertility preservation
  - Cost
- In preparation for a proposed study to biopsy and cryopreserve testicular tissue at diagnosis

### Survey Questions

#### **Baseline Assumptions**

- 50% Risk of infertility from treatment
- 1% Risk of Complications from biopsy
- 15% Chance technology develops
- \$350/year cost to store tissue family pays

#### **Parent and Survivor:**

Would you choose testicular biopsy? **Provider:** 

Would you recommend testicular biopsy?

### Results

#### **Preferred testicular biopsy**

- 110/153 (72%) parents
- 22/30 (73%) providers
- □ 52/77 (67%) cancer survivors
- Only factor: Parental income

 Some providers would not present biopsy in cases of lower risk of infertility and poor prognosis.

In contrast, parents (96%) and survivors (89%) wanted information on TBx before treatment began to ensure they had choice; no matter the factors of the case.

### Conclusions

 In the case of pre-pubertal testicular biopsy, survivors and parents want to know about testicular biopsy before treatment starts; no matter the physician's perceived risk vs benefit.

# **Psycho social considerations**

#### Pre Treatment Counseling

 Potential effects on fertility and possible fertility preservation methods should be discussed prior to treatment with patient and parents

#### Post treatment counseling

- ?Oocyte preservation for females at high risk for premature menopause or relapse
- Sperm banking for males at high risk for relapse
- Preserved gametes represent an insurance for the future but if IVF fails it represents a greater loss

# Ethics

- Informed choice for young patients
  - Is it the child's choice or the parents?
- Is it ethical to cryopreserve ovarian or testicular tissue when the technology is still considered experimental
- Assisted Human Reproductive act
   Sperm or ovum from under age 18 is only allowed for the purpose of creating a human being that is reasonably believed will be raised by the individual
- Concern regarding premature menopause may encourage pregnancy too early (measure AMH).
- Cost should it be covered by MSP?

# **Fertile Future**



- Canadian national non-profit organization
- Fertility preservation and support services to cancer patients and oncology professionals
- Cost reduction program
  - Reduced fees at affiliated fertility centres
  - Compassionate medications and hormones
  - Reimbursement
    - Females up to \$1000
    - Males up to \$350

### **Fertile Future**



- Affiliated fertility clinics in BC
  - Pacific Centre for Reproductive Medicine, Burnaby
  - Olive Fertility Centre, Vancouver
  - Genesis Fertility Centre, Vancouver
  - Victoria Fertility Centre
  - Kelowna Regional Fertility Centre

### Its too much

- Patients are too sick
- Urgency to start treatment
- So many tests to do, things to discuss
- No time
- Un-necessary stress for patient:
  - They can't afford it
  - Too sick
  - Low risk of infertility



### **Team Approach**

- Fertility preservation in children and adolescents requires a team approach
  - Oncology team (physician, social worker, nursing, family)
  - Fertility specialists
  - Endocrinology
  - Urology
  - Gynecology
  - Aministrators to facilitate proceedures
- Guidelines and Protocols

# The Bottom Line (ASCO)

 Use established methods of fertility preservation (semen cryopreservation and ooctye cryopreservation) for post pubertal children, with patient assent (if appropriate) and parental consent

 Present information on additional methods that are available for children but are still investigational (testicular and ovarian tissue cryoopreservation)

### Take Home Message 1

- Every patient deserves equal opportunity and access to INFORMATION regarding fertility preservation
- Decision to undergo procedures is optional

### Take Home Message 2

Assessing risk of infertility is difficult and depends on:

Age of exposure

Fertility reserve PRIOR to therapy

Type of exposure (dose of alkylating agent, RT)

Gender

### Keep it simple

WHO SHOULD GET THE **INFORMATION?** 

WHO SHOULD **PRESERVE?** 

### **EVERYONE UP TO THE**

# PATIENT

### Resources

- www.ayacancercanada.wix.com/resources
- Power of Hope Fertility Centres
   www.fertilefuture.ca/programs/power-of-hopefertility-centres/
- Cancer Knowledge Network
   www.cancerkn.com/oncofertility-referral-network/



