Fertility after Childhood Cancer

"Possibilities for Improving Success"

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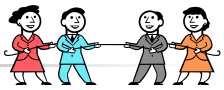
Disclosure



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

- Confession.
  - I am not:
    - An endocrinologist
    - A urologist
    - A gynecologist
    - A reproductive medicine specialist

Learning Objectives

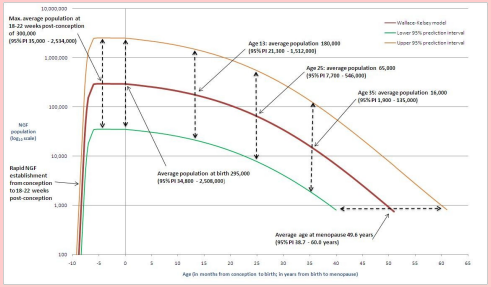
- To review mechanisms that can adversely affect fertility in survivors of childhood cancer
- To review methods of fertility prediction
- To review the currently available and potential future technologies for fertility preservation in this population

Female Oncofertility

- Ovarian Function
  - To produce mature oocytes and hormones
  - Females have a finite number of oocytes
    - In early embryonic life– several million follicles.
    - By puberty 180,000 are left
  - Healthy females will have 450 cycles over 37.5 years
  - Menopause occurs when approximately 1000 follicles remain. But fertility is usually lost 10 years before

Faddy, Human Reproduction 1996; Johnson, Nature 2004; Wallace, Cancer 2011

Follicle Population in healthy females from conception to menopause



Wallace and Kelsey, Plo S One 2010

Faddy, Gosden Hum Reprod 1996

Adverse Effects
Radiation-Effects on the Ovary

The Ovaries may be directly damaged by radiation to the abdomen, pelvis or craniospinal axis

- Oocytes are sensitive with an LD_{50} of < 2Gy.
- Causes an **increase in apoptosis** of the existing oocytes
- Effect on fertility varies according to:
  - Dose
  - Number of follicles present at the time of treatment
- May develop:
  - Acute ovarian failure
  - More commonly - Premature menopause

Sanders, Blood, 1996; Wallace, Clin Oncol 1989

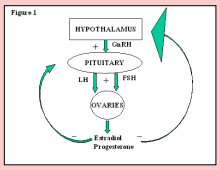
Wallace et al, Int J Radiat, Oncol Biol Phys 2005, 62(3) 738

Table 1. Predicted age at ovarian failure with 95% confidence limits for ages at treatment from 0 to 30 years and for doses 3, 6, 9, and 12 Gy

	3 Gy			6 Gy			9 Gy			12 Gy		
Age	Low	Mean	High	Low	Mean	High	Low	Mean	High	Low	Mean	High
0	31.2	35.1	39.0	18.7	22.6	26.5	9.8	13.7	17.6	4.0	7.9	11.8
1	31.3	35.2	39.1	19.0	22.9	26.8	10.1	14.3	18.5	4.8	8.7	12.6
2	31.5	35.4	39.3	19.3	23.2	27.1	10.9	14.8	18.7	5.5	9.4	13.3
3	31.6	35.5	39.4	19.7	23.6	27.5	11.5	15.4	19.3	6.2	10.1	14.0
4	31.7	35.6	39.5	20.1	24.0	27.9	12.1	16.0	19.9	6.9	10.8	14.7
5	31.9	35.8	39.7	20.5	24.4	28.3	12.7	16.6	20.5	7.7	11.6	15.5
6	32.1	36.0	39.9	20.9	24.8	28.7	13.3	17.2	21.1	8.4	12.3	16.2
7	32.2	36.1	40.0	21.3	25.2	29.1	13.9	17.8	21.7	9.1	13.0	16.9
8	32.4	36.3	40.2	21.7	25.6	29.5	14.6	18.5	22.4	9.9	13.8	17.7
9	32.6	36.5	40.4	22.1	26.0	29.9	15.2	19.1	23.0	10.6	14.5	18.4
10	32.8	36.7	40.6	22.6	26.5	30.4	15.8	19.7	23.6	11.4	15.3	19.2
11	33.0	36.9	40.8	23.0	26.9	30.8	16.5	20.4	24.3	12.1	16.0	19.9
12	33.2	37.1	41.0	23.5	27.4	31.3	17.1	21.0	24.9	12.9	16.8	20.7
13	33.4	37.3	41.2	23.9	27.8	31.7	17.8	21.7	25.6	13.6	17.5	21.4
14	33.6	37.5	41.4	24.4	28.3	32.2	18.5	22.4	26.3	14.4	18.3	22.2
15	33.9	37.8	41.7	24.9	28.8	32.7	19.1	23.0	26.9	15.1	19.0	22.9
16	34.1	38.0	41.9	25.4	29.3	33.2	19.8	23.7	27.6	15.9	19.8	23.7
17	34.3	38.2	42.1	25.9	29.8	33.7	20.5	24.4	28.3	17.0	20.5	24.4
18	34.6	38.5	42.4	26.4	30.3	34.2	21.2	25.1	29.0	18.0	21.3	25.2
19	34.9	38.8	42.7	27.0	30.9	34.8	21.8	25.7	29.6	19.0	22.0	25.9
20	35.1	39.0	42.9	27.5	31.4	35.3	22.5	26.4	30.3	20.0	22.8	26.7
21	35.4	39.3	43.2	28.0	31.9	35.8	23.2	27.1	31.0	21.0	23.5	27.4
22	35.7	39.6	43.5	28.6	32.5	36.4	23.9	27.8	31.7	22.0	24.3	28.2
23	36.0	39.9	43.8	29.1	33.0	36.9	24.6	28.5	32.4	23.0	25.0	28.9
24	36.3	40.2	44.1	29.7	33.6	37.5	25.3	29.2	33.1	24.0	25.7	29.6
25	36.7	40.6	44.5	30.3	34.2	38.1	25.9	29.8	33.7	25.0	26.5	30.4
26	37.0	40.9	44.8	30.8	34.7	38.6	26.6	30.5	34.4	26.0	27.2	31.1
27	37.3	41.2	45.1	31.4	35.3	39.2	27.3	31.2	35.1	27.0	27.9	31.8
28	37.7	41.6	45.5	32.0	35.9	39.8	28.0	31.9	35.8	28.0	28.7	32.6
29	38.0	41.9	45.8	32.5	36.4	40.3	29.0	32.6	36.5	29.0	29.4	33.3
30	38.3	42.2	46.1	33.1	37.0	40.9	30.0	33.2	37.1	30.0	30.1	34.0

Adverse Effects -Radiation
Effect on the Hypothalamic-Pituitary axis

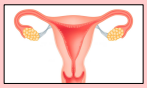
- >24Gy to anterior pituitary
  - Often causes gonadotropin deficiency
    - Delayed puberty or absent menses
- <24Gy to Pituitary affects inhibition of GnRH
  - Premature release of GnRH and premature puberty
  - At risk for ovarian failure later in life
  - At risk for pregnancy loss



Wallace, Cancer 2011

Adverse Effects
Radiation -Effect on the Uterus

- Uterus may be damaged by doses >10 Gy
  - Decreased uterine vasculature
  - Decreased muscular elasticity
  - Decreased growth and positional abnormalities for fetus
  - Cervical incompetence and pre-term birth



Bath, Br J Obst Gynaecol 1999

Adverse Effects
Chemotherapy:Effects on the Ovary

- No significant effect of chemotherapy on the
  - Hypothalamus/pituitary
  - Uterus

The ovary is chemosensitive:
- Follicular apoptosis
- Vascular shut down of ovarian cortical areas causing ischemia
  - Alkylating agents are the biggest culprits
  - Ovarian Failure does not usually happen immediately. Can take months to years

- Morse et al Pediatr blood cancer 2013

Calculation of Alkylator Equivalency

Dose equivalents of alkylators
Green DM. Pediatr Blood Cancer 2014;61:53-67

Agent dose mg/m^2	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

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Risk to Fertility based on Calculated Alkylator equivalency

Risk of alkylator Infertility

CTX equivalent mg/m²	Female
<4000	unlikely
4000-8000	30%
8000-20000	50%
>20000	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)

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Prediction
How can we Monitor Ovarian Reserve?

- Menstrual History and FSH – not very useful
- Antral follicle count is useful but labour intensive
- **Anti Mullerian Hormone**
  - Reflects total primordial follicle numbers
  - Declines within 5 years of menopause.
  - Questionable reliability in <20 year olds
  - Can be monitored sequentially to give rough estimate of ovarian reserve.
  - There are no methods to measure oocyte quality

Fertility Preservation

- Ovarian Shielding prior to XRT
- Ovarian transposition
  - Ovaries moved from radiation field to elsewhere in the abdomen
  - For patients due to receive pelvic radiation

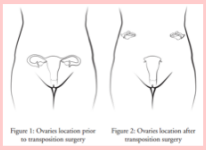


Figure 1: Ovaries location prior to transposition surgery Figure 2: Ovaries location after transposition surgery

Fertility Preservation
GnRH agonists

- GnRH agonists bind GnRH receptors in anterior pituitary. Prolonged activation disrupts the GnRH pulsatility which then downregulates secretion.
- GnRH agonists decrease vascularity in ovary thus decreasing chemo exposure
- Initial trials were disappointing but recent studies are more promising* and show benefit of GnRHa in fertility preservation in adult women.
  - Still controversial but seems to offer some protection against cyclophosphamide induced damage
- Can also be used to suppress menstruation during chemotherapy
- *Hickman Am J Obstst and gynecol Oct 2016

Fertility Preservation

- **Embryo cryopreservation**
  - Well established,
  - BUT –
    - Must be post pubertal
    - Oocyte stimulation and retrieval takes 2 weeks
    - Need a partner (or willing to use donated sperm) so not suitable for most of our patients
    - Expensive $5-10,000 per course
    - Success rate 18-25% per embryo but improving

Fertility Preservation

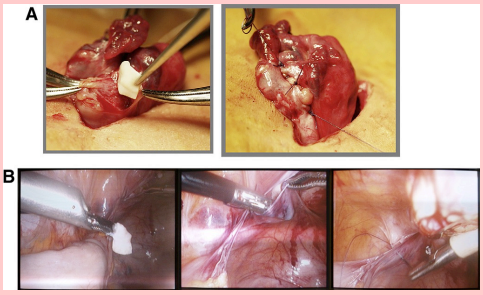
- **Oocyte Cryopreservation**
  - Vitrification now allows successful freezing of unfertilized oocytes
  - Successful, approx 10,000 live births
    - BUT-
      - Must be post pubertal
      - Oocyte stimulation and retrieval takes at least 2 weeks
      - Expensive – $5-10,000 per course
  - Now consider oocyte preservation after treatment if high risk of premature menopause
  - Monitor AMH to determine timing

Fertility Preservation

- **Cryopreservation of ovarian tissue**
  - Ovarian Cortical strips – high concentration of primordial follicles
  - Cryopreserved and later re-implanted
    - Still experimental but
      - OK for pre pubertal girls
      - No need for hormonal stimulation so no delay to treatment
      - Return of ovarian function in patients who are menopausal
      - 130 pregnancies reported
      - 1 pregnancy reported from prepubertal ovarian tissue transplantation
  - But
    - Risk of damage to ovary and invasive proceedure
    - **Risk of transplanting malignant tissue**

Donnez 2017 NEJM

Re-implantation of ovarian cortical strips



Schmidt KT et al, Fertil Steril, 2011,;95:696-701

Fertility Preservation Experimental Approaches

- **In Vitro Maturation of oocytes** –
  - Still experimental
  - 1 birth reported in an adult cancer patient.
- **Ovarian tissue Allo Transplant** from a sibling bone marrow donor
- **Whole ovary cryopreservation** and re-implantation
  - Animal data only
    - Seshadri, Br J Cancer,2006; Donnez, Hum Reprod 2011; Wallace, Cancer 2011

Fertility Preservation or Alternative

- **If ovaries OK but uterus damaged:**
  - Surrogate Mother
  - Transplanted uterus if uterus damaged
    - 8 babies born in Sweden after uterine transplant, 1 in USA (Lancet 2015, NYT nov 2017)
- **If ovaries damaged but uterus OK**
  - **Donated oocytes**

Pregnancy Outcome

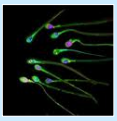
- For those who do achieve pregnancy
  - Previous uterine radiation - Monitor fetal growth
  - Previous hypothalamus/pituitary radiation –Monitor hormone status
  - Previous chemotherapy
    - No increase in risk of pregnancy loss or perinatal problems
    - No increase in genetic defects
    - Signorello et al J Clin Oncol 2012, Winther et al Am J Hum Genet 2004 74(6), 1282

Interventions to be considered

- Prior to start of treatment
  - Ovarian transposition
  - Oocyte cryopreservation
  - Ovarian tissue cryopreservation
- During Treatment
  - GnRH agonists
- After Completion of Treatment
  - Monitoring of ovarian reserve
  - Oocyte cryopreservation
- General Consideration
  - Risk of impaired fertility
  - Health of the patient
  - Cost of all procedures
  - Availability Expertise and Interest

Male Oncofertility

- Normal Testicular Functions
  - To produce spermatazoa
    - Spermatogonial stem cells
    - Sertoli (nurse) cells
      - 3 billion sperm / month, 100 per heart beat !!
      - Sperm maturation time =74 days
  - To produce male hormones
    - Leydig cells- produce testosterone



Adverse Effects
Radiation -Effect on the testis

- Testicular radiation
  - For leukemic infiltration (12-24 Gy)
  - TBI (10-12 Gy)

- Spermatogenesis is very sensitive to radiation
  - 0.1Gy can impair spermatogenesis
  - >1.2Gy can cause permanent azoospermia
  - Effects are immediate
  - May have some recovery over a few years
- Leydig cells are more resistant
  - Dysfunction
    - > 20Gy in prepubertal boys
    - >30Gy in mature males

BUT- long term Leydig cell damage occurs and testosterone levels may decrease 20 years later

Rowley MJ, radiation research 1974, Shalet, J Endocrinol, 1989

Adverse Effects - Radiation
Effect on the Hypothalamus/Pituitary

- Low dose cranial radiation (<2400)
  - less likely to cause precocious puberty in boys
- High dose cranial radiation (>2400cGy)
  - Gonadotropin deficiency– risk increases with dose
  - Treatment – testosterone replacement

Adverse Effects - Chemotherapy
Effects on the Testis

- Leydig cells rarely affected (high cumulative doses only)
- Germinal epithelium (spermatogenesis) is very sensitive to chemotherapy
- Alkylating agents are the main culprits
- Effects are immediate
- No significant effects on hypothalamus/pituitary
  - Wallace, Int J Androl, 1991

Calculation of Alkylator Equivalency

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Fertility Prediction
Investigation of Testicular Function

- Assessment of pubertal status
  - 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 = Gold standard
  - Sperm concentration, motility, morphology, volume, fructose level, pH,

Fertility Preservation

- Testicular shielding during radiation

- **Sperm Banking** prior to starting treatment
  - Must be Tanner 4-5
- Roadblocks to Sperm banking
  - Patient factors
    - Unwell or embarrassed
    - Time – may need to start treatment immediately
    - Poor sperm count because unwell
  - Family/ Caregiver Factors
  - System Factors
    - Access to cryopreservation
    - Facilities that are child/teen friendly
    - Cost - $200-400 for initial banking, $200 per year

Fertility Preservation -Surgical methods

- **Surgical sperm retrieval**
  - Small incision in the scrotum and extraction of sperm from the epididymis or testis
  - Sperm can be obtained from Tanner stage II boys
  - Roadblocks to surgical sperm retrieval
    - Organization- OR time, access to cryopreservation
    - Cost -$2000
- Experimental methods
  - Testicular tissue cryopreservation and re-implantation (risk of transplanting malignant cells)
  - In vitro maturation
    - Success in rats and primates so far
  - No viable options for pre pubertal boys

Interventions to Consider

- Pre treatment
  - Sperm banking
  - Testicular aspirate
  - Testicular biopsy?
- Post treatment
  - Semen analysis for counselling
  - Sperm banking only if have risk of relapse
  - If have adequate sperm count at end of therapy it is not expected to decrease until late in life
  - Long term monitoring of testosterone levels if had radiation

Team Approach

- Fertility preservation in children and adolescents requires a team approach
  - Oncology team (physician, social worker, nursing, family)
  - Fertility specialists
  - Endocrinology
  - Urology
  - Gynecology
  - Ethics
  - Administrators to facilitate procedures
  - Family doctor often has to organize fertility referral later on
- Guidelines and Protocols