REPRODUCTIVE HEALTH IN YOUNG ADULT CANCER SURVIVORS

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Disclosure

- The speaker has no financial or other conflict of interest
Objectives

- To describe how cancer and cancer treatment can affect fertility
- To review fertility assessment after cancer treatment
- To identify potential pregnancy complications after cancer therapy
- To discuss menopausal hormone therapy and contraception
Fertility as a Survivorship Issue

1.6M new cancer cases with ~10% younger than 45 years

- **40% of survivors** do not recall discussing fertility impact of cancer treatment with oncologist\(^1\)
  - Receiving this counseling is associated with less regret and greater quality of life for survivors

- **24% of young male cancer patients** pursued sperm banking\(^2\)

- **4% of young female cancer patients** pursued fertility preservation\(^3\)

\(^1\)Armuand GM et al, 2012
\(^2\)Trottman L et al, 2007
\(^3\)Letourneau JM et al, 2012
Factors Associated with Risk of Infertility

- Age at diagnosis and treatment
- Cancer type and stage of disease
- Gender
- Chemotherapeutic agents and mechanism of action
- Cumulative dose and duration of treatment
- Radiation exposure and dose
- Surgical therapy
- Genetic predisposition
The relative risk (RR) of pregnancy among female survivors was lower than in female siblings (RR 0.81, 95% CI 0.73-0.90).

Poor prognostic factors include:
- Hypothalamic/pituitary radiation dose ≥30 Gy
- Ovarian radiation dose >5 Gy or uterine dose >30 Gy
- High dose exposure of alkylating chemotherapy
- Treatment with cyclophosphamide (RR 0.80, 95% CI 0.68-0.93)
Female Infertility in CCSS

- Increased risk of clinical infertility compared with their siblings (RR 1.48, 95% CI 1.23-1.78)
- Higher risk of nonsurgical premature menopause than siblings (8 versus 0.8%; RR 13.21, 95% CI 3.26-53.51)
- Risk factors for nonsurgical premature menopause:
  - Age (RR 1.15)
  - Ovarian radiation (RR 4.3 to 109.59)
  - Alkylating chemotherapy (RR 2.3 to 5.78)
  - Hodgkin lymphoma diagnosis (RR 9.18)

1. Barton SE et al., 2013  
2. Sklar CA et al., 2006
Female Survivors have Fewer Pregnancies

Stensheim H et al., 2011

Oncofertility Program
Expanding parenthood options for life after cancer

![Graph showing pregnancy rates for different cancers](image)
Male infertility in CCSS

- Male survivors without surgical sterility were less likely to father a pregnancy than siblings (HR 0.56, 95% CI -0.49-0.63)

- Poor prognostic factors included:
  - Testicular radiation dose >7.5 Gy
  - High cumulative alkylating agent doses
  - Treatment with cyclophosphamide or procarbazine

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Green DM et al., 2010
Resumption of Menses after Cancer Therapy

- Transient or permanent infertility
- Cytotoxic drugs can lead to chemotherapy-induced amenorrhea (CIA) among younger patients
- In premenopausal breast cancer survivors,
  - 41% of women experienced an initial 6 months of CIA
  - An additional 29% had at least 1 year of CIA
  - Of the 23% of women who experienced an initial 2-year period of CIA, 10% resumed bleeding within 3 years, but none had regular menses

Kil WJ et al., 2006  Sukumvanich et al., 2010.
Normal Periods ≠ Normal Fertility

Letourneau et al. Cancer 2012
Female Fertility Assessment after Treatment

- Ovarian reserve markers:
  - Serum FSH and estradiol
  - Serum AMH
  - Antral follicle count
Serum AMH after Treatment

- Early indicator of ovarian aging, including the assessment of chemotherapy-induced ovarian follicle loss
- May be acutely reduced as a result of chemotherapy-related destruction of ovarian follicles
- AMH recovery reflects the resumption of follicle growth after completion of cancer therapy
- Although the trajectory of recovery of ovarian function may be unpredictable, it is likely related to pretreatment AMH
- Low AMH is a useful predictor of poor or no response to ovarian stimulation in infertility patients as well as breast cancer survivors

1. Brougham MF et al., 2012  
2. Charpentier AM et al., 2014  
3. Nardo LG et al., 2009  
4. Dillon et al., 2013  
5. Anderson RA et al., 2006
Male Fertility Assessment after Treatment

- Semen analysis
- Persistent severe oligospermia (<5M/mL) or azoospermia warrants further evaluation:
  - Serum FSH, LH, testosterone, E2
- Assisted reproduction with IUI and ICSI
- Urology referral for consideration of microdissection testicular sperm extraction (TESE) and ICSI

Hsiao W et al., 2011.
Data are overall reassuring

- Children of survivors are not at significantly increased risk for congenital anomalies
- No clear increased risk of adverse pregnancy outcomes among either female cancer survivors or female partners of male survivors

1. Signorello LB et al., 2012
2. Dodds L et al., 1993
3. Green DM et al., 1997
4. Green DM et al., 2003
5. Ruelen RC et al., 2009
Risk of Miscarriage in Cancer Survivors

- Increased risk of spontaneous miscarriage:
  - Danish cohort study of cancer survivors:
    - Increased risk compared to siblings = PR 1.23 (1.00 – 1.52)
    - Radiation exposure = PR 1.58 (1.15 – 2.17)
    - Pelvic radiation exposure = PR 2.8 (1.7 – 4.7)
  - Childhood Cancer Survivors Study:
    - Pelvic radiation exposure = RR 1.65 (1.05 – 2.59).
    - Craniospinal radiation exposure = RR 3.63 (1.70 – 7.78)

1. Winther et al., 2008. 2. Green DM et al., 2003
Pregnancy Outcomes after Pelvic Radiation

- Radiation induced physiologic changes:
  - Pelvic vasculature $\rightarrow$ decrease uteroplacental perfusion
  - Myometrial fibrosis $\rightarrow$ decrease uterine elasticity and volume
  - Endometrial injury $\rightarrow$ reduce implantation

- Potential adverse outcomes:
  - fetal growth restriction, preterm delivery, abnormal placentation, and stillbirth

- High dose estrogen therapy:
  - $<25$ Gy exposure $\rightarrow$ may be reversible
  - $>25$ Gy direct exposure $\rightarrow$ irreversible damage

1. Watanabe T et al., 2012
2. Larsen EC et al., 2004
3. Critchley HO et al., 2002
Risk of Adverse Pregnancy Outcomes increases with Radiation Dose

![Graph showing odds ratio for different radiation doses to uterus]
Preimplantation Genetic Diagnosis

- Genetic counseling should be offered to all young cancer survivors (new genetic panels)
- PDG can be used to identify single gene mutations associated with cancer risk

Tur-Kaspa I et al., 2014

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Hormone therapy should be considered in POI:
- Estrogen and progesterone in women with uterus
- Continue until approximately age 50

Use of hormone therapy depends on the type of cancer:
- Contraindicated in hormone sensitive tumors
- Engage with oncology team when considering hormonal therapy to ensure all parties are comfortable with treatment
Alternatives to Hormone Therapy for Vasomotor Symptom Relief

- Conflicting data on hormone therapy and risk of recurrence generally contradicts its use in patients with hormone-positive breast cancer

- Nonhormonal therapies may offer some relief:
  - SSRIs (paroxetine, fluoxetine, and citalopram)
  - SNRIs (venlafaxine)
  - Gamma-aminobutyric acid analogs (gabapentin)
  - Acupuncture

1. Holmberg L et al., 2004
2. Batur P et al., 2006
3. Bordeleau L et al., 2007
4. Biglia N et al., 2005
Importance of Contraception in Survivors

- Counseled to avoid pregnancy during chemotherapy and radiation
- Women with hormonal sensitive cancers frequently advised to avoid pregnancy until at lower risk of recurrence
- Many survivors may have completed childbearing or wish to avoid pregnancy indefinitely

Schwarz EB et al., 2009
Contraceptive Use in Cancer Survivors

- Lower contraceptive use and often use less effective methods
- Counseling full spectrum of options for family planning → improve contraception compliance

### Contraceptive type | Cancer survivors | General Population | p-value
---|---|---|---
Any contraception | 57.4 (51.5-63.2) | 68.6 (67.3-70.0) | <0.01
WHO I-II Sterilization Hormonal | 34.2 (28.8-40.0) | 53.0 (51.5-54.5) | <0.01
WHO III-IV Condoms Withdrawal Periodic abstinence | 23.2 (18.4-28.5) | 15.6 (14.5-16.6) | <0.01

Dominick S et al., 2015
Nonhormonal methods should be considered first:

- Barrier methods
- Sterilization
- Copper IUD

May consider progestin-only methods:

- Depot medroxyprogesterone acetate (DMPA)
- Mirena IUD
- Oral progestins

Further study of the safety of this approach is warranted.
Summary Points

- Disease process or treatment can cause infertility, which may be temporary or permanent
- Fertility assessment is challenging because fertility may be transiently impaired
- In general, offspring are not at increased risk of congenital or chromosomal anomalies
- Pregnancy in women who have received prior pelvic irradiation appears to be associated with significant complications
- Discussion of hormone therapy and contraception should be part of survivorship counseling
Questions

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