The Adolescent: A Patient at Risk: Ovarian Failure in Adolescent Cancer Survivors

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Will she ever be able to have children?
Learning Objectives
By the end of this presentation, you will be able to:

1. Estimate the risk of ovarian failure in childhood/adolescence cancer survivors.

2. Outline the risk of ovarian failure following various cancer treatments.

3. Recognize how essential HRT is to normal pubertal development.

4. Design an HRT treatment plan for the adolescent cancer survivor.

5. Recognize the fertility prospects in young women who’d survived childhood/adolescence cancer
Ovarian Failure

- What is the chance it will happen?
- Reversible?
- Reproductive future?
ACUTE OVARIAN FAILURE (AOF) IN ADOLESCENT CANCER PATIENTS

Acute ovarian failure (AOF): loss of ovarian function within 5 years of diagnosis.

The Childhood Cancer Survivor Study: 6.3% of patients (215 cases) developed AOF amongst the 3390 female survivors.

Green et al, J Clin Oncol 2009;27;2374-2381
Chemaitilly et al, J Clin Endocrin Metab 2006; 91(5): 1723-8
Cumulative incidence curves of nonsurgical premature menopause in survivors compared with siblings

Green et al, J Clin Oncol. 2009 May 10; 27(14): 2374–2381
The mean age at cancer diagnosis was 9.8 years.

56% had childhood cancer (0-12 years old)

44% were adolescents (13-20 years old).
The Risk of Radiation Therapy

- Radiotherapy to the ovaries was the most significant risk factor for AOF.

- 54% of survivors with AOF received at least 1000 cGy to the ovaries.

- With at least 2000 cGy, 70% developed AOF.
Percentage of subjects with acute ovarian failure (AOF) by age at diagnosis of cancer of 0 to 12 years, 13 to 20 years, and radiation dose to the ovary.

Green et al, J Clin Oncol. 2009 May 10; 27(14): 2374–2381
The Risk of Chemotherapy

- Alkylation agents, specifically procarbazine and cyclophosphamide - associated with the highest risk (25% and 55%, respectively).

- Exposure to procarbazine - an independent risk factor for AOF, regardless of age, cyclophosphamide significantly increased the risk only in subjects treated at an older age (13-20 years old).
Which Cancer is associated with the highest risk for AOF?

- Wilms Tumor
- Acute lymphoblastic leukemia
- Hodgkin disease
Cancers at highest risk for AOF

- Hodgkin disease (31%)
- Wilms Tumor (16%),
- Acute lymphoblastic leukemia (14%)
- Soft-tissue sarcoma (13%).
Reported incidence of AOF - variable

- 0 - 53% - chemotherapy alone
- 11 - 100% - Bone Marrow Transplant (BMT)
- 26 - 100% - radiation alone or with chemotherapy.
Cumulative incidence curves of nonsurgical premature menopause in survivors according to treatment exposures. (A) Survivors treated with alkylating agents (AA) but not with abdominal-pelvic radiation therapy (A-P RT). (B) Survivors treated with A-P RT but not AA. (C) Survivors treated with AA and A-P RT.

Green et al, J Clin Oncol. 2009 May 10; 27(14): 2374–2381
AMH (Antimüllerian hormone) as a measure of reproductive function in female childhood cancer survivors

- median AMH: 0.74 ng/mL
- 31 pts (58%): DOR, AMH <1 ng/mL.
- 17 pts (32%): DOR, FSH >12 IU/L.
- 15 pts (48%): low AMH but normal FSH

AMH (Antimüllerian hormone) values vary by cancer treatment risk
## Risk factors of low AMH

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>P value</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>High-risk chemotherapy</td>
<td>4.1</td>
<td>.02</td>
<td>(1.2, 14.0)</td>
</tr>
<tr>
<td>High-dose cyclophosphamide (&gt;7.5 g/m²)</td>
<td>12.0</td>
<td>.03</td>
<td>(1.3, 107.4)</td>
</tr>
<tr>
<td>Pelvic radiation</td>
<td>8.6</td>
<td>.05</td>
<td>(1.0, 73.8)</td>
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Lunsford et al 2014; Fertil steril 101(1): 227-231
Should AOF be treated?

The ovary - an endocrine organ, providing a dynamic hormonal milieu necessary for the proper growth and development of the female child.

Turner Syndrome – a model. It is unthinkable that these girls, born with non-functioning (streak) ovaries, would be left untreated.

Most young women with Turner syndrome will require hormone replacement with sex steroids to either enter puberty or to complete pubertal growth and development.

Bondy, 2007 J Clin Endocrinol Metab 92:10-25
Why would young girls, whose ovaries had been damaged by cancer treatment, be treated differently?

Is there any controversy that these girls need hormone replacement?

Would you even consider not giving thyroid hormone to a hypothyroid child? Steroids to an Addisonian? GH to a hypopituitary child?
Treatment of AOF (2)

- Hypogonadal girls will not go through puberty without treatment.

- Ovarian estrogen plays a key role in puberty, which is the obligatory bridge, involving physical, sexual and psychosocial maturation, which the child has to cross in order to reach adulthood.

Treatment of AOF (3)

- The onset of puberty - controlled by the GnRH neuron and is triggered when inhibition of the neuron is removed.

- GnRH will then induce FSH and LH, which in turn stimulate the ovaries.

- Simultaneously, increases in E levels stimulate GH and IGF-I) lead to the pubertal growth spurt.

- Hormone replacement therapy with estrogen is a viable treatment option for hypogonadal children.

Epigenetic repression of puberty
Sequence of normal puberty in girls, after Tanner 1989
HRT for AOF

The overall goal: to induce normal secondary sexual characteristics in a patient at an age commensurate with her peer group:

✓ pubertal breast development
✓ induction of menses
✓ normal bone
✓ normal brain development

DiVasta and Gordon, Ann NY Acad Sci 2008; 1135:204-11
Estrogen has to be given with care

At low dose estrogen stimulates longitudinal growth

At higher doses it may cause premature closure of the epiphyses and growth arrest.

DiVasta and Gordon, Ann NY Acad Sci 2008; 1135:204-11
HRT protocol (1)

- HRT for adolescents should consist of 3 phases, in order to closely mimic normal pubertal changes and the corresponding increases in 17 beta estradiol throughout Tanner’s 5 stages of puberty.

- In the absence of any secondary sex characteristics, low-dose HRT is generally begun at approximately age 12 years.

- Breast development is induced with estrogen-only therapy

DiVasta and Gordon, Ann NY Acad Sci 2008; 1135:204–11
Bondy, J Clin Endocrinol Metab 2007;92:10-25
HRT protocol (2): Target Estradiol Levels according to Tanner Stages

- I: 5 pg/ml
- II: 15 pg/ml
- III: 35 pg/ml
- IV: 50 pg/ml
- V: 60 pg/ml

DiVasta and Gordon, Ann NY Acad Sci 2008; Bondy, J Clin Endocrinol Metab 2007;92:10-25
At what phase of HRT is Progestin added?

- Phase 1
- Phase 2
- Phase 3
HRT protocol (3)

- Phase 1: 6–18 months

- Phase 2: Progestin added; breast development completed; menarche; bone build-up

- Phase 3 is the final, long-term phase: maintenance doses of estrogen and progestin

DiVasta and Gordon, Ann NY Acad Sci 2008; 1135:204–11
Bondy, J Clin Endocrinol Metab 2007;92:10-25
Estrogen side effects

- Dosage of estrogen to be weighed out carefully

- High dose in adolescents is beneficial for bone, brain and cardiovascular development

- But also associated with increased risk of thrombotic complications and hypertriglyceridemia

- Oral estrogen therapy increases renin substrate and the risk of hypertension.
Transdermal estrogen patch

- Preferable - doesn’t have the suppressive effect oral estrogens exhibit on both baseline and GH-stimulated insulin-like growth factor-I (IGF-I) levels.

- Transdermal HRT was also reported to have a positive effect on serum lipid profiles, inflammatory markers, and blood pressure.

Lissett and Shalet, J Clin Endocrinol Metab 2003; 88:4668-4672
What about the WHI?

- The Women’s Health Initiative Study was done on menopausal women.

- Did not include the adolescent population.

- Significant endothelial dysfunction (a risk for cardiovascular disease) in young women with POF – reversed within 6 months of HRT.

- Young hypoestrogenic women - also at risk for osteoporosis, vaginal atrophy, and menopausal symptoms.

DiVasta and Gordon, Ann NY Acad Sci 2008; 1135:204-11
Fertility in Childhood/Adolescence
Cancer survivors (1)

- The Childhood Cancer Survivor Study (CCSS): a 5 year cancer survivors from 26 Canadian and US institutions who were younger than 21 years at the time of diagnosis (1970-1986).

- 3531 survivors and 1366 female sibling controls.

- Compared with their siblings, survivors had an increased risk ([RR] 1.48) of clinical infertility,

Barton et al, The Lancet Oncology 2013;14(9): 873 - 881
Fertility in Childhood/Adolescence Cancer survivors (2)

- Infertility most pronounced at early reproductive ages:
  - RR 2.92 ≤24 years
  - RR 1.61 in 25–29 years old
  - RR 1.37 in 30–40 years old

- Survivors less likely than were their siblings to be prescribed drugs for treatment of infertility (0.57 [95% CI 0.46–0.70], p<0.0001).

- Increasing doses of uterine radiation and alkylating agent chemotherapy strongly associated with infertility.

Barton et al, The Lancet Oncology 2013;14(9): 873 - 881
Fertility in Childhood/Adolescence Cancer survivors: The Good News

Although survivors had an increased time to pregnancy compared with their siblings, 292 (64%) of 455 participants with self-reported clinical infertility achieved a pregnancy.

Barton et al, The Lancet Oncology 2013;14(9): 873 - 881
Return of Fertility post BMT

- 4 young adult patients following BMT
- 2 - Hodgkin’s Disease
- 2 - advanced breast cancer
- reversal of AOF
- pregnancy 1-2 years after BMT.

Diagram depicting in vitro oogenesis, whereby patient-specific pluripotent stem cells could be differentiated into PGCs and cocultured with follicle support cells derived from the same patient-specific pluripotent stem cells. In vitro maturation of the follicle would need to be performed to generate a resulting product capable of being fertilized by standard IVF methods.

Easley et al 2014; Fetril Steril 101(1): 14-19
1. The risk of AOF is 6.3%.

2. RT to the ovary and BMT highest risk, followed by chemo.

3. Cyclophosphamide and procarbazine – the worst.

4. HRT essential for pubertal development with AOF.

5. Estrogen should be given parallel to the 5 Tanner stages (E: 5;15;35;50;60 pg/ml, respectively).

6. 64% of childhood/adolescent cancer survivors desiring fertility will reach motherhood.