

Fertility in Cancer Survivorship: Assessment, Decision-Making and Outcomes

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Presentation Outline

- Gonadal toxicity of cancer therapy
- Assessment: Desire, Concerns, Risk Estimation
- Decision-Making: Educational Intervention, Fertility Status Assessment, Family Building
- Outcomes and Costs
- Recommendations

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Cancer Treatment Affecting Fertility

Radiation:

- Hypothalamus/Pituitary (head/brain/TBI)
- Ovaries/uterus (abdominal/pelvic/TBI)
- Testis (pelvic/gonadal/TBI)

Chemotherapy:

- Alkylating agents

Surgery:

- Removal of reproductive organs
- Damage pelvic nerves, abdominal-pelvic staging surgeries

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Mechanisms of Infertility Post Cancer Treatment

Female

- **Reduced estrogen**
- **Shorter period of fertility due to depletion of oocytes**
 - Early menopause
- **Germ cell failure**
 - Acute ovarian failure
- **Interference with fertilization and implantation**
 - Uterine/tube fibrosis
- **Inability to maintain pregnancy**
 - Uterine vascular insufficiency

Male

- **Reduced testosterone**
 - Leydig cell dysfunction
- **Oligospermia / Azoospermia**
- **Damage to vas deferens**
- **Pelvic nerve damage**
 - Erectile dysfunction
 - Ejaculatory dysfunction

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Fertility After Treatment For Childhood Cancer

Female

Risk of Ever Being Pregnant

| | | Ever Pregnant N (%) | Relative Risk* (95% CI) |
|-----------|------|------------------------|----------------------------|
| Siblings | 1441 | 613 (42.5%) | 1.00 |
| Survivors | 5149 | 1506 (29.2%) | 0.81 (0.73, 0.90) |

* Adjusted for age at diagnosis, race/ethnicity, education, marital status, smoking status

CCSS
An NCI-funded Resource

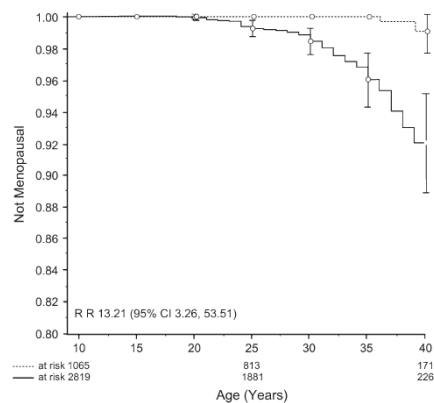
Green DM et al., J Clin Oncol, 2009

Fertility After Treatment For Childhood Cancer

Premature Menopause

Non-surgical menopause

- 8% cancer survivors vs. 0.8% siblings
- RR 13.2 (95% CI 3.3 – 53.5)
- Risk factors included:
 - Older attained age
 - Radiation to the ovaries
 - Alkylating agents
 - Hodgkin lymphoma



CCSS
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Sklar, CA et al., JNCI, 2006

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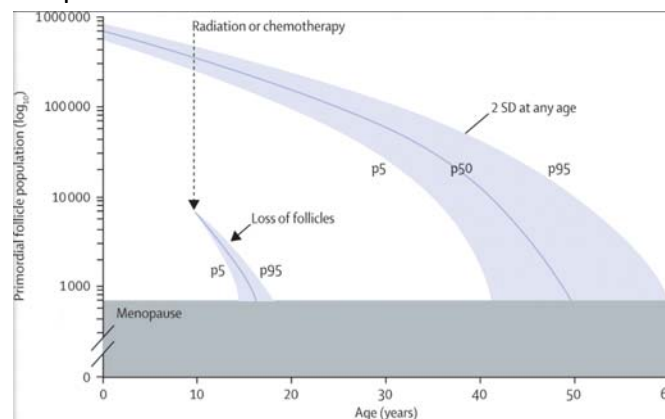
Who is at Highest Risk? - FEMALES

| FEMALES | Low | Moderate | High |
|------------------|---|---|---|
| chemo | 1-7.5 gm/m2 CED Heavy metals | 7.5-15 gm/m2 CED | >15 gm/m2 CED *or any combination of CED with BMT |
| radiation | Whole abdomen/pelvis Spine (lumbar/sacral) 1-10 Gy pre- pubertal 1-5 Gy pubertal | Whole abdomen/pelvis Spine (lumbar/sacral) 10-15 Gy pre- pubertal 5 - 10 Gy pubertal | Whole abdomen/pelvis Spine (lumbar/sacral) > 15 Gy pre pubertal > 10 Gy pubertal TBI Cranial > 30 *any combination of CED with TBI or pelvic radiation |
| | Most Leukemia/Lymphoma | | Most Solid Tumor, BMT |
| surgery | Pelvic surgery Removal of 1 ovary | | Removal of both ovaries |

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What causes female infertility?

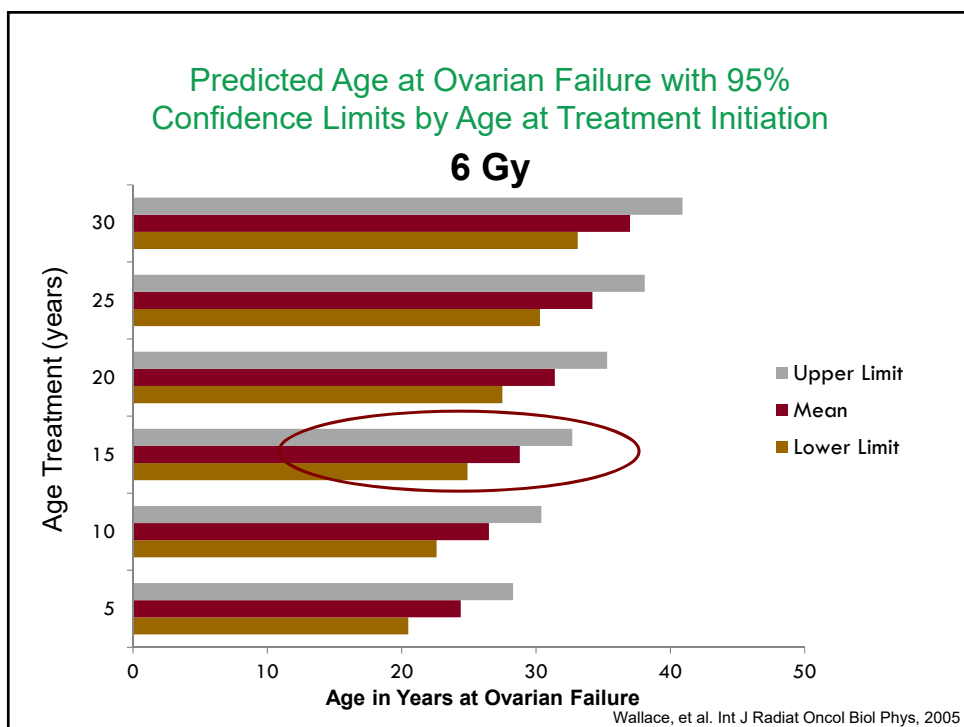
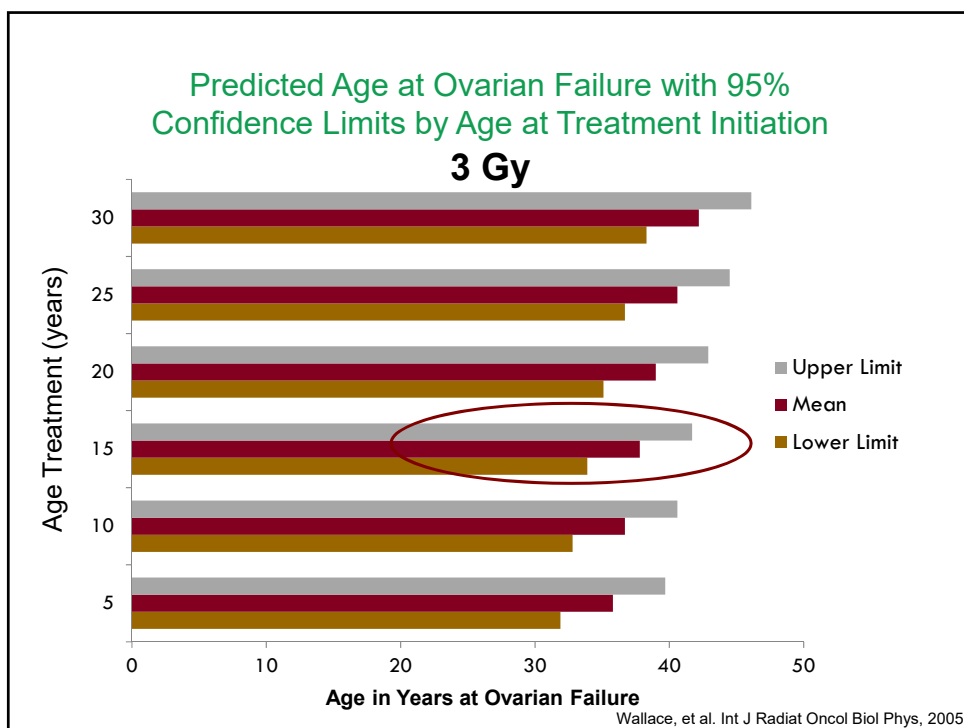
- Females
 - Born w/ 1 million eggs, gradually lose over lifespan until menopause occurs.



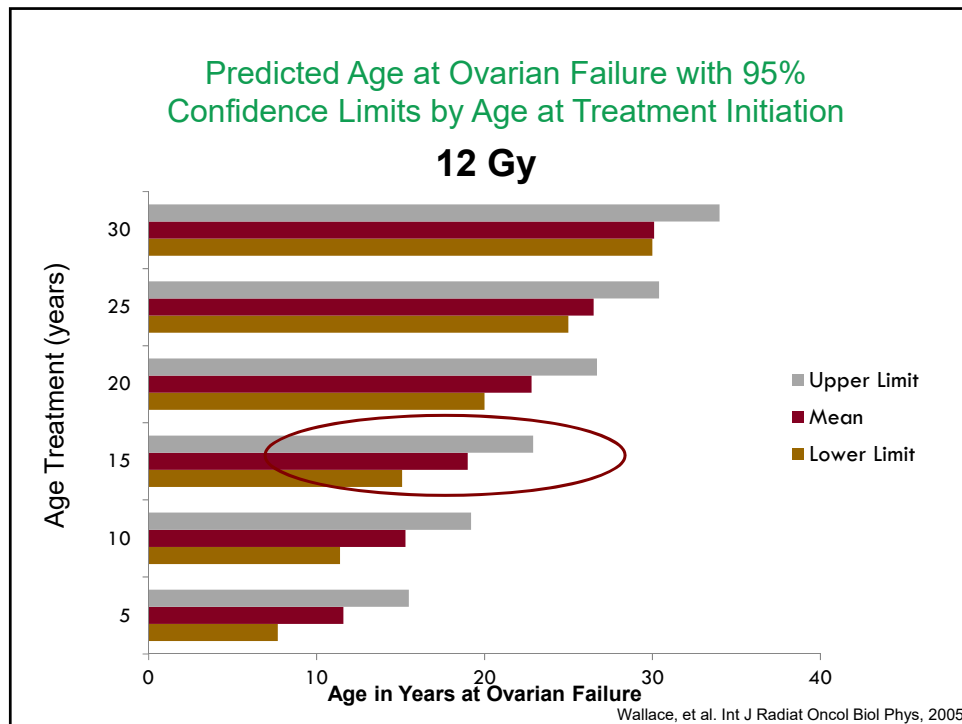
De Vos, et al. 2010, The Lancet

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Fertility After Treatment For Childhood Cancer

Male

Risk of Ever Being Pregnant

| | | Ever Pregnant N (%) | Relative Risk* (95% CI) |
|-----------|------|------------------------|----------------------------|
| Siblings | 1449 | 477 (32.9%) | 1.00 |
| Survivors | 6224 | 1042 (16.7%) | 0.57 (0.50, 0.65) |

* Adjusted for age at diagnosis, race/ethnicity, education, marital status, smoking status

CCSS
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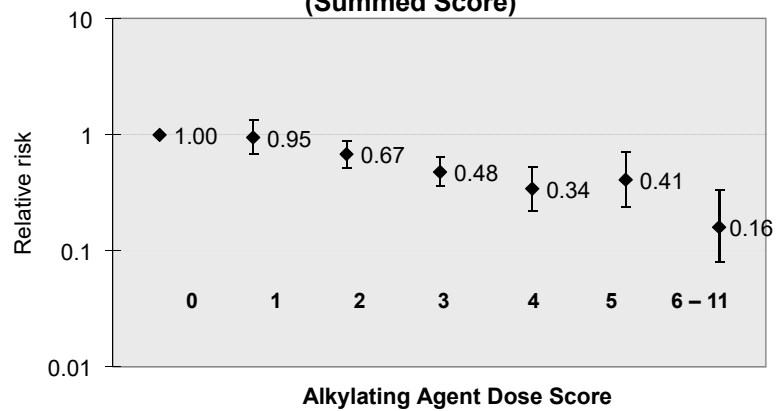
Green DM et al., J Clin Oncol, 2010

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Fertility After Treatment For Childhood Cancer

Male

Risk by Alkylating Agent Exposure (Summed Score)



* Adjusted for pituitary RT, testicular RT, age at diagnosis, race/ethnicity, education, marital status, smoking status, other chemotherapy

Who is at Highest Risk? - MALES

| MALES | Low | Moderate | High |
|------------------|---------------------------------------|---|---|
| Chemo | < 4 gm/m2 CED Heavy metals | 4-7.5 gm/m2 CED Cisplatin >500mg/m2 | > 7.5 gm/m2 CED *or any CED with BMT |
| Radiation | Testicular 0.2- 0.7 Gy | Testicular 1-2 Gy *or scatter from abd/pelvis | Testicular >3-7 Gy Cranial >30 Gy; (>20 Gy risk of testosterone insufficiency) TBI *any combination of CED with TBI or radiation to the testes |
| | Most Leukemia/Lymphoma | | Most Solid Tumor, BMT |
| Surgery | Removal of 1 testis Pelvic surgery | GU surgery (RPLD) | Removal of both testes |

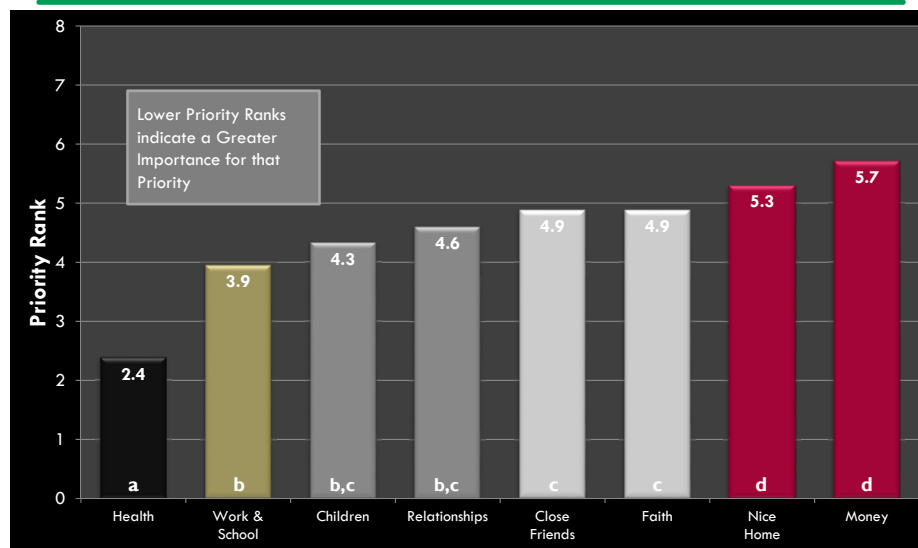
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Assessing Fertility and Associated Concerns among AYA Survivors

Desire
Concerns
Risk-Estimation



Desire: Fertility as a Priority



Klosky et al, 2015 SCC

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Survivors Desire Children

- 76% of childless cancer survivors desire children
- Biological offspring are preferred
- Expectations of being good parents
- Infertility associated with risk of psychological distress
- Banking gametes associated with psychological relief
- Cancer patients may choose less toxic treatments in order to preserve fertility
- If fertility is such a priority for survivors, then why is fertility preservation underutilized?

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erika T. Wang, and Alison W. Loren

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on April 5, 2018.

K.O. and A.W.L. were Expert Panel members and contributed equally to this work.

Clinical Practice Guideline Committee approved: January 25, 2018.

Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations with comprehensive review and analysis of the relevant literature for each recommendation. Additional information, including an abbreviated table, is available at www.asco.org/guidelines.

ABSTRACT

Purpose

To provide current recommendations about fertility preservation for adults and children with cancer.

Methods

A systematic review of the literature published from January 2013 to March 2017 was completed using PubMed and the Cochrane Library. An Update Panel reviewed the identified publications.

Results

There were 61 publications identified and reviewed. None of these publications prompted a significant change in the 2013 recommendations.

Recommendations

Health care providers should initiate the discussion on the possibility of infertility with patients with cancer treated during their reproductive years or with parents/guardians of children as early as possible. Providers should be prepared to discuss fertility preservation options and/or to refer all

ASRM PAGES

Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

Patients preparing to undergo gonadotoxic medical therapy or radiation therapy or gonadectomy should be provided with prompt counseling regarding available options for fertility preservation. Fertility preservation can best be provided by comprehensive programs designed and equipped to confront the unique challenges facing these patients. (Fertil Steril® 2013;100:1214–23. ©2013 by American Society for Reproductive Medicine.)
Earn online CME credit related to this document at www.asrm.org/learn

Discuss: You can discuss this article with its authors and with other ASRM members at <http://www.fertstertforum.com/asrmpractice-fertility-preservation-chemotherapy-cancer/>



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ASCO/ASRM Key recommendations:

- Discuss FP w/ all patients of reproductive age and w/ parents of children and adolescents if infertility is a potential risk of therapy
- Address FP **as early as possible, before** treatment starts
- Use **established methods** of FP (sperm and oocyte {egg} cryopreservation) for post - pubertal patients (now includes ovarian tissue cryopreservation for pre-pubertal patients).
- Present information on **additional methods** that are investigational for children, and refer when available and appropriate (e.g. testicular tissue cryopreservation)

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Standard of Care: Fertility Preservation

Sperm Cryopreservation

- Tanner III or higher
- Age 13 or higher
- Any risk level
- Assessment of candidacy
 - Desire for bio children
 - Development
 - Assent/consent

Oocyte Cryopreservation

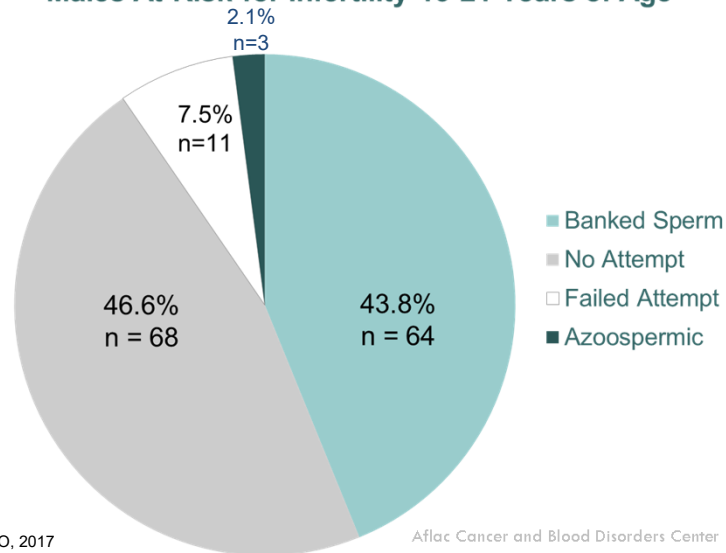
- Menarche
- Age 14
- Moderate to high risk
- Assessment of candidacy
 - Desire of bio children
 - Development
 - Candidacy confirmed: labs and imaging
 - Timing and costs
 - Assent/consent

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Adolescent Collection Attempt (N=146)

Males At-Risk for Infertility 13-21 Years of Age



Overall Model – Collection Attempt

| Identified Relevant Variables | Odds Ratio | 95% CI | P-value |
|--|------------|---------------|---------|
| Adolescent Report - Health Beliefs | | | |
| Perceived benefits of banking | 1.21 | 0.97 – 1.51 | .085 |
| Development | | | |
| Tanner Stage | 5.42 | 1.75 – 16.78 | .003 |
| Adolescent Report - Parent Recommended Banking | | | |
| Yes | 12.30 | 2.01 – 75.94 | .007 |
| Adolescent Report – Met with a Fertility Specialist | | | |
| Yes | 29.96 | 2.48 – 361.41 | .007 |

Klosky et al. JCO, 2017

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Overall Model – Successful Sperm Banking

| Identified Relevant Variables | Odds Ratio | 95% CI | P-value |
|--|------------|--------------|---------|
| Adolescent Report - Health Beliefs | | | |
| Banking Self-Efficacy/Confidence | 1.23 | 1.05 – 1.45 | .012 |
| Adolescent Report – Medical Team Recommendation | | | |
| Yes | 4.26 | 1.45 – 12.43 | .008 |
| Adolescent Report - Parent Recommended Banking | | | |
| Yes | 4.62 | 1.46 – 14.73 | .010 |
| Adolescent Report – History of Masturbation | | | |
| Yes | 5.99 | 1.25 – 28.50 | .025 |

Klosky et al. JCO, 2017

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Barriers to Fertility Preservation at Dx

- Timing/Cost/Procedural demands/Poor candidates
- Poor communication by medical teams/recs for banking
- Difficult discussions/disagreements within families
- Developmental status/Health status of pt
- Psychological factors (health beliefs, anxiety at dx, overwhelmed)
- Religion/Culture/Tradition
- Moral objections to ARTs
- Lack of desire for biological children in the future
- The majority of survivors do not bank materials
- Developmental shifts across cancer continuum
- Perception of fertility risk

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Survivors' Perceptions of Infertility Risk

On-line surveys were completed by cancer survivors aged 22 – 43 years

- 82% reported they knew about their risk for infertility
- 75% recalled being told they were at risk
- 29% didn't believe it
- 49% had not completed fertility status assessment

Recall of Discussion of Fertility Risk at Dx

- 102 ND AYA males & parents reported fertility risk

| | None | Low | Moderate | High |
|------------|------|-----|----------|------|
| Oncologist | 0% | 33% | 41% | 25% |
| AYA | 5% | 38% | 50% | 7% |
| Parent | 1% | 27% | 60% | 12% |

- AYA – 59.8% inaccurately reported fertility risk
 - 43% under-reported risk
 - 17% over-reported risk
- Parents – 58.7% inaccurately reported fertility risk
 - 35% under-reported risk
 - 23% over reported

Consequences of Inaccurate Risk Perceptions

Under-estimations:

- Perceive their risk level is lower than actual risk
 - Confusion/anger/disappointment at FB challenges
 - Fewer biological options
 - Occasional decisional regret for not pursuing FP

Over-estimations:

- Perceive their risk level is higher than actual risk
 - Unnecessary worry/concern
 - Adverse impact on establishing/maintaining relationships
 - Risky sexual behavior and unplanned pregnancy

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Decision-Making in Survivorship

Educational Intervention
Fertility Status Assessment
Family Building

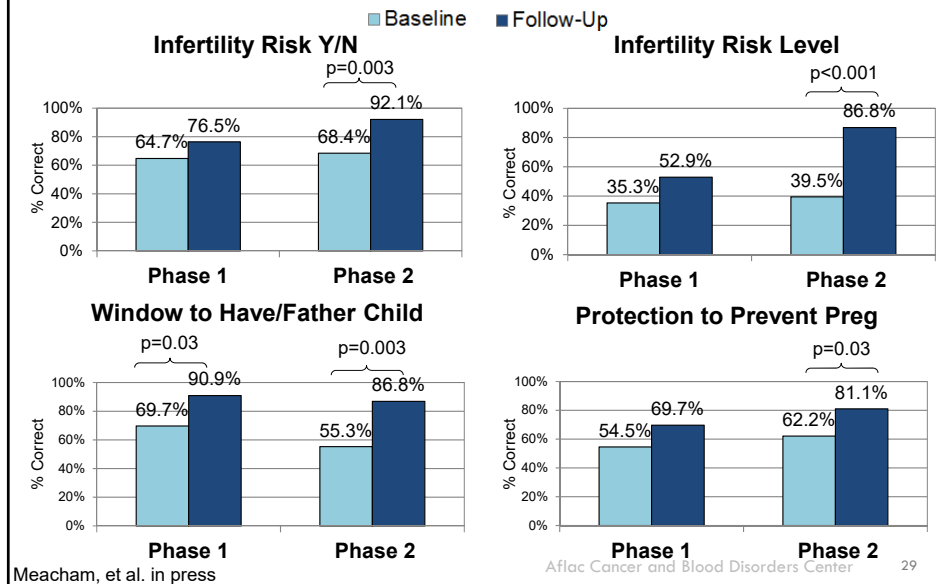
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Educational Intervention



Fertility Status Assessment*

Males

- Semen analysis
 - Volume
 - Concentration of sperm
 - Motility
 - Progression
 - Morphology
 - Total motile sperm
- Hormonal assessment
 - Testosterone

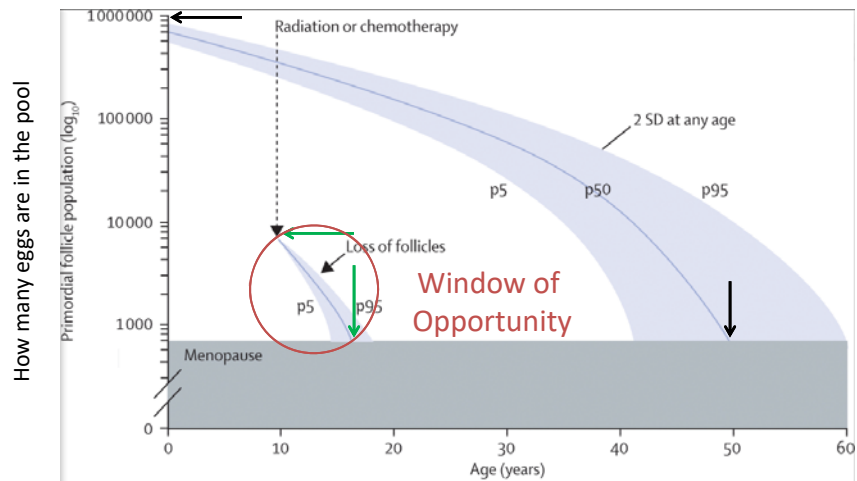
Females

- Ultrasound
 - Transvaginal
 - Transabdominal
- Hormonal assessment
 - AMH
 - FSH
 - LH
 - Serial assessment

*Current status

Assessing Ovarian Reserve after Cancer Tx

Ovarian Reserve - “Egg Pool”, estimated by AMH, anti-mullerian hormone



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Assistive Reproductive Technologies (ARTs)

- Ovarian stimulation and oocyte harvest
 - Cryopreserve eggs
 - Fresh transfer
- ICSI as part of in vitro fertilization (IVF)
- Gamete Intrafallopian transfer (GIFT)
- Zygote Intrafallopian transfer (ZIFT)

Associated options which may be of interest to survivors

- Preimplantation genetic testing
- Insemination
- TESE/TESA

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Biological options for family building - Women

- Attempt traditional approach for pregnancy
- Use previously banked materials
 - Frozen eggs
 - Tissue (whole ovary or cortical strips)
 - Embryos
- IVF
- Donor eggs
- Donor embryos
- Surrogate/Gestational Carrier

Alternative family building options - Women

- Adoption
- Foster Mom
- Step-mother
- God mother
- Motherly role in parenting partner's or other children
- Parenthood flexibly defined
- Promotion of non-traditional definitions of motherhood

Biological options for family building - Men

- Attempt traditional approach for pregnancy
- Use previously banked materials
 - Sperm
 - Tissue (experimental)
 - Spermatogonial stem cells (experimental)
- TESE
- Donor sperm
- Donor embryos

Alternative family building options - Men

- Adoption
- Foster Dad
- Step-father
- God father
- Fatherly role in parenting partner's or other children
- Flexibly defined
- Promotion of non-traditional definitions of fatherhood

Outcomes and Costs



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Costs of In- or Sub-Fertility

- Financial costs – regardless of pathway pursued
- Physical costs – procedural tolerance, protocol demands
- Psychological costs – fertility-related distress, uncertainty, disappointment, anger, resentment, sadness, grief/loss
- Social costs – effects on romantic relationships, social comparison, parent (and in-law) pressure
- Costs of changes in identity formation – self and within community

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Recommendations for Fertility Counseling among AYAs



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From a psychosocial perspective....

- Work w/ survivor to clarify goals at the beginning of the encounter
- Serial assessment of fertility needs throughout CA trajectory
- Accurate and timely provision of information
- Tailor the decision-making process to the survivor
- Above all else, promote decisional satisfaction
- Engage in appropriate management of:
 - Psychological factors affecting process and outcome
 - Familial context and associated considerations
 - Assent (for minors) and consent
 - Procedural distress
 - Prompt follow-up as needed
 - Resources

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Considerations in counseling survivors

- Don't make assumptions
- Cognitive reframing
- Gently correct misperceptions/misconceptions
- Work from a developmental framework/perspective
- Normalize, no right or wrong decisions
- Utilize multidisciplinary team
- Anticipate barriers and non-linear process
- Relax and get comfortable asking the difficult questions
- Become expert on the fertility processes at your institution and knowing when and how to make appropriate referrals
- Remember role and scope of care

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THANK YOU & QUESTIONS

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