

Fertility in Survivorship

What do you need to KNOW?

What do you need to DO?

Dr. Jennia Michaeli, MD
ObGyn, REI

Speaker disclosure statement

Jennia Michaeli has no financial disclosure or conflict of interest with the presented material

Common misconceptions about fertility in survivorship

I had cancer and now:

- ❁ I can't become/ make someone, pregnant.
- ❁ I can't carry a pregnancy.
- ❁ I don't need to use contraception.
- ❁ My children might be unhealthy.

I got my period/ have an erection/ ejaculation after cancer therapy:

- ❁ Everything is OK!
- ❁ I don't need any fertility follow-up.
- ❁ There is no way to preserve my fertility once I am exposed to chemo/ radiation.

Survivors' perceptions of fertility risk

JAMA
Network | **Open**



Original Investigation | Obstetrics and Gynecology

Perceived and Objective Fertility Risk Among Female Survivors of Adolescent and Young Adult Cancer

Hena Naz Din, PhD; Savitri Singh-Carlson, PhD; Heather L. Corliss, PhD; Sheri J. Hartman, PhD; David Strong, PhD; Hala Madanat, PhD; H. Irene Su, MD, MSCE

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this cohort study, survivors of AYA cancer had high rates of perceiving increased infertility risk but frequently overestimated or underestimated their risk. These findings suggest that counseling on infertility risk throughout survivorship may reduce misalignment between perceptions and actual risk, decrease fertility-related psychological distress, and inform family planning decisions.

JAMA Network Open. 2023;6(10):e2337245. doi:10.1001/jamanetworkopen.2023.37245

Key Points

Question How do female survivors of adolescent and young adult (AYA) cancer perceive their fertility?

Findings In this cohort study of 785 participants, most female survivors (62%) of AYA cancer perceived increased risk of infertility, particularly with increased estimated gonadotoxicity of cancer treatment or an abnormal menstrual pattern. However, their perceptions of infertility risk had minimal agreement with objective risk.

Meaning These findings suggest that infertility risk counseling throughout cancer survivorship is needed for AYA cancer survivors to reduce misalignment between perceptions and actual risk, decrease fertility-related psychological distress, and inform family planning decisions.

Qualitative studies

JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
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DOI: 10.1089/jayao.2015.0024

Original Article

Fertility Issues in Adolescent and Young Adult Cancer Survivors

Catherine Benedict, PhD, Elyse Shuk, MA, and Jennifer S. Ford, PhD

Life narrative

Female; 16 years old;
Sertoli Leydig tumor
of the right ovary

“I have one ovary taken out, and like my dream has always—like I used to always play Barbies when I was little, and I would always have families, and that’s been my dream forever. And it was really, really scary for me.”

31%

20%

Male; 16 years old;
Berkitt’s lymphoma

“That was a really bad day ... they were like, “Oh, you might not be able to have kids.” And that was sort of like the straw that just really—I think that was the first time that I realized it [cancer] would affect the rest of my life.”

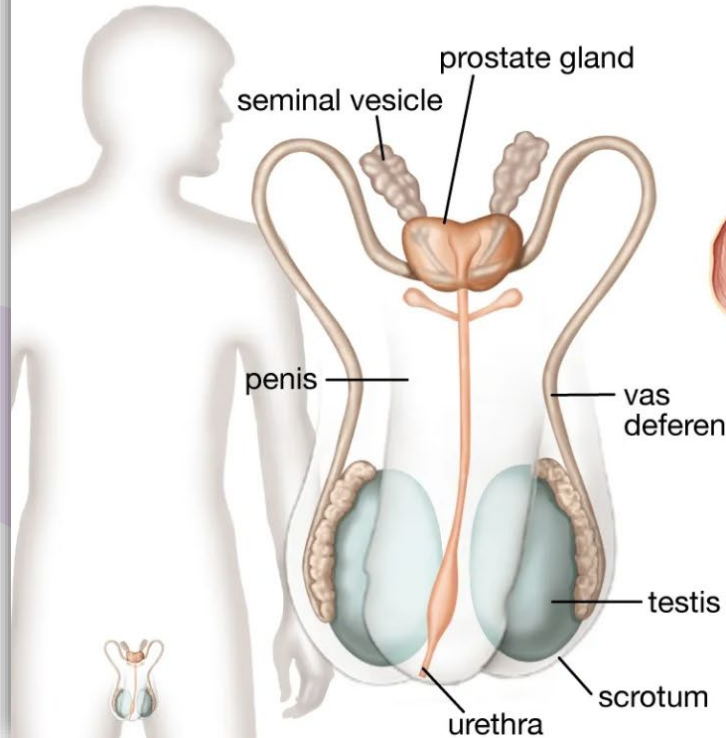
Quotes are divided by subthemes. Within each subtheme, quotes are grouped by sex, with those from female participants listed first, and ordered by age.

Objectives

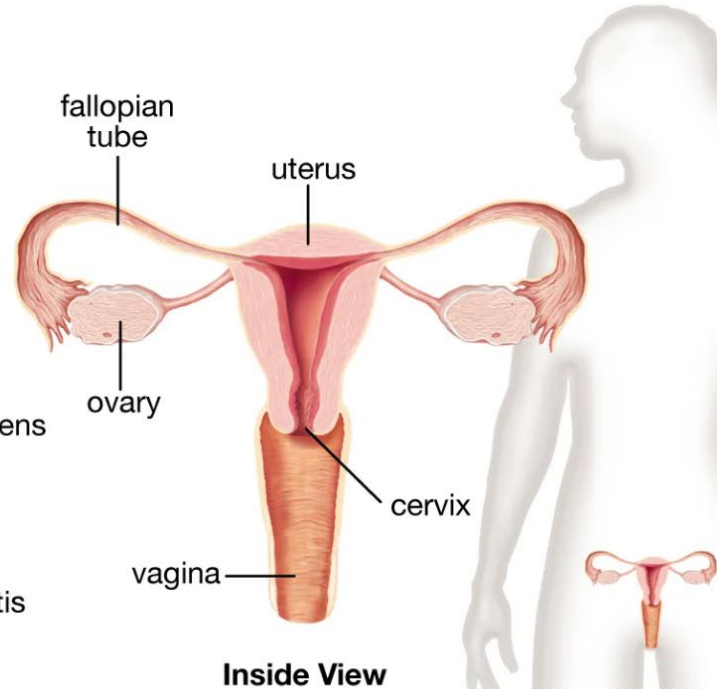
- ❁ Review late fertility effects of gonadotoxic therapy.
- ❁ Review ways to assess fertility function.
- ❁ Review strategies to preserve fertility after cancer.
- ❁ Review strategies for parenthood.

Reproductive anatomy

Male Reproductive System



Female Reproductive System



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Effects of gonadotoxic therapy – Ovary

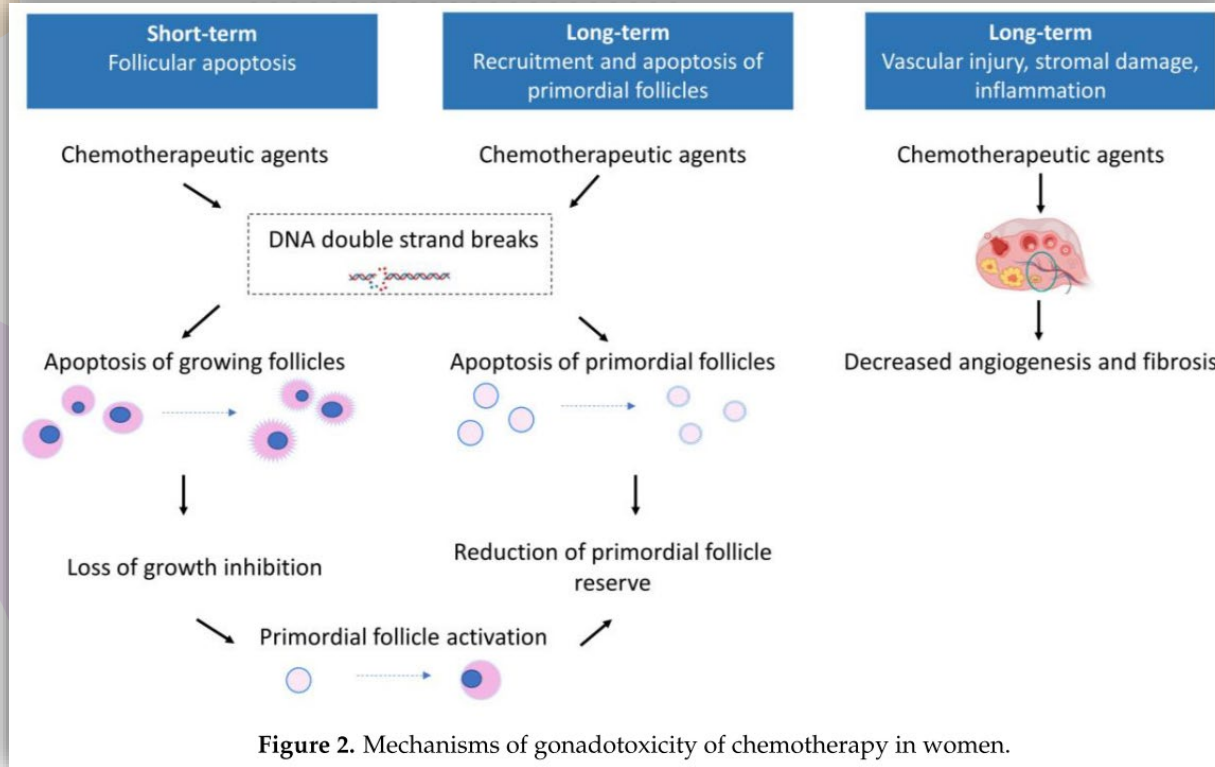


Figure 2. Mechanisms of gonadotoxicity of chemotherapy in women.

Effects of gonadotoxic therapy – Testis

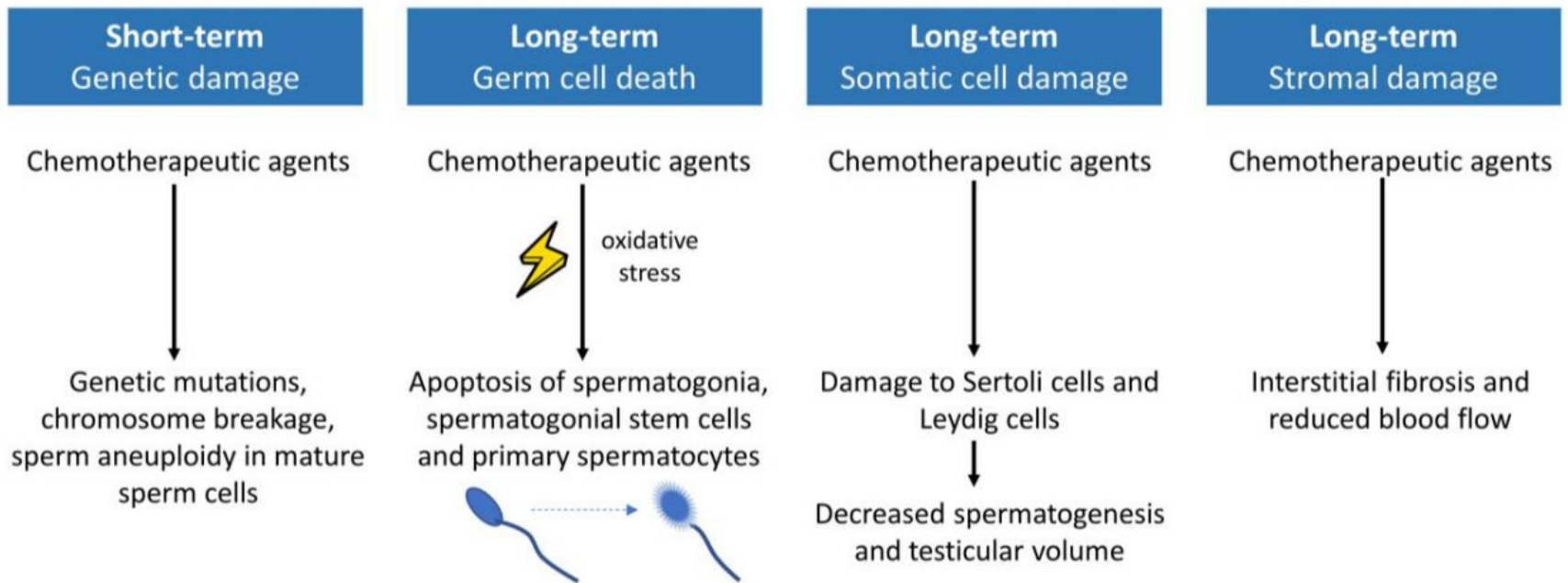


Figure 3. Mechanisms of gonadotoxicity of chemotherapy in men.

Factors affecting gonadotoxic risk

- Age at exposure.
- Type of exposure/ agents.
- Dose of exposure.
- Need for surgery.
- Individual response.

Table 2: Female Level of Risk for Gonadal Failure / Infertility above that for the general population

		Minimally Increased Risk	Significantly Increased Risk	High level of Increased Risk
Alkylators CED* gm/m2	Prepubertal	CED < 8	8-12	> 12
	Pubertal	CED <4	4-8	>8
Heavy Metal		Cisplatin Carboplatin		
HSCT				Alkylator +/-TBI Myeloablative and Reduced intensity
Radiation exposure	Ovary	Prepubertal	<15 Gy	≥ 15 Gy
		Pubertal	<10 Gy	≥ 10 Gy
	Hypothalamus	22-29.9	> 30-39.9 Gy	> 40 Gy

Table 3: Male Level of Risk for Infertility above that for the general population

		Minimally Increased Risk	High level of significantly increased risk	
Alkylators CED* gm/m2		CED <4	CED ≥ 4	
HSCT			Alkylator based and /or TBI Myeloablative and Reduced intensity	
		Minimally Increased Risk	Significantly Increased Risk	High level of Significantly Increased Risk
Heavy Metal mg/m2		Cisplatin Carboplatin	Cisplatin>500	
Radiation Exposure	Testicular	0.2-0.6Gy	0.7-3.9 Gy	≥4.0 Gy
	Hypothalamus#	26-29.99	> 30-39.9 Gy	> 40 Gy
Surgery			RPLND	

Myth Buster #1

- ✿ People who have had cancer are **not** always completely infertile.
- ✿ Should use contraception if wish to avoid pregnancy.
- ✿ Children of cancer survivors are healthy.

Chances of pregnancy after cancer therapy

Human Reproduction, pp. 1–8, 2021
doi:10.1093/humrep/deab036

human
reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Risk of infertility in female adolescents and young adults with cancer: a population-based cohort study

MP Velez^{1,2,3*}, H Richardson², NN Baxter^{3,4}, Chad McClintock², E Greenblatt⁵, R Barr⁶, and M Green^{3,7}

¹Department of Obstetrics and Gynecology, Queen's University, Kingston General Hospital, Kingston, ON, Canada ²Department of Public Health Sciences, Queen's University, Kingston, ON, Canada ³ICES, Toronto, ON, Canada ⁴Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia ⁵Department of Obstetrics and Gynecology, University of Toronto, Toronto, ON, Canada ⁶Department of Pediatrics, McMaster University, Hamilton, ON, Canada ⁷Department of Family Medicine, Queen's University, Kingston, ON, Canada

*Correspondence address: Department of Obstetrics and Gynecology, Queen's University, Kingston General Hospital, Victory 4, 76 Stuart St., Kingston, ON K7L 2N7, Canada; Tel: 613-548-1372; Fax: 613-548-1330; E-mail: mana.velez@queensu.ca

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Table II Proportion of infertility diagnosis among female AYA with cancer and unexposed women

	AYA with cancer N = 14,316	Unexposed N = 60,975	P-value*
All	1,649 (11.5%)	5,616 (9.2%)	<0.001
Brain cancer	61 (0.6%)	226 (9.0%)	0.06
Breast cancer	338 (8.9%)	1023 (6.5%)	<0.001
Colorectal cancer	32 (8.9%)	118 (7.8%)	0.43
Leukemia	40 (13.7%)	118 (9.2%)	0.01
Hodgkin lymphoma	215 (17.3%)	661 (12%)	<0.001
Non-Hodgkin lymphoma	109 (14.7%)	348 (10.9%)	0.001
Thyroid cancer	615 (12.0%)	2223 (10.2%)	<0.001
Melanoma	239 (11.0%)	899 (9.6%)	0.03

*P values from unadjusted modified Poisson regression models.

MAIN RESULTS AND THE ROLE OF CHANCE: Mean age at cancer diagnosis was 31.4 years. Overall, the proportion of infertility diagnosis was higher in cancer survivors compared to unexposed women. Mean age of infertility diagnosis was similar among cancer survivors and unexposed women (34.8 years and 34.9 years, respectively). The overall risk of infertility diagnosis was higher in cancer survivors (RR 1.30; 95% CI 1.23–1.37). Differences in infertility risk varied by type of cancer. Survivors of breast cancer (RR 1.46; 95% CI 1.30–1.65), leukemia (RR 1.56; 95% CI 1.09–2.22), Hodgkin lymphoma (RR 1.49; 95% CI 1.28–1.74), non-Hodgkin lymphoma (RR 1.42; 95% CI 1.14, 1.76), thyroid cancer (RR 1.20; 95% CI 1.10–1.30) and melanoma (RR 1.17; 95% CI 1.01, 1.35) had a higher risk of infertility diagnosis compared to women without cancer. After stratification by parity, the association remained in nulliparous women survivors of breast cancer, leukemia, lymphoma and melanoma, whereas it was attenuated in parous women. In survivors of thyroid cancer, the association remained statistically significant in both nulliparous and parous women. In survivors of brain or colorectal cancer, the association was not significant, overall or after stratification by parity.

The health of children of cancer survivors

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ORIGINAL ARTICLE

Paediatric and Perinatal Epidemiology WILEY

Association of maternal cancer with congenital anomalies in offspring

Nathalie Auger^{1,2,3,4} | Amanda Maniraho^{1,2} | Aimina Ayoub^{1,2} | Laura Arbour⁵

¹University of Montreal Hospital Research Centre, Montreal, Quebec, Canada

²Institut national de santé publique du Québec, Montreal, Quebec, Canada

³Department of Social and Preventive Medicine, School of Public Health, University of Montreal, Montreal, Quebec, Canada

⁴Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

⁵Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence

Nathalie Auger, Bureau d'information et d'études en santé des populations, Institut national de santé publique du Québec, Montreal, Quebec, Canada.
Email: nathalie.auger@inspq.qc.ca

Funding information

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Abstract

Background: Congenital anomalies are common, but the possibility that maternal cancer increases the chance of having a child with a birth defect is not fully understood.

Objectives: To examine the association between maternal cancer before or during pregnancy and the risk of birth defects in offspring.

Methods: We conducted a retrospective cohort study of live births in Quebec, Canada, between 1989 and 2022 using hospital data. The main exposure measure was maternal cancer before or during pregnancy. The outcome included birth defects detected in offspring during gestation or at birth. We estimated risk ratios (RR) and 95% confidence intervals (CI) for the association of maternal cancer with birth defects using log-binomial regression models adjusted for potential confounders.

Results: In this study of 2,568,120 newborns, birth defects were present in 6.0% and 6.7% of infants whose mothers had cancer before or during pregnancy, respectively, compared with 5.7% of infants whose mothers never had cancer. Cancer during pregnancy was associated with heart (RR 1.58, 95% CI 1.03, 2.44), nervous system (RR 4.05, 95% CI 2.20, 7.46) and urinary defects (RR 1.72, 95% CI 1.01, 2.95). Among specific types of malignancies during pregnancy, breast cancer was the most prominent risk factor for birth defects (RR 1.55, 95% CI 1.02, 2.37). **Cancer before pregnancy was not associated with any type of birth defect or with defects overall (RR 1.01, 95% CI 0.92, 1.11). Moreover, no specific type of cancer before pregnancy was associated with an increased risk of birth defects.**

Conclusions: Maternal cancer during pregnancy is associated with the risk of congenital anomalies in offspring, however, cancer before pregnancy is not associated with this outcome.

KEYWORDS

cancer, cancer survivors, congenital anomaly, heart defects, mothers, neoplasms

Pregnancy complications in cancer survivors

Expert Reviews

ajog.org

Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group

 Check for updates

Anne-Lotte Lolkje Femke van der Kooi, MD, PhD; Renee L. Mulder, PhD; Melissa M. Hudson, MD; Leontien C. M. Kremer, MD; Rod Skinner, MBChB, PhD; Louis S. Constone, MD; Wendy van Dorp, MD, PhD; Eline van Dulmen-den Broeder, PhD; Jeanette Falck-Winther, DMSc, MD; W. Hamish Wallace, MD; Jason Waugh, MBBS, FRCOG, FRANZCOG; Teresa K. Woodruff, PhD; Richard A. Anderson, MD; Saro H. Armenian, DO, MPH; Kitty W. M. Bloemenkamp, MD; Hilary O. D. Critchley, MD; Charlotte Demoor-Goldschmidt, MD; Matthew J. Ehrhardt, MD; Daniel M. Green, MD; William A. Grobman; Yuriko Iwahata, MD; Iris Krishna, MD, MPH; Joop S. E. Laven, MD, PhD; Gill Levitt, MBBS, FRChP; Lillian R. Emily S. Miller, MD, MPH; Annemarie Mulders, MD, PhD; Angela Polanco, MRes; Cécile M. Ronckers, PhD; Amber Samuel, MD; Tom Walwyn, MBBS; Jennifer M. Levine, MD; Marry M. van den Heuvel-Eibrink, MD

TABLE 2

Harmonized recommendations for counseling and surveillance in pregnancy

General recommendation

Healthcare providers should discuss the risk of adverse obstetrical outcomes based on the specific cancer treatment exposures with all female CAYA cancer survivors of reproductive age.

Who needs preconception counseling?

Female CAYA cancer survivors and their healthcare providers should be aware that there is no evidence to support that survivors have an increased risk of giving birth to a child with congenital anomalies (high-quality evidence).

Female CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus and their healthcare providers should be aware of the risk of adverse obstetrical outcomes such as miscarriage (moderate-quality evidence), premature birth (high-quality evidence), and low birthweight (high-quality evidence).

Who needs specific obstetrical surveillance during pregnancy?

High-risk obstetrical surveillance is recommended for CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus owing to the risk of premature birth and low birthweight (high-quality evidence).

Who needs specific cardiac surveillance during pregnancy? (based on IGHG cardiomyopathy guideline⁴³)

Cardiomyopathy surveillance is reasonable before pregnancy or in the first trimester for all female survivors treated with anthracyclines and chest radiation (moderate-level recommendation, moderate-quality evidence).⁴³

No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal left ventricular systolic function immediately before or during the first trimester of pregnancy (moderate-level recommendation, low-quality evidence).⁴³

CAYA, childhood, adolescent, and young adult; IGHG, International Late Effects of Childhood Cancer Guideline Harmonization Group.

van der Kooi. IGHG recommendations for management of obstetrical risks for female CAYA survivors. *Am J Obstet Gynecol* 2021.

Myth Buster #2

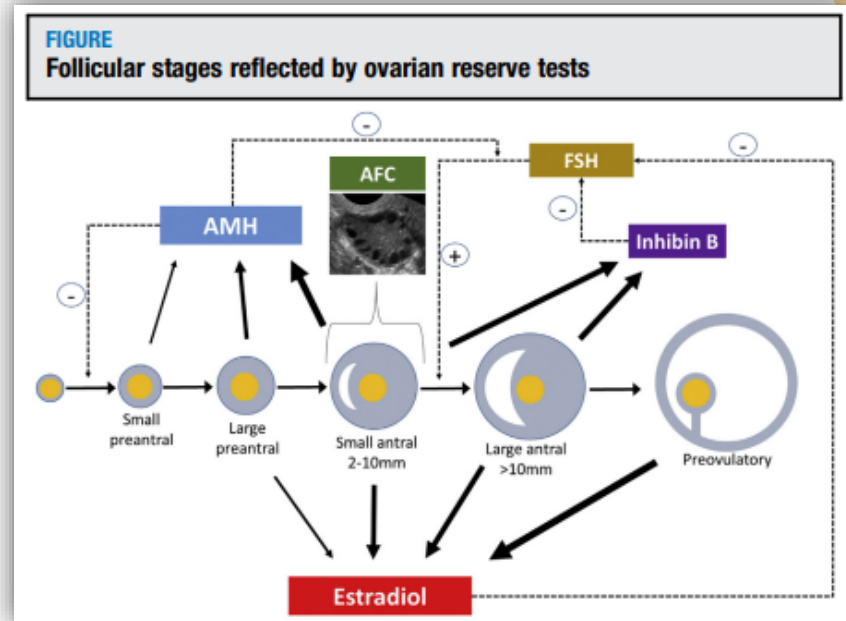
- ❁ Resumption of menses is not a guarantee of future fertility.
- ❁ Erection and ejaculation of semen, do not guarantee normal sperm production.
- ❁ Following ovarian reserve markers is advised to identify the need for fertility preservation or timing of pregnancy.

Ways to assess fertility function – people with ovaries

Ovarian reserve markers:

• Sonography – Antral Follicle Count.

• Hormonal testing – AMH, FSH, E2.



AMH decline in cancer survivor

CLINICAL RESEARCH ARTICLE

Differential Rates of Change in Measures of Ovarian Reserve in Young Cancer Survivors Across the Reproductive Lifespan

Katherine Cameron,¹ Mary D. Sammel,^{1,2} Maureen Prewitt,¹ and Clarisa

¹Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology of Pennsylvania, Philadelphia, Pennsylvania 19104; and ²Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104

ORCID numbers: 0000-0002-0859-0741 (K. Cameron); 0000-0003-1248-4199 (M. D. Sammel); 0000-0001-7617-3643 (C. Gracia).

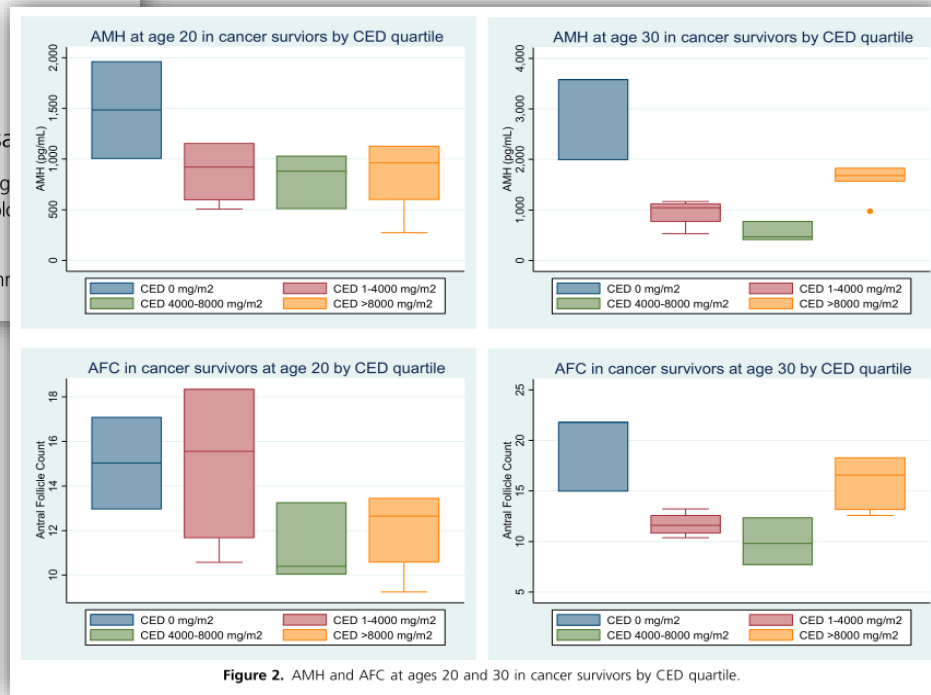


Figure 2. AMH and AFC at ages 20 and 30 in cancer survivors by CED quartile.

AMH – what is it good for?

AMH is predictive of:

- ❁ Functional Ovarian Reserve and the number of oocytes retrieved in fertility treatment/ egg freezing.

AMH is NOT predictive of:

- ❁ Natural fertility.
- ❁ The success of fertility treatment.
- ❁ How long will fertility last.

Pregnancy despite low AMH

Low concentration of circulating antimüllerian hormone is not predictive of reduced fecundability in young healthy women: a prospective cohort study

Casper P. Hagen, M.D.,^a Sonja Vestergaard, Ph.D.,^b Anders Juul, Dm.S.C.,^a Niels Erik Skakkebaek, Dm.S.C.,^a Anna-Maria Andersson, Ph.D.,^a Katharina M. Main, Ph.D.,^a Niels Henrik Hjøllund, Ph.D.,^{c,d} Erik Ernst, Ph.D.,^{d,e} Jens Peter Bonde, Dm.S.C.,^{d,f,g} Richard A. Anderson, Ph.D.,^h and Tina Kold Jensen, Ph.D.^{a,b}

Objective: To evaluate whether circulating levels of antimüllerian hormone (AMH) predict fecundability in young healthy women.
Design: Prospective cohort study.

Setting: General community.

Patient(s): A total of 186 couples who intended to discontinue contraception to become pregnant were followed until pregnancy or for six menstrual cycles.

Intervention(s): None.

Main Outcome Measure(s): Fecundability was evaluated by the monthly probability of conceiving (i.e., fecundability ratio [FR]). In addition, circulating levels of LH, FSH, T, and sex hormone-binding globulin (SHBG) were evaluated in 158 of 186 women.

Result(s): Fifty-nine percent of couples conceived during the study period. Compared to the reference group of women with medium AMH (AMH quintiles 2–4), fecundability did not differ significantly in women with low AMH (AMH quintile 1) (FR 0.81; 95% confidence interval [CI] 0.44–1.40). In contrast, women with high AMH (AMH quintile 5) had reduced fecundability (FR 0.62; 95% CI 0.39–0.99) after adjustment for covariates (woman's age, body mass index [BMI], smoking, diseases affecting fecundability, and oligozoospermia). Irregular menstrual cycles were more prevalent in women with high AMH compared with women with low or medium AMH levels, and they had higher levels of LH (geometric mean: 8.4 vs. 5.3 IU/L) and LH:FSH ratio (2.4 vs. 1.8). After exclusion of women with irregular cycles, women with high AMH still had reduced fecundability (FR 0.48; 95% CI 0.27–0.85) and elevated LH:FSH ratio (2.4 vs. 1.7).

Conclusion(s): Low AMH in healthy women in their mid-20s did not predict reduced fecundability. Even after exclusion of women with irregular cycles, the probability of conceiving was reduced in women with high AMH. (Fertil Steril® 2012;98:1602–8. © 2012 by American Society for Reproductive Medicine.)

Key Words: AMH, MIS, time to pregnancy, fecundity, fecundability, PCOS

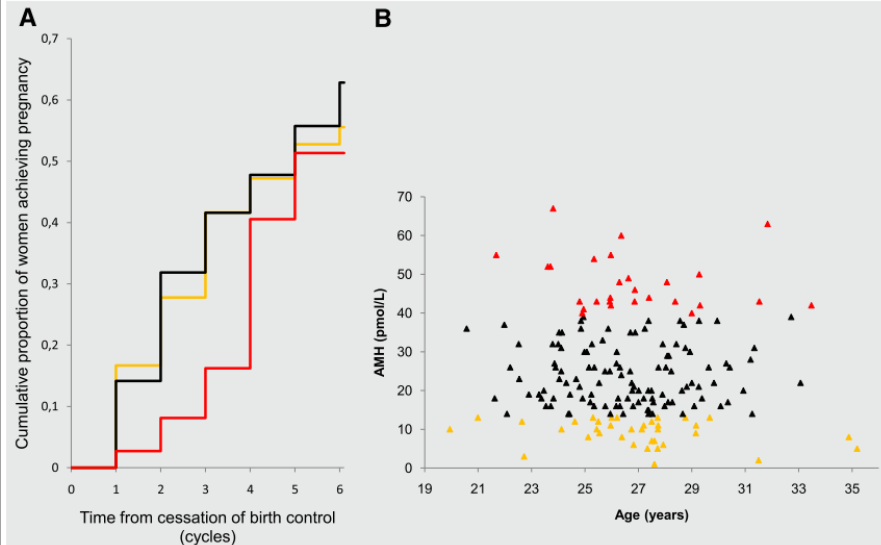
Discuss: You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/hagencp-anti-mullerian-hormone-fecundability/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

FIGURE 1

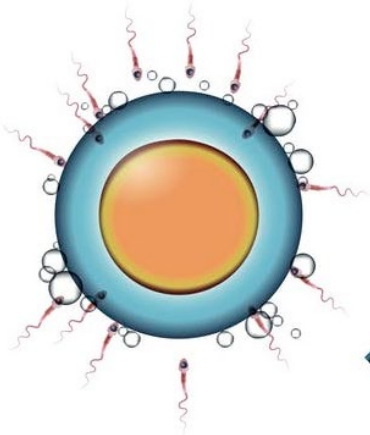


(A) Kaplan-Meier curves showing cumulative proportion of pregnancy by serum level of antimüllerian hormone (AMH). Low AMH (quintile 1) orange line, medium AMH (quintiles 2–4) black line, high AMH (quintile 5) red line. *P* value describes difference between curves (log-rank test); *P* = .289. (B) Antimüllerian hormone level as a function of age in 186 participating women. Colors correspond to subgroups of AMH levels: low (orange), medium (black), and high (red).

Hagen. Low AMH predicts normal fecundability. *Fertil Steril* 2012.

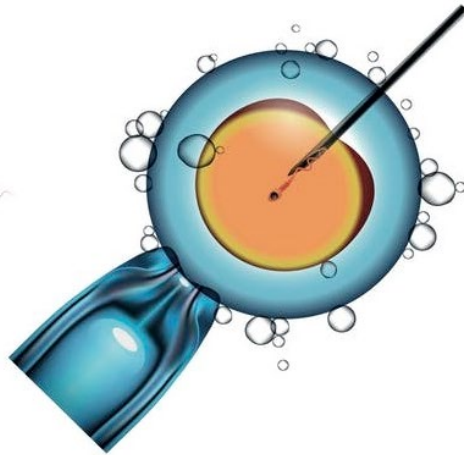
Ways to assess fertility function – people with sperm

IVF



Self-employed
Penetration sperm in
Egg after addition
process sperm

ICSI



Injection of a sperm into a
Egg under microscopic control

TABLE 1. Reference values for semen parameters according to different editions of the WHO Manual for the Examination and Processing of Human Semen

Semen characteristics	WHO 1999	WHO 2010	WHO 2021
Volume (ml)	≥2	1.5	1.4
Sperm concentration (10^6 /ml)	≥20	15	16
Total motility (%)	≥50	40	42
Normal morphology (%)	14	4	4
Normozoospermia	31 (3.9%)	138 (17.5%)	126 (16.0%)
1 semen abnormality	217 (27.5%)	269 (34.1%)	257 (32.6%)
2 semen abnormalities	293 (37.2%)	235 (29.8%)	238 (30.2%)
3 semen abnormalities	247 (31.3%)	146 (18.5%)	167 (21.2%)

Male fertility after childhood cancer

J Cancer Surviv (2014) 8:437–447
DOI 10.1007/s11764-014-0354-6

Male infertility in long-term survivors of pediatric cancer: a report from the childhood cancer survivor study

K. Wasilewski-Masker · K. D. Seidel · W. Leisenring · A. C. Mertens · M. Shnorhavorian · C. W. Ritenour · M. Stovall · D. M. Green · C. A. Sklar · G. T. Armstrong · L. L. Robison · L. R. Meacham

Abstract

Purpose The purpose of this study was to assess the prevalence of male infertility and treatment-related risk factors in childhood cancer survivors.

Methods Within the Childhood Cancer Survivor Study, 1,622 survivors and 274 siblings completed the Male Health Questionnaire. The analysis was restricted to survivors (938/1,622; 57.8 %) and siblings (174/274; 63.5 %) who tried to become pregnant. Relative risks (RR) and 95 % confidence intervals (CI) for the prevalence of self-reported infertility were calculated using generalized linear models for demographic variables and treatment-related factors to account for correlation among survivors and siblings of the same family. All statistical tests were two-sided.

Results Among those who provided self-report data, the prevalence of infertility was 46.0 % in survivors versus 17.5 % in siblings (RR=2.64, 95 % CI 1.88–3.70, $p<0.001$). Of survivors who met the definition for infertility, 37 % had reported at

least one pregnancy with a female partner that resulted in a live birth. In a multivariable analysis, risk factors for infertility included an alkylating agent dose (AAD) score ≥ 3 (RR=2.13, 95 % CI 1.69–2.68 for AAD ≥ 3 versus AAD <3), surgical excision of any organ of the genital tract (RR=1.63, 95 % CI 1.20–2.21), testicular radiation ≥ 4 Gy (RR=1.99, 95 % CI 1.52–2.61), and exposure to bleomycin (RR=1.55, 95 % CI 1.20–2.01).

Conclusion Many survivors who experience infertility father their own children, suggesting episodes of both fertility and infertility. This and the novel association of infertility with bleomycin warrant further investigation.

Implications for Cancer Survivors Though infertility is common, male survivors reporting infertility often father their own children. Bleomycin may pose some fertility risk.

Keywords Infertility · Cancer · Male · Long-term survivors · Pediatrics

What to DO?

Awareness of reproductive window of opportunity:

- ✿ Fertility preservation to delay childbearing.
- ✿ Fertility treatment to attempt conception.
- ✿ Alternatives.

To delay childbearing

Ways to preserve fertility after cancer:

🌸 People with Ovaries –

🌸 Freeze mature eggs/ embryos

🌸 People with sperm –

🌸 Freeze sperm

Preservation of fertility – Eggs / Sperm freezing

Eggs

- ✿ Injectable medicine to grow multiple follicles.
- ✿ Visits for BW and US – monitoring follicle growth.
- ✿ Egg retrieval procedure under conscious sedation.

Sperm

- ✿ Masturbation// Electroejaculation// Testicular sperm retrieval.

Preservation of fertility – Egg freezing

Egg Freezing Process



Day 1-2

Initial Consultation & Fertility Assessment



Day 3-10

Ovarian Stimulation & Monitoring



Day 11-13

Trigger Shot & Preparation for Egg Retrieval



Day 14

Egg Retrieval Procedure



Day 15-16

Fertilization, Selection & Vitrification



Post-procedure

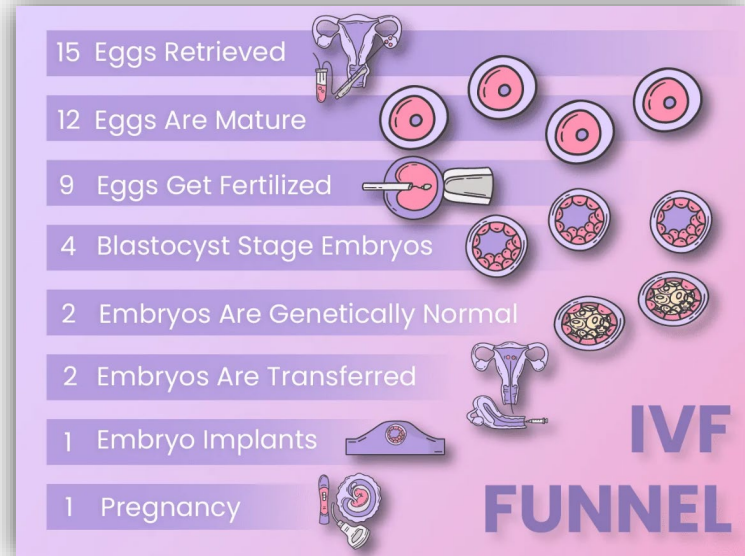
Storage & Ongoing Monitoring of Frozen Eggs

Special considerations if pregnancy is desired

- ❁ Careful family planning – optimize chances for natural pregnancy.
- ❁ Assisted Reproductive Technologies.
- ❁ Third-party reproduction.
- ❁ Alternative ways for parenthood.

Assisted Reproduction Technology Options

- ❁ Controlled ovarian stimulation.
- ❁ Intrauterine insemination.
- ❁ In-Vitro-Fertilization (+/- ICSI).



Success of TESE in male cancer survivors



Table 1
Sperm retrieval rate per diagnosis.

Diagnosis	Number of Patients	Number of TESE	Sperm found (%)
Hodgkin lymphoma	13	16	4 (33.3%)
Seminoma	4	9	8 (88%)
Non Hodgkin lymphoma	3	3	1 (33.3%)
Leukemia	5	5	0
Solid tumors	11	11	4 (36%)

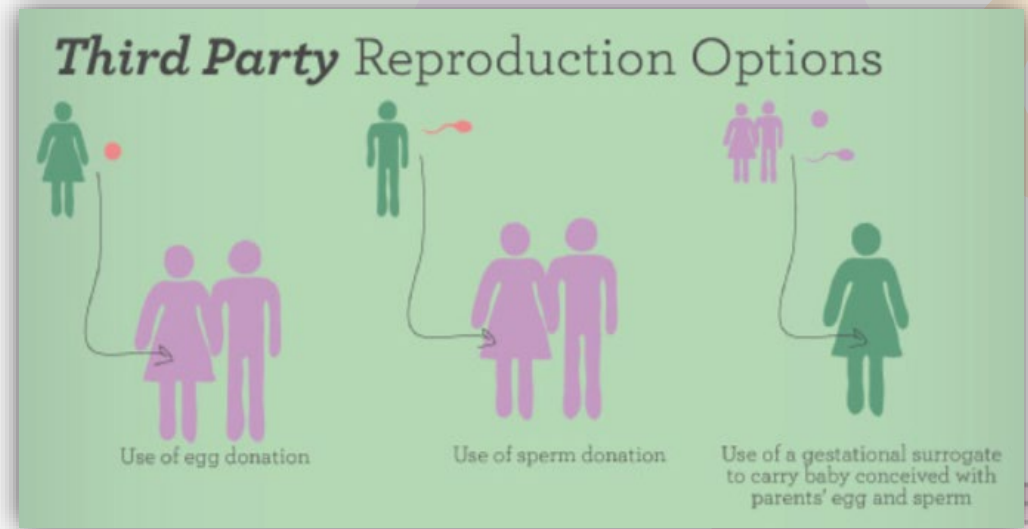
Alternative paths for parenthood

Third-party reproduction:

- ❁ Donor eggs.
- ❁ Donor sperm.
- ❁ Gestational carrier.

Other alternatives:

- ❁ Adoption.
- ❁ Child-free living.



Take home messages

- ✿ Natural fertility is **possible!**
- ✿ Fertility **preservation** and treatment can help extend the window of opportunity.
- ✿ Follow-up and planning is a **Key**.
- ✿ Many ways for **parenthood**.

Thank you!

Dr. Jennia Michaeli, MD
ObGyn, REI