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Fertility and Family Building after a Breast Cancer Diagnosis: The Smaller Pieces that Make the Big Picture

Terri Lynn Woodard, MD
Director, MD Anderson Oncofertility Program
Associate Professor

Department of Gynecologic Oncology and Reproductive Medicine,
The University of Texas MD Anderson Cancer Center

Division of Reproductive Endocrinology and Infertility, Baylor College of Medicine

Objectives

- Discuss the importance and relevance of fertility issues in reproductive age individuals with breast cancer
- Examine options for fertility preservation prior to cancer treatment
- Review special considerations that are made for women who purse assisted reproductive technologies
- Explore the process of pursuing pregnancy after a breast cancer diagnosis
- Highlight alternative options for family building post-cancer treatment
- Investigate barriers to fertility care and potential solutions

Take Home Points

- Make no assumptions about “appropriateness”
- Menses does not equal fertility
- Fertility counseling is important at all phases
- It is a process

Why is this important?

- Survivors want to have children (Schover, 1999)
- Significant cause of distress (Canada & Schover, 2012)
- Tenet of holistic and comprehensive care
- It is the right thing to do

Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K; American Society of Clinical Oncology. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006 Jun 20;24(18):2917-31.

Canada AL, Schover LR. The psychosocial impact of interrupted childbearing in long-term female cancer survivors. Psychooncology. 2012 Feb;21(2):134-43.

American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients

- "As part of **education and informed consent** before cancer therapy, health care providers **should address** the possibility of infertility with patients treated during their reproductive years and **be prepared to discuss possible fertility preservation options and/or to refer** all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, the Update Panel encourages providers to advise patients regarding potential threats to fertility as **early as possible** in the treatment process so as to allow for the widest array of options for fertility preservation.

Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, Wallace WH, Wang ET, Loren AW. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018 Jul 1;36(19):1994-2001.

Breast Cancer in Reproductive Age Women

- Breast cancer is the most common cancer in women
  - Over 270,000 new diagnoses of invasive breast cancer this year in the United States
- More than 5-7% of new breast cancers are diagnosed under the age of 40

https://www.cancer.net/cancer-types/breast-cancer/statistics
Accessed 4/15/2020

Anders CK et al. Breast cancer before age 40 years. *Semin Oncol*. 2009;36:237-49.

Hayat et al. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist*. 2007;12:20-37.

Prognosis

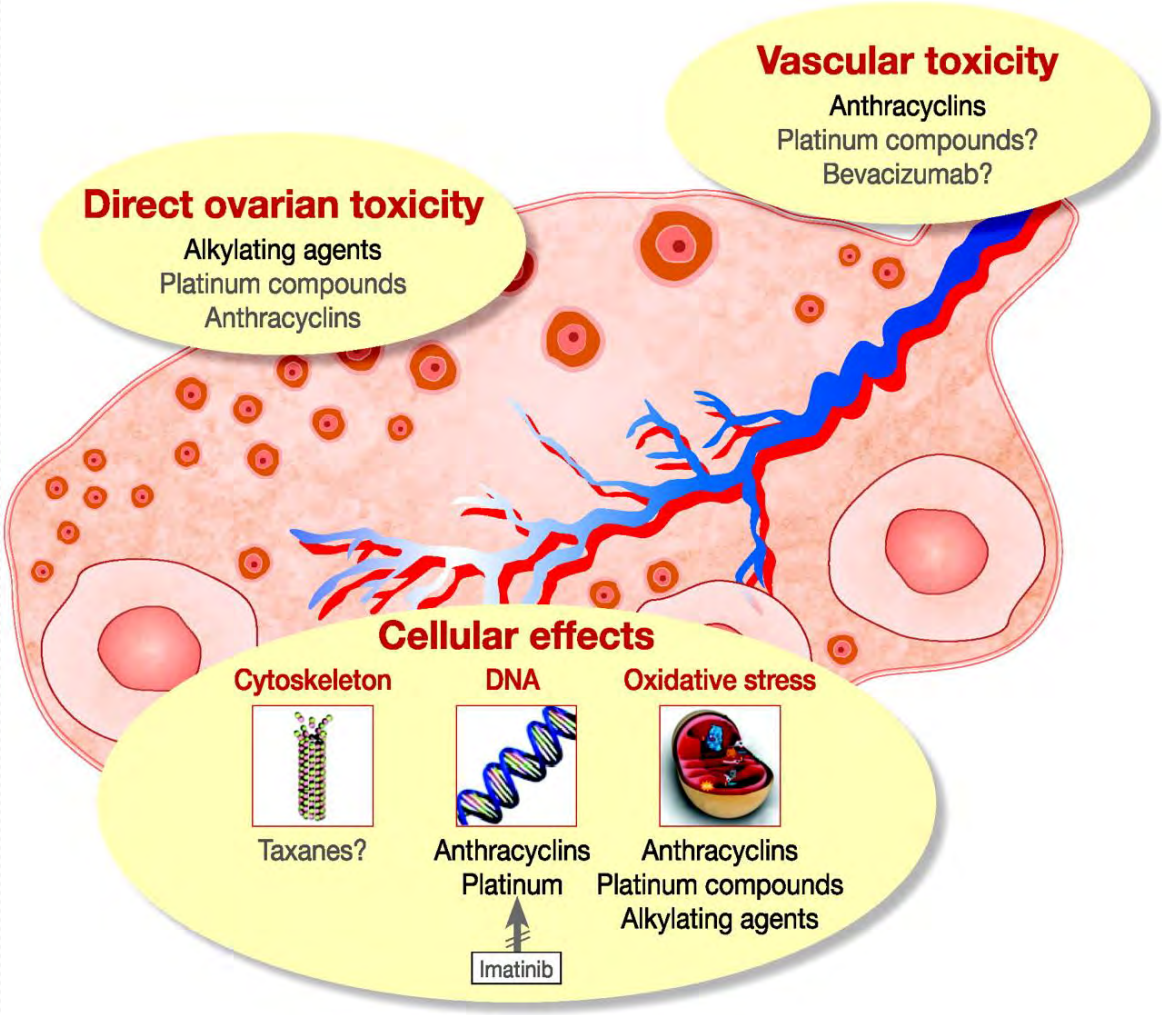
- 5-year female cancer survival is dependent on stage at diagnosis but is currently 90% for breast cancer
- Life after cancer and survivorship issues are important
- Very few go on to have a pregnancy

Cancer Facts and Figures. Atlanta, Ga, USA: American Cancer Society; 2011.

Threats to Fertility

- Depends on age
- Depends on baseline fertility
- Depends on treatment
  - Surgery
  - Radiation
  - Chemotherapy

Figure 1 Suggested mechanisms for ovarian toxicity.



Ben-Aharon I , and Shalgi R Reproduction 2012;144:153-163

Effects of common chemotherapeutic regimens on menses

High Risk: More than 80% of women develop amenorrhea post-treatment.

- CAF x 6 cycles in women ages 40 and older (cyclophosphamide, doxorubicin, 5-FU)
- CEF x 6 cycles in women ages 40 and older (cyclophosphamide, epirubicin, 5-FU)
- CMF x 6 cycles in women ages 40 and older (cyclophosphamide, methotrexate, 5-fluorouracil)

Intermediate Risk: Approximately 30-70% of women develop amenorrhea post-treatment.

- CMF x 6 cycles in women ages 30-39 (cyclophosphamide, methotrexate, 5-fluorouracil)
- CEF x 6 cycles in women ages 30-39 (cyclophosphamide, epirubicin, 5-FU)
- CAF x 6 cycles in women ages 30-39 (cyclophosphamide, doxorubicin, 5-FU)
- AC x 4 cycles in women ages 40 and older (doxorubicin, cyclophosphamide)

Low Risk: Less than 20% of women develop amenorrhea post-treatment.

- AC x 4 cycles in women ages 30-39 (doxorubicin, cyclophosphamide)
- CAF x 6 cycles in women under 30 (cyclophosphamide, doxorubicin, 5-FU)
- CEF x 6 cycles in women under 30 (cyclophosphamide, epirubicin, 5-FU)
- CMF x 6 cycles in women under 30 (cyclophosphamide, methotrexate, 5-fluorouracil)

Very Low/No Risk: No effects on menses.

- methotrexate, 5-FU

Unknown Risk: There has been limited research on this treatment.

- Trastuzamab (Herceptin)
- Paclitaxel (Taxanes used in AC protocols)
- Docetaxel (Taxanes used in AC protocols)

Menses ≠ Fertility

So what is the risk?

Impact of Age on Fertility

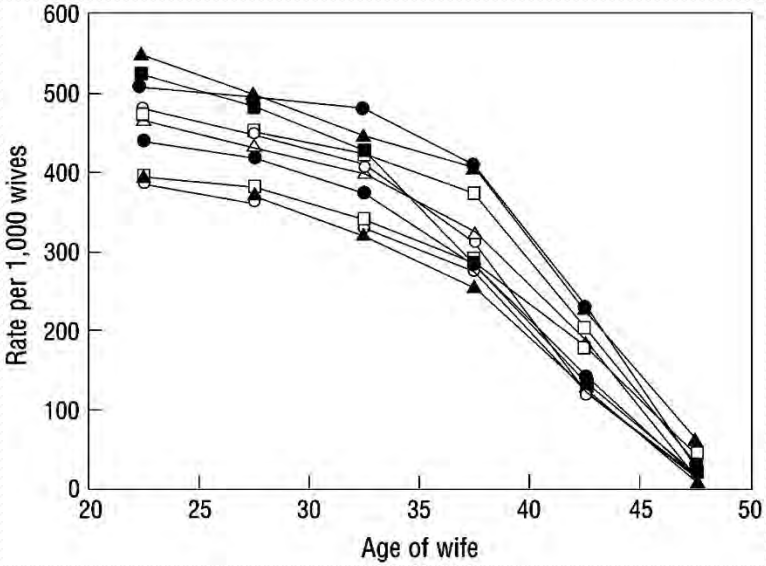


Figure 1. Marital fertility rates by 5-years age group. The ten population (in descending order at age 20–24 years) are Hutterites, marriages from 1921–30 (▲); Geneva bourgeoisie, husbands born in 1600–49 (▪); Canada, marriages 1700–30 (●); Normandy, marriages 1760–90(○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840–59(▵) Normandy, marriages 1674–1742 (●); Norway, marriages 1874–76 (□); Iran, village marriages, 1940–50 (▲); Geneva bourgeoise, husbands born before 1600 (○); From Menken J, Trussel J, Larsen U, Age and Sciensce 1986;233;1389–94

Committee on Gynecologic Practice of American College of Obstetricians and Gynecologists; Practice Committee of American Society for Reproductive Medicine. Age-related fertility decline: a committee opinion. Fertil Steril. 2008 Nov;90(5 Suppl):S154-5.

Ovarian Reserve

- the capacity of the ovary to provide eggs that are capable of fertilization resulting in a healthy and successful pregnancy.
- Determined indirectly
  - Follicle Stimulating Hormone and Estradiol (FSH/E2)
  - Inhibin B
  - Antimullerian Hormone (AMH)
  - Antral Follicle Count (AFC)

Antral Follicle Count

http://www.cherish-uk.com/fertility-scans-birmingham.html

Components of the Oncofertility Consult

- Review of medical history
- Baseline ovarian reserve testing
- Risk assessment
- Exploration of options for fertility preservation
- Brief discussion of pregnancy planning
- Discussion of alternative options for family building
- Follow up planning

Fertility and Family Building

Thinking about options

Before

(fertility preservation)

vs.

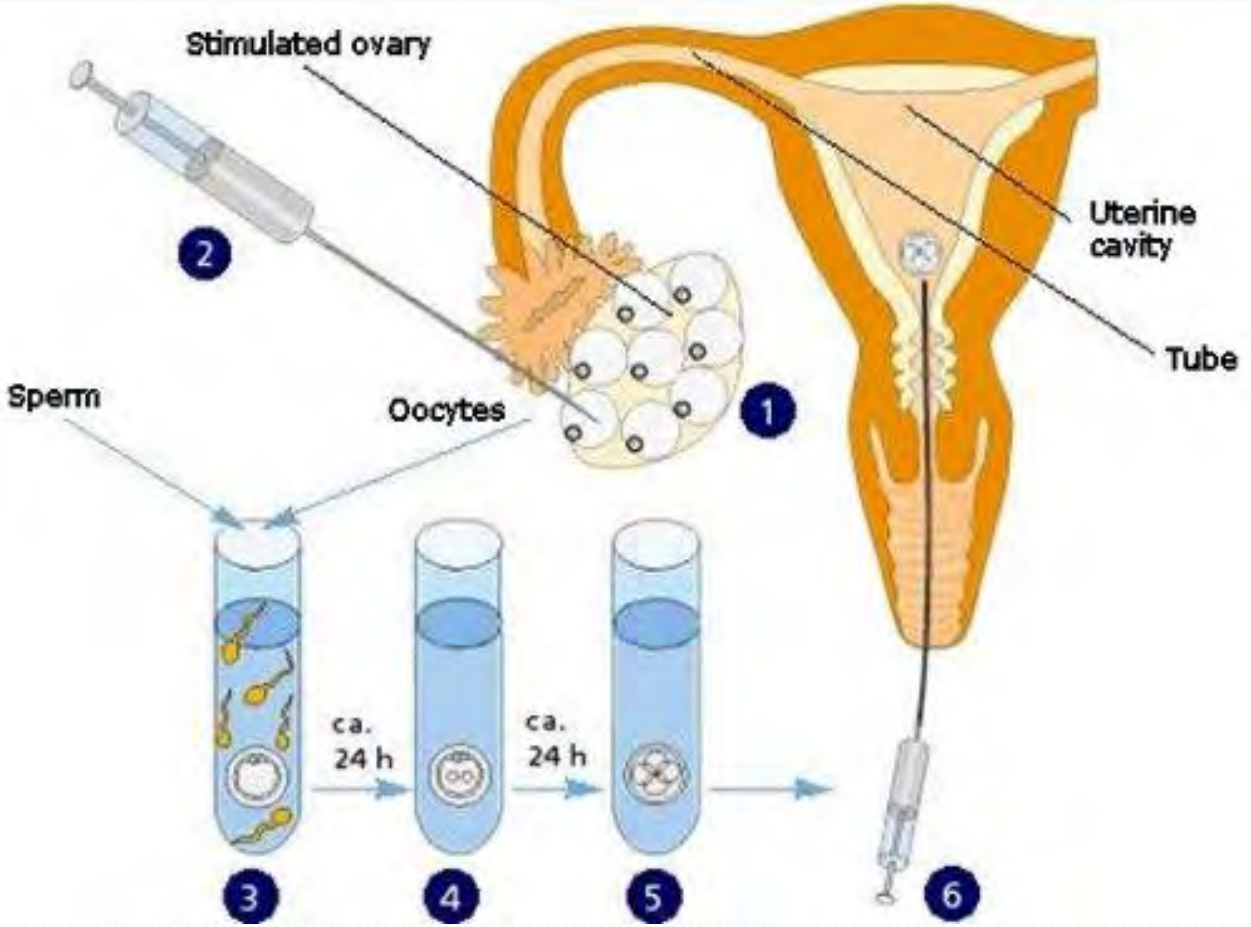
After

(working with what you have)

Options for Fertility Preservation

- Assisted Reproductive Technologies (ART)
  - Embryo cryopreservation
  - Oocyte cryopreservation
    - Mature
    - Immature
- Ovarian tissue cryopreservation
- Ovarian Suppression
- Ovarian transposition
- Conservative surgery
- Hormonal management

Ovarian Hyperstimulation and IVF



ART: Special Considerations when Taking Care of Patients with Cancer

- Health of the patient
- Timing
- Safety
- Hereditary Cancer Syndromes
- Setting of Expectations

Health of the Patient

- Medication management
- Collaboration with oncology and other medical specialists
- Anesthesia and post-op planning

Timing

- Random Start Protocols
  - Late follicular phase
    - If the follicle cohort following the lead follicle was <12 mm and stayed <12 mm before a spontaneous LH surge, ovarian stimulation was initiated without GnRH antagonist; however, it was started after an LH surge--when the secondary follicle cohort reached 12mm. If the follicle cohort following the lead follicle reached 12mm **before** the spontaneous LH surge, GnRH antagonist was initiated and continued until triggering final oocyte maturation with hCG or GnRH agonist
      - **OR**
    - Ovulation induced with hCG or GnRH agonist when the dominant follicle reached 18 mm in diameter and ovarian stimulation was started 2–3 days after trigger
  - Luteal phase
    - Start ovarian stimulation without antagonist and initiate it when 12mm
  - Outcomes comparable excepted slightly longer stimulation, more gonadotropins
- Consecutive Ovarian Stimulation Cycles
  - Can significantly increase oocyte/embryo yield without significantly delaying cancer treatment.

Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril. 2013;100:1673-80.

Turan V, Bedoschi G, Moy F, Oktay K. Safety and feasibility of performing two consecutive ovarian stimulation cycles with the use of letrozole-gonadotropin protocol for fertility preservation in breast cancer patients. Fertil Steril. 2013 Dec;100(6):1681-5.

Safety

- Hormone-sensitive cancers: use of aromatase inhibitors
  - Co-administration of letrozole 5mg
  - Trigger criteria: need larger follicles
  - Does not result in poorer outcomes; may even enhance response to stimulation
- Avoidance of Ovarian Hyperstimulation Syndrome (OHSS)
  - GnRH agonist trigger improves safety of controlled ovarian stimulation by decreasing incidence of OHSS
  - May also improve yield of MII oocytes and 2PN embryos available for cryopreservation

Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol. 2005;23:4347-53.

Turan V, Bedoschi G, Emirdar V, Moy F, Oktay K. Ovarian Stimulation in Patients With Cancer: Impact of Letrozole and BRCA Mutations on Fertility Preservation Cycle Outcomes. Reprod Sci. 2018 Jan;25(1):26-32.

Pereira N, Kelly AG, Stone LD, Witzke JD, Lekovich JP, Elias RT, Schattman GL, Rosenwaks Z. Gonadotropin-releasing hormone agonist trigger increases the number of oocytes and embryos available for cryopreservation in cancer patients undergoing ovarian stimulation for fertility preservation. Fertil Steril. 2017 Sep;108(3):532-538.

Protocols for Women with Breast Cancer

- Natural cycle IVF
- Letrozole
  - Get multifollicular development without significant rise in estradiol levels.
  - In 79 patients who used this protocol, hazard ratio for recurrence was not increased and survival was not compromised.
- Tamoxifen
  - Similar findings

Oktay et al. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol 2005;23:4347-53.

Azim et al. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol 2008;26:2630-5

Embryos or Oocytes?

Embryos	Oocytes
Most common and successful	Experimental label removed
Need a partner or donor sperm	No partner required; provides reproductive autonomy; Bypasses some religious objections
Takes approximately 2 weeks	Takes approximately 2 weeks
Requires ovarian stimulation	Requires ovarian stimulation
Success rates approximately 30-35%	Success rates rapidly improving: 25%
$10,000 + medications	$8000 + medications

Other ART Considerations for Women with Breast Cancer

- BRCA carriers
  - Decreased ovarian reserve?
  - Risk-reducing bilateral salpingo-oophorectomy
  - Concern for offspring

Pre-implantation Genetic Testing

- PGT-A
  - Tests for number of chromosomes and sex
- PGT-M
  - Tests for a specific gene mutation

Ethical concerns

- Sex selection
- Indication for testing (fatal versus non-fatal disease)
- HLA typing aka “savior sibling”
- Selection (against or for)
- Eugenics
- Patients struggle
    - Many individuals agree that PGD should be offered, but only a minority would consider this for themselves
    - Importance of counseling and thinking through the decision
- *“PGD for adult-onset conditions is ethically justified when the condition is serious and no safe, effective interventions are available. It is ethically allowed for conditions of lesser severity or penetrance. The Committee strongly recommends that an experienced genetic counselor play a major role in counseling patients considering such procedures (Ethics Committee of the American Society for Reproductive Medicine, 2013).”*

Daum H, Peretz T, Laufer N. BRCA mutations and reproduction. Fertil Steril. 2018 Jan;109(1):33-38.

Rich TA, Liu M, Etzel CJ, Bannon SA, Mork ME, Ready K, Saraiya DS, Grubbs EG, Perrier ND, Lu KH, Arun BK, Woodard TL, Schover LR, Litton JK. Comparison of attitudes regarding preimplantation genetic diagnosis among patients with hereditary cancer syndromes. Fam Cancer. 2014 Jun;13(2):291-9.

BRCA and PGD: review of the literature

- First report of a live birth following PGD for BRCA-1 mutation in 2008
- Outcomes
  - Out of 145 PGD cycles, 720 embryos were tested, and 294 (40.8%) were BRCA negative
  - In 87 fresh cycles with 1-2 embryos transferred, there were 34 clinical pregnancies (39.1% per embryo transfer). (Derks-Smeets et al, 2014)

M.J. Jasper, J. Liebelt, N.D. Hussey. Preimplantation genetic diagnosis for BRCA1 exon 13 duplication mutation using linked polymorphic markers resulting in a live birth Prenat Diagn, 28 (2008), pp. 292-298.

T.N. Sergentanis, A.A. Diamantaras, C. Perlepe, P. Kanavidis, A. Skalkidou, E.T. Petridou. IVF and breast cancer: a systematic review and meta-analysis. Hum Reprod Update, 20 (2014), pp. 106-12J.

Kotsopoulos, C.L. Librach, J. Lubinski, J. Gronwald, C. Kim-Sing, P. Ghadirian, et al. Infertility, treatment of infertility, and the risk of breast cancer among women with BRCA1 and BRCA2 mutations: a case-control study. Cancer Causes Control, 19 (2008), pp. 1111-1119.

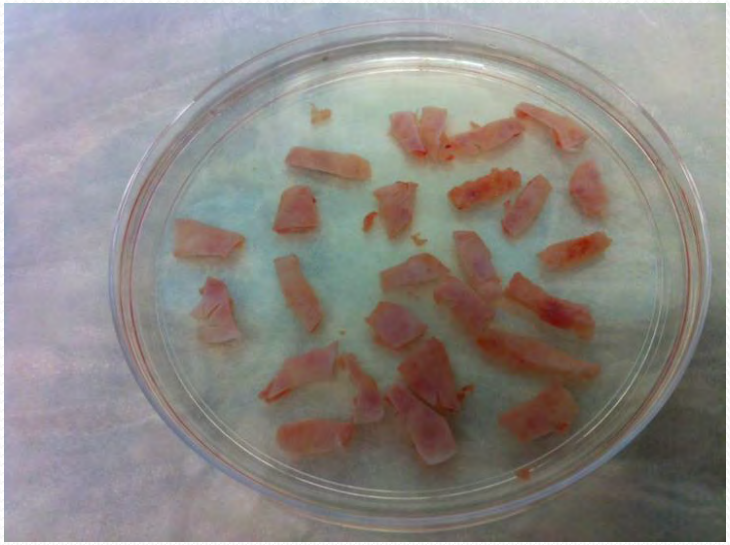
I.A. Derks-Smeets, C.E. de Die-Smulders, S. Mackens, R. van Golde, A.D. Paulussen, J. Dreesen, et al. Hereditary breast and ovarian cancer and reproduction: an observational study on the suitability of preimplantation genetic diagnosis for both asymptomatic carriers and breast cancer survivors. Breast Cancer Res Treat, 145 (2014), pp. 673-681.

In Vitro Maturation

- Retrieval of immature oocytes
- Experimental
- Minimal or no stimulation
- Avoids high estrogen levels
- Timely
- Can combine with ovarian tissue freezing
- Success rates not known

Ovarian Tissue Cryopreservation

- Experimental (no longer!)
- Timely : 1 hour, outpatient laparoscopic procedure
- Does not require stimulation
- Method of choice for prepubescent girls
- Success rates: Over 130 live births
  - Most from adult women but 2 from premenarchal girls
  - Cumulative clinical and LB + OG rates were 57.5% and 37.7%, respectively, and the endocrine restoration rate was 63.9%
- Can be done with prior exposure to chemo
- Has been done for patients with leukemia



Silber SJ. Ovary cryopreservation and transplantation for fertility preservation. Mol Hum Reprod. 2012 Feb;18(2):59-67.

Pacheco F, Oktay K. Current Success and Efficiency of Autologous Ovarian Transplantation: A Meta-Analysis. Reprod Sci. 2017 Aug;24(8):1111-1120.

Meirow D, Ra'anani H, Shapira M, et al. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril. 2016;106:467-474.

Ovarian Suppression

- Use of GnRHa (Gonadotropin Releasing Hormone analogs)
- Experimental
- May be covered for “menstrual suppression”
- Controversial
  - Pregnancy occurred in more women in the goserelin group than in the chemotherapy-alone group (21% vs. 11%)
  - Rate of POI was 14.1% in the GnRHa group and 30.9% in the control group and a total of 37 (10.3%) patients had at least one post-treatment pregnancy in the GnRHa group versus 20 (5.5%) in the control group

Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D, Francis PA, Goldstein LJ, Gomez HL, Vallejos CS, Partridge AH, Dakhil SR, Garcia AA, Gralow J, Lombard JM, Forbes JF, Martino S, Barlow WE, Fabian CJ, Minasian L, Meyskens FL Jr, Gelber RD, Hortobagyi GN, Albain KS; POEMS/S0230 Investigators. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015 Mar 5;372(10):923-32.

Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, Unger JM, Anderson RA, Mehta K, Minton S, Poggio F, Albain KS, Adamson DJA, Gerber B, Cripps A, Bertelli G, Seiler S, Ceppi M, Partridge AH, Del Mastro L. Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. J Clin Oncol. 2018 Jul 1;36(19):1981-1990.

After Cancer Treatment

- Offspring of cancer survivors not thought to be at higher risk, in general
  - Genetic syndromes: Can consider Preimplantation genetic diagnosis (PGD)
- Options
  - Natural Conception
  - Assisted reproduction
  - Assisted Reproductive Technology
  - Donor Egg
  - Gestational Surrogacy
  - Adoption
  - Living without children

Special Considerations for Women with Breast Cancer

- Women with hormone receptor positive cancer
  - Use of tamoxifen
  - Does not seem to impact ovarian function but she is AGING

Pregnancy after Breast Cancer

- Meta-analyses
  - Azim et al
    - 14 studies with 1244 cases and 18,145 controls
    - For overall survival, pooled relative risk was 0.59 (95% CI: 0.50-0.70), favoring survivors with subsequent pregnancy
  - Valachis et al,
    - 9 studies
    - Pooled hazard ratio of death was 0.51 (95% CI: 0.42-0.62), favoring survivors with subsequent pregnancy

Pregnancy after Breast Cancer

- Azim et al, 2013
- Retrospective cohort study
- 333 pregnant patients and 874 matched non pregnant patients with 686 having estrogen receptor positive disease
- No difference in disease free survival between pregnant and non pregnant patients in the ER-positive group (Hazard ratio = 0.91; 95% CI: 0.67 to 1.24,)

Azim et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol.* 2013; 1(1):73-9

Access to Fertility Services

Common misconceptions about fertility preservation

- We can definitively predict who is at risk for fertility problems in the future
- The patient is not an appropriate candidate for a consultation
- Options are limited
- It takes too much time
- It is dangerous
- A consult is only useful prior to cancer treatment
- It is a straightforward medical decision

Barriers to Referral

- Lack of knowledge
- Lack of time
- Difficulty in referral
- Cost

Research Questions

How can we improve access?

How can we improve decision support?

Creation of a Patient Decision Aid (DA)

- What is a decision aid?
  - DAs are educational materials designed to assist with treatment decision-making, addressing individual values and preferences.
  - Novel formats using computer-based, interactive technologies have been shown to improve patient knowledge and decision satisfaction, even in patients with low health literacy.

Our Specific Aims

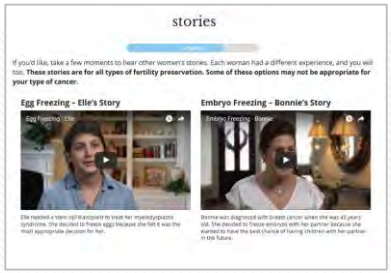
- Aim 1: To conduct a formal needs assessment to identify the factors and priorities that patients with cancer use to make real-world decisions about FP.
- Aim 2: To design and produce a web-based DA to support women with cancer who are considering FP.

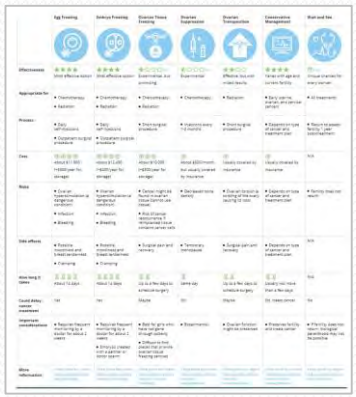
What did we learn from our needs assessment?

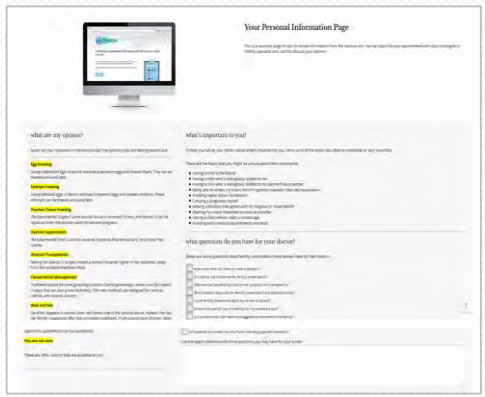
- Clinicians
  - They think discussions about fertility are important but cite multiple barriers
  - They think a fertility decision aid is a good idea, BUT
  - They want minimal involvement with it
  - Specific recommendations for length, content, format
- Patients
  - Wanted information
  - Wanted to know “what they didn’t know”
  - Wanted to be able to access when they wanted
  - Didn’t want too strong of a focus on “motherhood”

pathways
fertility preservation

a fertility preservation decision aid for women with cancer





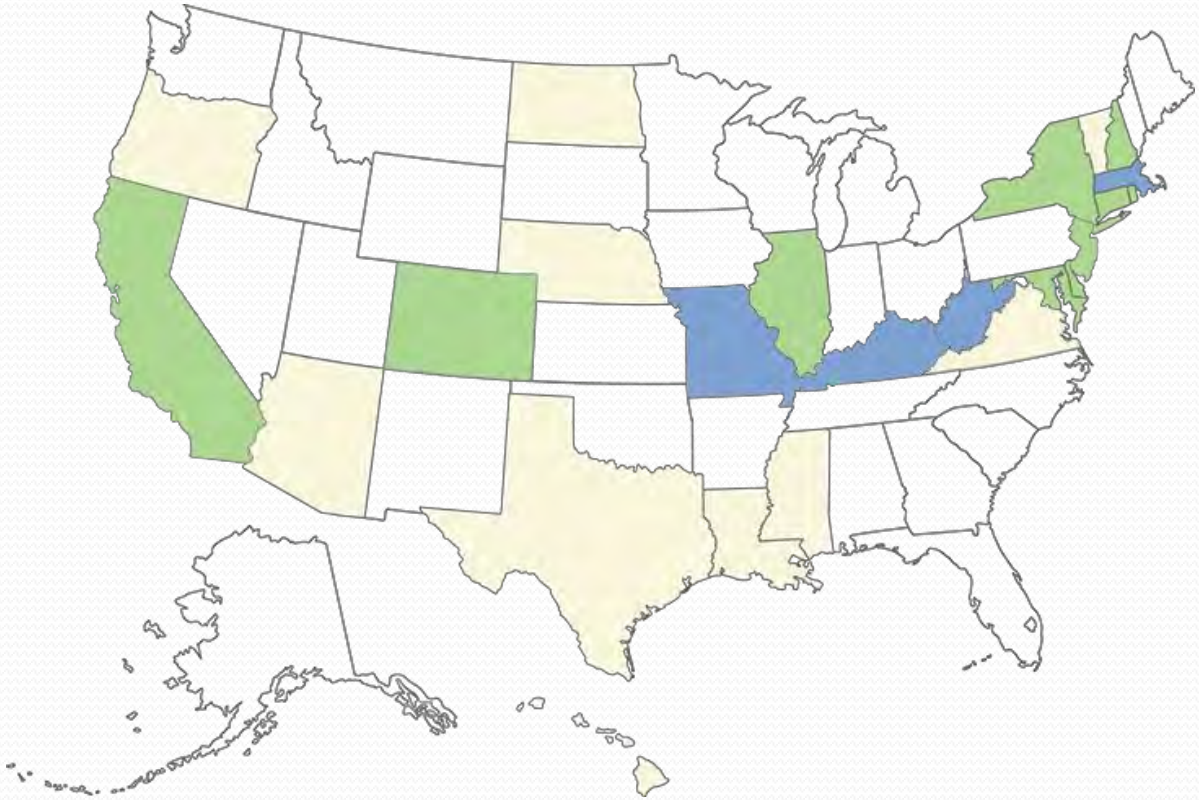


Woodard TL, Hoffman AS, Covarrubias LA, Holman D, Schover L, Bradford A, Hoffman DB, Mathur A, Thomas J, Volk RJ. The Pathways fertility preservation decision aid website for women with cancer: development and field testing. J Cancer Surviv. 2018 Feb;12(1):101-114.

Advocacy

- *How do we navigate the political arena to promote legislation that supports FP coverage?*
  - State Legislators
  - Organizations
    - ASRM
    - RESOLVE
    - Alliance for Fertility Preservation
    - Fertile Action
    - Coalition to Protect Parenthood After Cancer

Fertility Preservation Legislation by State



Fertility Preservation Coverage | Active Legislation | Inactive Legislation | No Coverage/No Legislation

Why Advocacy Matters…..

COVID-19 and Fertility Preservation for Patients with Cancer - ASRM

- Update #1 (3/30/20)
  - Suspending initiation of new treatment cycles, including ovulation induction, intrauterine inseminations (IUIs), in vitro fertilization (IVF) including retrievals and frozen embryo transfers, as well as non-urgent gamete cryopreservation
  - Strongly considering cancellation of all embryo transfers whether fresh or frozen
  - Continuing to care for patients who are currently "in-cycle" or who require urgent stimulation and cryopreservation
  - Suspending elective surgeries and non-urgent diagnostic procedures
  - Minimizing in-person interactions and increasing utilization of telehealth
- Update #2 (4/13/2020)
  - **While it is not yet prudent to resume non-emergency infertility procedures, the Task Force recognizes it is also time to begin to consider strategies and best practices for resuming time-sensitive fertility treatments in the face of COVID-19.**

Joint Statement from the Alliance for Fertility Preservation and the Oncofertility Consortium on Fertility Preservation for Patients Receiving Gonadotoxic Therapies During the COVID-19 Pandemic

During this uncertain and unprecedented time, the oncofertility community is working together to provide up-to-date fertility preservation information for patients and providers. We are aware of the recommendations from ASRM's COVID-19 Task Force which suggests new IVF cycles not be initiated at this time. **While this pause in services does not apply to urgent fertility preservation for patients receiving gonadotoxic therapies, we recognize it may impact practices' standard operations which could, inadvertently affect these patients' access to some services.** Based on dialogue with clinicians and leaders in the fertility preservation community, providers remain committed to handling these urgent cases, but we are aware that evolving geographic, legal, and practical constraints may cause interruptions or delays.

Conclusion

- Fertility is an important issue that needs to be addressed
- Viable options for fertility preservation and family building exist
- Advocacy efforts may allow all patients access to fertility services