Fertility and Breast Cancer: Educational Opportunities and Preservation Options

Kristin N Smith
Patient Navigator
I have no disclosures to report.

I will not discuss any “off-label” use of medications.
Objectives

• Describe the state of the science of fertility preservation
• Discuss experimental and standard fertility preservation options available
• Identify challenges and opportunities for fertility preservation and methods for fertility preservation
• Illustrate programmatic processes for establishing a fertility preservation service and educational opportunities
The History
Of Northwestern’s Program

• Oncofertility Consortium
  – A national, interdisciplinary initiative designed to explore the reproductive future of cancer survivors. It was supported by the National Institutes of Health through the NIH Roadmap for Medical Research/Common Fund. The Consortium is now supported by a U54 grant.
  • Patient Navigation: Full time navigator hired in 2006
The Oncofertility Consortium
National Physician’s Cooperative
Patient Navigation

• Process by which an individual – a Patient Navigator – guides patients through and around barriers in a complex healthcare environment to help ensure diagnosis and treatment.

Risks of Infertility

• Variety of factors influence fertility after treatment:
  – Treatment and Dose
    • Chemotherapy (alkylating, platinum agents)
    • Radiation (cranial, spinal, pelvic)
    • Surgery
  – Previous treatment(s)
  – Age
Females

**Birth:**
1 million follicles

**Puberty:**
300,000 follicles

**Normal Ovarian Reserve**

**Menopause:**
Follicles exhausted

**Death**

---

Average Age (years)

<table>
<thead>
<tr>
<th></th>
<th>Birth:</th>
<th>Puberty:</th>
<th>Fertility</th>
<th>Subfertility</th>
<th>Infertility</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1 million follicles</td>
<td>300,000 follicles</td>
<td>0.0</td>
<td>12.5</td>
<td>51.0</td>
<td>80.7</td>
</tr>
</tbody>
</table>

---

Back to Biology Basics

**Infertility**

**Subfertility**

**Fertility**

- Fallopian tubes
- Ovaries
- Uterus
- Cervix
- Vagina

Northwestern Medicine
Back to Biology Basics

- **FSH**: Stimulates development of ovarian follicles. Communicates with enzymes in ovaries to increase estrogen production.

- **Estradiol**: Increases bone mineral density and bone age; closes growth plates; stimulates breast development; increases fat mass; triggers production of LH mid-cycle.

- **LH**: Stimulates ovarian theca cells to manufacture androgens; needed for ovulation to occur mid-cycle.

- **Progesterone**: Produced by the corpus luteum in the ovaries and the placenta during pregnancy; helps the endometrium to grow and stay lush.

Diagrams show the menstrual cycle, including follicular and luteal phases, basal body temperature, hormone levels (FSH, LH, estrogen, progesterone), ovaries, and uterus.
New Biology

- Anti-mullerian hormone (AMH)
  - In females
    - Secreted by granulosa cells in ovaries
    - Peaks at age 24, declines with age
    - Does not fluctuate with menstrual cycles
    - More accurate measurement of a woman’s fertility
How Does Cancer Therapy Affect Female Fertility?

- **Chemotherapy**
  - May induce focal fibrosis, damage to blood vessels and neovascularization
  - Graulosa cells reveal ultrastructural changes
  - May target the oocytes in the primordial and smaller primary follicles where as the larger follicles had apoptotic graulosa cells
  - Chemotherapy + older patient = increased risk of ovarian failure

- **Radiation**
  - Abdominal and TBI
  - Risk of infertility is related to number of follicles in reserve and dose of XRT

- **Surgery**

---

**Wallace, Cancer, 2011**

In Other Words

Chemotherapy
Fertility Preservation Options

- Embryo/Oocyte cryopreservation
- Hormone suppression
  - Conflicting data regarding usefulness
- Ovarian Tissue cryopreservation
- Ovarian shielding
- Surgical interventions
Embryo/Oocyte Cryopreservation

- Most commonly used fertility preservation techniques but there are some caveats:
  - Patient must be post pubertal
  - Patient must be emotionally/psychologically ready for multiple transvaginal ultrasounds, blood draws, etc
  - Patient/physician must be able to delay cancer treatment for at least 2 weeks
  - Patient must be healthy enough to undergo oocyte retrieval
  - Will require hormonal stimulation – daily injections
  - Oncology must be ok with hormonal stimulation
Embryo Cryopreservation

- FSH/LH medications for 8-13 days
- GnRH Antagonist midcycle to prevent ovulation
- HCG triggers ovulation 36 hours prior to retrieval

In Vitro Fertilization

1. Egg production stimulated by hormone therapy
2. Eggs retrieved from ovary
3. Sperm sample provided
4. Eggs and sperm combined to allow fertilization
The Retrieval

- Retrieval done under conscious sedation with TVUS and needle guide
- Patient will know immediately how many eggs were retrieved
- Patient will find out how many eggs successfully fertilized usually the following day – frozen at various stages
Cryopreservation Techniques

• Slow Freeze
  – Programmable steps are used to “freeze down” a sample
  – Sample treated with cryoprotectants
  – Temperature dropped at 1°C/min

• Vitrification
  – New technique to prevent ice crystal formation
  – Cryoprotectants are added to protect the sample and to act like antifreeze and increase viscosity
  – No phase change from liquid to solid, the amorphous state is like a “solid liquid”
Pregnancy After Egg/Embryo Cryopreservation

Embryo
- Patient undergoes uterine preparation – estrogen/progesterone
- Controlled thaw
- Zygotes mature if necessary
- Preimplantation genetic diagnosis (PGD) can be done at blastocyst

Success Rates:
- < 35 : 44.4%
- 35-37 : 40.6%
- 38 – 40: 36.1%
- 41 – 42 : 31.6%
- > 42 : 21.2%

Oocyte
- Patient undergoes uterine preparation – estrogen/progesterone
- Controlled thaw
- Intracytoplasmic sperm injection (ICSI)
- Maturation
- PGD

Success Rates:
- Live birth rates per egg (before 2005)
  - Slow freeze: 2%
  - Vitrification: 4%
- Live birth rates from egg donors (43.2%)

SART data from 2013

Northwestern Medicine
What about hormone sensitive tumors?

- Each year, more than 200,000 women are diagnosed with breast cancer. Estimated that 11,000 of those are under 40.

SEER Database (2008)

Alterations in the ovarian hormonal milieu deregulate the centrosome cycle in mammary epithelial cells, leading to aneuploidy and cancer (in mice)

**ORIGINAL ARTICLE**

*Ovarian hyperstimulation induces centrosome amplification and aneuploid mammary tumors independently of alterations in p53 in a transgenic mouse model of breast cancer*

EL Milliken¹, KL Lozada¹, E Johnson¹, MD Landis¹, DD Seachrist¹, I Whitten¹, ALM Sutton¹, FW Abdul-Karim²,³ and RA Keri¹,⁴
The Proposal

• Using tamoxifen or letrozole with low–dose gonadotropin for ovarian stimulation
  • Letrozole – potent 3rd generation aromatase inhibitor that competitively inhibits the activity of aromatase enzyme in estrogen reception positive cells and suppresses estrogen levels
  • Tamoxifen is a selective estrogen receptor modulator

The Data

  – Outcomes: Recurrence rate in the 29 women that did FP was similar to the 31 patients who did not undergo FP

  – Outcomes: no increase in recurrence or death in 79 breast cancer patients who chose to have embryos stored before treatment using letrozole compared with 136 patients who were evaluated but declined FP

• 2012 – Westphal – Gyn Onc - Integration and safety of fertility preservation in a breast cancer program.
  – Outcomes: 2 local breast cancer recurrences out of the 44 breast cancer patients who underwent ovarian stimulation with a mean follow up of 47 months
Additional Thoughts

• Is it as black and white as assumed?

RANDOMIZED STUDY COMPARING CHEMOTHERAPY WITH AND WITHOUT ESTROGEN PRIMING IN ADVANCED BREAST-CANCER

A randomized trial was performed to determine if combination chemotherapy (CT) with estrogen (E) priming (E+ study arm) was superior to CT alone (E- study arm) in patients with advanced breast cancer. CT for both arms included adriamycin + vincristine (AV) starting on day 7 alternating with cytoxan + methotrexate + fluorouracil (CMF) starting on day 28, the entire cycle repeated every 6 weeks. Estrogen priming consisting of 2 mg estradiol + 1 mg estriol (E+ arm) was given orally twice daily beginning on day 1 and continuously through CT until disease progression or unacceptable toxicity. Performance status (KPS) for all patients (n=19, E+ arm; n=22, E- arm) ranged between 70-100%. Mean age (53 y, E+ arm; 56 y, E- arm), menopausal and estrogen receptor status and treatment duration (approximately 38 weeks) were similar for both groups. Estrogen priming did not alter or enhance CT toxicity. Objective responses (CR,PR) were noted in 79% on the E+ arm (CR=11%, PR=68%) and in 73% on the E- arm (CR=9%, PR=64%). Thus, estrogen priming in this cohort of patients with advanced breast cancer did not appear to add to the toxicity or palliative benefit of CT.

GnRH Analogues
Gonadotropin Releasing Hormones

Moore HC, et al, *NEJM*, 2015: 135 pre-menopausal hormone receptor negative breast cancer patients were randomized to chemotherapy alone or chemotherapy with gosarelin. Outcomes showed that 8% of patients in the gosarelin group vs 22% of patients in the chemotherapy alone group experienced ovarian failure. 21% vs 11% of the gosarelin vs chemotherapy alone were able to get pregnant.


Yang, et al, *Breast*, 2013: Meta-analysis of 274 patients who received GnRH agonist vs 254 patients who received chemotherapy alone showed that ‘maybe’ there is some benefit to patients in the GnRH agonist group in rates of premature ovarian failure in the 1st year after treatment but there was no significant effect on return of menses or pregnancy rates.
Ovarian Tissue Cryopreservation

- Ovarian tissue frozen worldwide for over a decade without knowledge of how it could be used.
- Strips of cortical tissue now frozen - not entire ovary
- Most centers only perform this under IRB approved protocols
- Sample protocols and support through the National Physician's Cooperative of...
Use of Cryopreserved Tissue to Initiate a Pregnancy

• Autologous orthotopic transplant results in human pregnancies (13 reported)
• Explants only last about 16 months
• Contraindicated in BRCA+ patients, hematological malignancies

IN VITRO FOLLICLE MATURATION (IVFM)
• Isolate immature follicles from frozen tissue and mature in the laboratory
• Use mature oocytes (MII) to perform IVF
• NO human pregnancies to date
Assembling the Team
‘If you build it, they will come’

The Obvious
• Oncology Nurses
• Oncology LCSW
• Hem/Onc MD
• Urologist(s)
• Reproductive Endocrinologist(s)
• Laboratory Staff
• Navigator
• REI/Urology Nurses

The Not So Obvious
• Phone Receptionists
• Inpatient Unit Clerks
• Billing Professionals
• Psychologists
• Chaplain services
• Fellows/Residents
• CRAs
• Administration
EPIC Questionnaire

Current Questionnaires
FERTILITY PRESERVATION OPTIONS [2100]

<table>
<thead>
<tr>
<th>Adv</th>
<th>Question</th>
<th>Answer</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FERTILITY PRESERVATION OPTIONS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Has the patient been informed about the impact their treatment may have on fertility?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the patient interested in fertility preservation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient referred for fertility preservation consult</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Funnel Effect

- Epic Questionnaire
- In person (page, phone call)
- In Basket
- Email
• **The Challenge:**
  - A patient who has just been told they have cancer now having to think/learn about fertility on the verge of information overload

• **Our Goal**
  - Make the patient feel comfortable
  - Get a decent health history
  - Learn about the short and long term treatment plans
  - Provide an understandable menu of options
    - Include disadvantages, risks and benefits
  - Discuss cost/insurance coverage
  - Offering mental health support/counseling
  - Be done talking in 20 minutes so there is plenty of time for questions w/out information overload

• **The Key**
  - Separating what is important from what is not important!!!
Intake Forms

- Patient Demographic
  - **Name, DOB, address, preferred phone, email**
- Disease
  - **Stage, location, treatment plan, treating physician**
- Menstrual history
  - **LMP, onset of menses, cycle length, OCP use**
- General Health History
  - **Surgical hx, medical hx, alcohol & tobacco use, exercise, dietary restrictions, allergies**
- Fertility Preservation Options
- Additional office visit
  - **REI/Urology visits scheduled**
- Financial Assistance/Insurance
Tools

PATIENT NAVIGATOR

PERSONAL STORIES

These stories shared here are from actual patients who underwent fertility preservation. Click on their videos to hear their stories.

LIVESTRONG FOUNDATION

fertileHOPE

SAVE MY FERTILITY

Options for Fertility...

Fertility Options

Selected Timeline: After

Embryo Banking

Egg Banking (Experimental)

Ovarian Tissue Banking (Experimental)

Radiation Shielding

Ovarian Transposition

iSaveFertility

Provider Pocket Guides

Information for healthcare professionals regarding fertility preservation options for men, women, and children.

Patient Fact Sheets

Information for patients and families about fertility and hormonal health after cancer treatment.

Northwestern Medicine

FERTLINE 512-600-0079

E.R. TE VELDE ET AL., 1998
The Reproductive Endocrinology Office

**NEEDS**
- Offers embryo/oocyte cryopreservation
- Ability to see patients within 1 business day
- Does not ‘batch’ patients for hyperstimulation
- Understands cancer diagnoses, treatments
- Inpatient consults

**WANTS**
- Offers ovarian tissue cryopreservation
- Open 7 days/week
- Performs procedures in office
- Discounted services
- Psychology services
- Same facility
Insurance

• Insurance Verification
  – Each patient has “Fertility Preservation” benefits verified

• Insurance Billing
  – Despite response on verification, insurance is billed with appropriate
cancer diagnosis as primary and fertility preservation (V26.42 or V26.82)
as secondary
  – Appeals – 1st, 2nd and peer to peer discussions

• Package prices
  – $5,000 – embryo cryopreservation
  – $4,000 – oocyte cryopreservation
  – Subsequent discounts for thaw/fertilization and transfer

• Storage
  – $75 - $275 for eggs/sperm/ovarian tissue
  – $106 - $400 for embryos
Financial Assistance

• Clinic
  – Does the REI/Urology clinic offer a discount? Ask!

• Sharing Hope
  – If no insurance coverage and if patient meets income requirements, can obtain discounted services at certain providers, discounted storage and free EMD Serono fertility medications

• HeartBeat
  – Free Ferring fertility drugs through Walgreens

• Advocacy Funding
  – Location specific funding

• Social fundraising
  – Giveforward.com
Barriers / Facilitators

• Many Moving Parts
  – Interdisciplinary clinic
• Provider outreach / education
  – Grand rounds, in-services, tumor board
• Patient outreach / education
  – Patient conferences, brochures
• Logistical challenges
  – FP Champion / ENRICH program for Oncology Nurses
• Institution buy-in
  – ASCO/ASRM/NCCN guidelines, AYA expectations
SAVEMYFERTILITY

ASC0
American Society of Clinical Oncology
Making a world of difference in cancer care

FERTLINE
866-708-FERT (3378)

the Oncofertility Consortium
AT NORTHWESTERN UNIVERSITY

fertile HOPE

MyOncofertility.org

stupidcancer.org

Northwestern Medicine
• It takes an interdisciplinary TEAM
  • REI/Urology office needs to be able to accommodate these patients first
  • Oncology healthcare professionals and patients need easy access to clinics
  • Be nice!!

• Over communicate
  • Keep every provider in the loop with each step

• Patience is a virtue
  • Not every provider will be on board at first, not every patient is going to understand at first
Questions?
Thank You

Kristin N Smith
Patient Navigator for Fertility Preservation
ksmith@nm.org