Overview

1. How does breast cancer and treatment impact fertility?
2. Is it safe to become pregnant after breast cancer?
3. How do we measure fertility in survivorship?
4. How do we preserve fertility in survivorship?
5. What resources are available?
Breast cancer in young women

• Breast cancer is the leading cancer in women younger than 40

• 13,000 young women between 18 and 40 years old are diagnosed with cancer each year

• 90% of young women will be long-term survivors

Cancer Facts and Figures, American Cancer Society, 2012
Cancer diagnosis and treatment
Surgery, radiation, chemotherapy, biologic therapy, hormone therapy

Improved Survival

Late effects
Reproductive Survivorship
1. How does breast cancer and treatment impact fertility?
Does cancer itself impact fertility?

- Subtle difference in egg or embryo number in fertility preservation cases compared to infertility patients

- Does the age of diagnosis matter?

Su, Breast Cancer Research and Treatment, 2013; Quintero, Fert Stert, 2010; Robertson, Fert Stert 2011
Threats to future fertility

Future Fertility

Chemotherapy
Age
Predictors TBD
Endocrine therapy
Radiation
Surgery

Clinical Resources: Fertile Hope Risk Calculator (www.fertilehope.org); iSaveFertility app
Cancer treatment can differentially affect ovarian reserve

Egg number (Millions)

Loss of fertility

Birth 10s 20s 30s 40s 50s

Cancer treatment

Normal women
Low toxicity
Moderate toxicity
High toxicity

Loss of fertility
Fertility is decreased in cancer survivors compared to controls

• Parenthood by age 35 is less likely in cancer survivors than age-matched controls

• Pregnancy is less likely in cancer survivors than siblings

• Precise estimates of risk of infertility are not known for most cancer treatments

Green, 2009; Magelson, 2008;
Higher risks of infertility and early ovarian failure
Fertility preservation consultations prior to treatment

• Patients should be informed of the possibility of infertility with cancer treatments.  
  --ASCO, ASRM, AAP

• About half of patients decide to proceed with a procedure

• Patients wish they heard fertility preservation options, even if they are unable to undertake them

• Individualized options

Lee, JCO, 2006; Quinn, JCO, 2009
Fertility preservation methods

Standard of Care
- Embryo banking
- Egg banking
- Gonadal shielding/ovarian transposition
- Fertility-sparing surgery

Experimental
- Ovarian tissue banking
- Ovarian suppression with GnRH analogues

ASCO guidelines, 2006
Few young women undergo specialized fertility preservation counseling or treatment

1041 newly diagnosed young women

560 counseled by oncologist

45 counseled by reproductive specialist

36 did fertility preservation procedure

- Breast, lymphoma, leukemia, GI
- Diagnosed 1993-2007
- Age 18-40 at survey

5% of population

- 4% of population
- 50% used standard of care procedures

Letourneau, Cancer, 2011
How do young survivors view future fertility and parenthood?
No choice or control over fertility

“...as far as like being concerned [about fertility at diagnosis], I definitely was. But no one was willing to have that conversation with me until it was like a serious issue.”

“I didn’t even know that it would affect fertility but as soon as, then, pretty quickly they started talking about it... I remember they told me in the doctor’s office that they said something about freezing eggs ...I said okay, here, I can do that. But then when they told me that I was, my cancer was estrogen positive and they weren’t going to be able to freeze eggs and I just like burst into tears.”

2. Is it safe to become pregnant after breast cancer?
Impact of pregnancy on overall survival

<table>
<thead>
<tr>
<th>Author, year</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper 1970</td>
<td>0.64 (0.31, 1.31)</td>
</tr>
<tr>
<td>Mignot 1986</td>
<td>0.86 (0.34, 2.18)</td>
</tr>
<tr>
<td>Ariel 1989</td>
<td>0.85 (0.55, 1.33)</td>
</tr>
<tr>
<td>Sankila 1994</td>
<td>0.21 (0.10, 0.45)</td>
</tr>
<tr>
<td>Malamos 1996</td>
<td>0.55 (0.39, 0.77)</td>
</tr>
<tr>
<td>Lethaby 1996</td>
<td>0.78 (0.58, 1.05)</td>
</tr>
<tr>
<td>Velentgas 1999</td>
<td>0.80 (0.30, 2.30)</td>
</tr>
<tr>
<td>Birgisson 2000</td>
<td>0.54 (0.25, 1.13)</td>
</tr>
<tr>
<td>Gelber 2001</td>
<td>0.44 (0.21, 0.96)</td>
</tr>
<tr>
<td>Blakely 2004</td>
<td>0.47 (0.27, 0.82)</td>
</tr>
<tr>
<td>Mueller 2003</td>
<td>0.54 (0.41, 0.71)</td>
</tr>
<tr>
<td>Ives 2007</td>
<td>0.59 (0.37, 0.95)</td>
</tr>
<tr>
<td>Kroman 2008</td>
<td>0.73 (0.54, 0.99)</td>
</tr>
<tr>
<td>Largillier 2009</td>
<td>0.23 (0.10, 0.52)</td>
</tr>
</tbody>
</table>

Pooled Relative Risk* 0.59 (0.50, 0.70)

Azim, Eur J Cancer, 2011
• No randomized studies will ever be performed

• Following groups of young women, pregnancy does not appear to increase recurrence or death

Azim, J Clinical Oncology, 2013
• Pregnancy terminations occur frequently

• Some data suggest pregnancy termination does not decrease recurrence

• The safety of pregnancy < 2 years is not clear

Azim, J Clinical Oncology, 2013
Pregnancy outcomes after breast cancer are reassuring

• No higher risk of congenital malformations, genetic disorders, skewed gender ratios

• No higher risks of stillbirth, decreased fetal weight, preterm delivery

• Chemotherapy exposure not lead to higher risk of pregnancy complications

3. How do we measure fertility in survivorship?
Measuring ovarian function

1. Pregnancy attempts
2. Pregnancy attempts
3. Pregnancy attempts

4. Ovarian reserve markers
   – Follicle Stimulating Hormone (FSH)
   – Anti-Mullerian Hormone (AMH)
   – Antral Follicle Count (AFC)

5. Menstrual pattern

Markers can change over time!

Bath, 2003; Larsen, 2003; Su, 2008; Su, 2009
FSH, AMH and hot flashes after breast cancer diagnosis suggest they may measure ovarian recovery.

Can we use FSH, AMH and hot flashes to measure remaining window of fertility?

Su, unpublished
In the absence of good data on the window of fertility:

• Window of fertility will be shorter
• Menses ≠ fertility
• Think about attempting pregnancy earlier or fertility preservation
• Serial measurements of ovarian reserve using AMH, FSH and estradiol
4. How do we preserve fertility in survivorship?
Embryo banking

• Highest likelihood of success

• Primary challenges:
  1. Timing (2-4 weeks)
     a) IVF stimulation with start of menses
     b) 2 weeks from stimulation start to retrieval
     c) Cancer treatment may begin 2 days after retrieval
  2. Estrogen levels
  3. Expense
Embryo banking – estrogen levels

- Most breast cancers are ER+ and/or PR+
- Concern of increased estrogen and progesterone during ovarian stimulation → cancer growth
- Strategies:
  - Conservative stimulation
  - Letrozole IVF protocol

Table 2. Comparison of Cycle Characteristics and Embryo Yield Among Tam-IVF (12 patients, 13 cycles) TamFSH-IVF (seven patients, nine cycles), and Letrozole-IVF (11 patients, 11 cycles) Patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tam-IVF (a) Mean ± Standard Deviation</th>
<th>TamFSH-IVF (b) Mean ± Standard Deviation</th>
<th>Letrozole-IVF (c) Mean ± Standard Deviation</th>
<th>a v b</th>
<th>a v c</th>
<th>b v c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>36.6 ± 1.6</td>
<td>38.3 ± 1.9</td>
<td>38.5 ± 1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline FSH, mU/mL</td>
<td>9.4 ± 1.5</td>
<td>9.4 ± 1.5</td>
<td>6.2 ± 1.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PeakE₂, pg/mL</td>
<td>419 ± 39</td>
<td>1,182 ± 271</td>
<td>380 ± 67</td>
<td>&lt; .05</td>
<td>&gt; .05</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Total follicles, No.</td>
<td>2 ± 0.3</td>
<td>6 ± 1</td>
<td>7.8 ± 0.9</td>
<td>&lt; .01</td>
<td>&lt; .001</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Follicle &gt; 17 mm, No.</td>
<td>1.2 ± 0.1</td>
<td>2.6 ± 0.4</td>
<td>3.2 ± 0.4</td>
<td>&lt; .05</td>
<td>&lt; .001</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Total oocytes, No.</td>
<td>1.7 ± 0.3</td>
<td>6.9 ± 1.1</td>
<td>12.3 ± 2.5</td>
<td>&lt; .05</td>
<td>&lt; .001</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Mature oocytes, No.</td>
<td>1.5 ± 0.3</td>
<td>5.1 ± 1.1</td>
<td>8.5 ± 1.6</td>
<td>&lt; .05</td>
<td>&lt; .001</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Total embryos, No.</td>
<td>1.3 ± 0.2</td>
<td>3.8 ± 0.8</td>
<td>5.3 ± 0.8</td>
<td>&lt; .05</td>
<td>&lt; .001</td>
<td>&gt; .05</td>
</tr>
</tbody>
</table>

Oktay, JCO, 2005
Egg banking

• Recent advances in vitrification
• Option for patients with no partners or religious objections to embryos
• Primary challenges:
  1. Success rate largely unknown
  2. Similar issues as embryo banking
Ovarian tissue banking

- Remove part of or whole ovary
- Cryopreserve pieces of ovary cortex
- Option for patients who do not have time or cannot undergo embryo/egg banking
Clinical uses of banked ovarian tissue: Re-transplant

15 live births in the world

Donnez, 2011
Clinical uses of banked ovarian tissue: In vitro ovarian follicle maturation

1. Rodent model

2. Non-human primate model

3. Human follicles!

Woodruff, Stauffer, Zelinsky labs
5. What resources are available?
Oncofertility Resources

Providers

• Oncofertility consortium  
  oncofertility.northwestern.edu/

• Fertile Hope: risk calculator, application for Sharing Hope  
  fertilehope.org/healthcare-professionals/index.cfm

• iSaveFertility app  
  http://savemyfertility.org/

Patients

• Fertile Hope.org
• Myoncofertility.org
• Savemyfertility.org
• Society of Assisted Reproductive Technology
  – Clinics
  – Success rates
How do we improve fertility and parenthood options after breast cancer?
Talk about reproductive survivorship

1. Consultation
2. Fertility preservation procedures
   • Embryo banking
   • Egg banking
   • Ovarian tissue banking
   • Surgical and medical treatments

1. Counseling and monitoring
2. Attempting pregnancy earlier
3. Fertility preservation procedures
   • Embryo banking
   • Egg banking
   • Ovarian tissue banking
Health care providers need to talk about fertility

“I mean I was embarrassed that they talked to me about [fertility] when I was 17… but at the same time I’m glad that has always been something that like I’ve known and can talk about.”

“… I mean, if you’re a woman and you’re at an age where you have your period… you should totally know about that.”

“I just wish my doctor would have talked about it more with me because she kind of would dance around the subject so we never really got to talk about it.”

Tackle unanswered questions through research

• Can we predict who will become infertile?

• When is the window of fertility in survivorship?

• Can we develop a measure for medical teams to use to assess reproductive concerns in young survivors?
Take home messages

1. How does breast cancer and treatment impact fertility?
   - Breast cancer itself likely has little impact on fertility
   - Chemotherapy and tamoxifen may adversely impact fertility

2. Is it safe to become pregnant after breast cancer?
   - Although there are no randomized studies, survivors who become pregnant do not appear at higher risk of recurrence or death
   - Tamoxifen is teratogenic, so this must be discontinued prior to attempting pregnancy
Take home messages

3. How do we measure and preserve fertility in survivorship?
   • Consider attempting pregnancy earlier and/or bank embryos or eggs
   • Serial AMH, FSH and estradiol levels

4. There are many ways to building a family.

5. Please consider participating in clinical studies on fertility outcomes.