Fertility/Family Planning for Survivors

Erica T. Wang MD MAS
Associate Professor
Department of Obstetrics & Gynecology
Division of Reproductive Endocrinology & Infertility
Cedars-Sinai Medical Center
Disclosure

No Conflicts to Disclose
• Loss of reproductive potential negatively impacts quality of life

• 30-40% reproductive-age survivors endorse:
  – Loss of control over reproductive future
  – Discontent with number of children
  – Inability to talk openly about fertility
Objectives

Assisted Reproduction Technology (ART, aka IVF) for Survivors

• Fertility preservation (egg freezing)
• Fertility treatment options
• Family building alternatives
• Preimplantation genetic diagnosis

Pregnancy for Survivors

• Safety
• Timing
Biological Clock

[Graph showing the number of germ cells (millions) over time, with peaks during infancy and a decline until adulthood.]
Fertility Preservation

• “As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer patients to reproductive specialists.”
Post treatment fertility preservation

• Fertility preservation = egg freezing

• You should talk to a fertility specialist about whether you are a candidate to freeze eggs post treatment

  – Age ≤40 or ≤45
  – Return of menstrual cycles
  – Assess ovarian reserve (how many eggs you have left)
Egg Freezing Process

Figure 2

Ovarian follicles, stimulated by ovulation medications, visible on ultrasound. The dark, circular areas are the follicles.

Figure 3
Egg retrieval procedure

Egg retrieval is usually performed through the vagina with an ultrasound-guided needle.
Ovarian Stimulation With Letrozole Does Not Increase Recurrence Risk In Breast Cancer

Published in: Jayeon Kim; Volkan Turan; Kutluk Oktay; The Journal of Clinical Endocrinology & Metabolism 2016, 101, 1364-1371. DOI: 10.1210/jc.2015-3878 Copyright © 2016
Egg Freezing Process

Figure 4

A mature, unfertilized egg.
Are Survivors More Likely to Face Infertility?

• Retrospective cohort study
  – All women who had their first IVF treatment between 2004-2009 in NY, TX, IL
  – 53,426 women total, 441 diagnosed with cancer within the last 5 years
  – Breast cancer survivors were 80% less likely to conceive and have a baby

• Childhood Cancer Survivor Study (cohort)
  – 3531 childhood cancer survivors and 1366 female sibling controls
  – Survivors had a 50% increased risk of infertility
  – BUT ...
  – 64% of participants (292/455) with self-reported infertility achieved a pregnancy

Barton, Lancet Oncology 2013
Are BRCA mutations associated with reduced ovarian reserve?

• BRCA genes play an important role in the repair of damaged DNA
• Could BRCA mutations lead to an accelerated loss of eggs?

• Cohort study from Cedars-Sinai Medical Center
  – 62 BRCA1 carriers
  – 27 BRCA2 carriers
  – 54 controls
• Serum anti-Mullerian hormone (AMH) – measure of egg reserve

• BRCA1 carriers had lower age-adjusted serum AMH levels than controls

• We need larger studies to make a conclusion!!

Wang, Fert Steril 2014
Fertility Treatment Options

• FIRST STEP
  – You should see a fertility specialist to assess your egg reserve
  – Other tests that are part of a fertility workup

• In vitro fertilization (IVF)

• Non-IVF fertility treatment (NIFT)
  – Clomiphene citrate pills
  – Intrauterine inseminations
Family Building Alternatives

• Third Party Reproduction
  – Gestational carrier
  – Donor egg

• Adoption
What is Preimplantation Genetic Diagnosis (PGD)?

- Process of selecting embryos without a genetic mutation

- Mutations for PGD
  - Hereditary cancer syndrome BRCA 1&2
  - Autosomal recessive cystic fibrosis
  - X linked condition Duchenne muscular atrophy
  - Autosomal dominant Huntington disease
IVF PGD Process

**Figure 5**
Larger tube that holds the egg still

*Intracytoplasmic sperm injection (ICSI), in which a sperm is injected directly into an egg to facilitate fertilization.*

**Figure 6**
Small glass tube through which the sperm is injected into the egg

*A fertilized egg has divided once and is now a two-cell embryo.*

www.asrm.org (patient resources)
Reproductive Decision-Making in Women with BRCA Mutations

• 1081 carriers
  – Penn Cancer Risk Evaluation Program
  – FORCE (1/3)

• 59%: PGD should be offered

• 35%: would consider undergoing PGD

• 56%: prenatal diagnosis should be offered

• 30%: would use prenatal diagnosis

• 4%: would terminate if the pregnancy carried the mutation
Motives and Considerations for PGD

• Motives and considerations to test for BRCA:

“I strongly feel that I want it to stop with me.”

“I couldn’t feel at ease with consciously burdening my child with this.”

“My mother died because of cancer, I am a mutation carrier myself. My breasts are removed. Therefore, I don’t want my child to experience the same things that I did.”

• Motives and considerations to refrain from PGD:

“To me, it felt very serious, needing an IVF treatment while we are normally fertile.”

“I slowly began to realize that there would also be embryos which will be, well, discarded. And although they are affected, they are still embryos and therefore children, if you look at it that way. I’ve never been able to shake that off…”

“It makes you start thinking… imagine you would have a girl, yet another thirty years along the road medical science will look completely different. Who knows if they don’t have a vaccine for breast cancer by then?”
Is pregnancy safe for breast cancer survivors?

- THERE ARE NO OFFICIAL GUIDELINES!!

- Based on the best retrospective data we have, there is no harm and may even be protective
Health of Mom

Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr. a,b, Luigi Santoro c, Nicholas Paulidis d, Shari Gelber e, Niels Kroman f, Hamdy Azim g, Fedro A. Peccatori h,*

a Department of Medical Oncology, Jules Bordet Institute, Brussels, Belgium

• 41% reduced risk of death with pregnancy
  – Especially in node negative disease

• “Healthy Mother Effect” (Selection Bias)

Azim HA, European Journal of Cancer 2010
Health of Baby

• Childhood Cancer Survivor Study
  – Babies born a little smaller, a little earlier
  – No increase risk of miscarriages
  – No increase risk of birth defects
  – No increase risk in genetic disease or cancer (except in the case of a hereditary syndrome such as BRCA)
Timing of Pregnancy for Survivors

• THERE ARE NO OFFICIAL GUIDELINES!!

• Practical advice
  
  – wait 2 years from diagnosis to attempt conception (allow for early recurrences to manifest)

  – wait 6 months after completion of chemotherapy (based on egg production cycle)

• What about endocrine therapy (ie. tamoxifen)?
Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE) Trial

- Cedars-Sinai Principal Investigator – Dr. Philomena McAndrew
POSITIVE Trial

- ≤42yo hormone sensitive early breast cancer
- Completed 18-30 months of endocrine therapy
- **Wish to interrupt endocrine therapy to attempt pregnancy**
- 3 months washout
- Up to 2 years treatment pause to allow for potential conception, delivery, breast feeding, trying
- Resume endocrine therapy to complete 5-10 year course
- Endpoints – breast cancer recurrence, offspring outcome
Take Home Messages

• We need to educate survivors, physicians, and other providers about the importance of fertility and family planning.

• In terms of fertility, the first step is to see a specialist to assess your egg reserve post-cancer treatment.

• Preimplantation genetic diagnosis is a personal choice. There is no right or wrong answer.

• There are no official guidelines on pregnancy in breast cancer survivors.
  – The best data we have suggest that pregnancy is safe for mom and baby.