FERTILITY AND PREGNANCY AFTER BREAST CANCER

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SPECIAL THANKS TO DR. MINDY CHRISTIANSON
INTRODUCTION

- About 6-7% of breast cancers are diagnosed in women <40 years old
- ~11,000 women per year
- Estimated 400,000 breast cancer survivors <40 yo in 2010

www.seer.cancer.gov

OBJECTIVES

1. Is it safe to have a baby after breast cancer?
2. What are the risks to fertility from breast cancer treatment?
3. Fertility preservation options
4. Treatment of ovarian failure after breast cancer
Is Pregnancy Safe after Diagnosis and Treatment of Breast Cancer?
PREGNANCY AFTER BREAST CANCER

• Historically, physicians had assumed pregnancy after breast cancer was dangerous
  • High estrogen
  • High progesterone
  • Exposure to prolactin and placental lactogens
AZIM META-ANALYSIS 2010

• Included 14 case-control, population-based and hospital-based studies published between 1970 and 2009
  • 18,145 breast cancer patients
  • 1417 pregnancies (1244 patients)
AZIM META-ANALYSIS

• Patients who became pregnant had a 41% reduced risk of death compared with breast cancer patients who did not (hazard ratio 0.59, 95% CI 0.5-0.7)
• Protective effect mostly seen in patients under 35 years of age with lymph node negative disease
HEALTHY MOTHER EFFECT??

• Must be considered
• Women with breast cancer who subsequently conceive are a self-selected healthier group with a better prognosis

Sankila et al, Amer J Ob Gyn 1994
BREAST FEEDING AFTER BREAST CANCER

- Milk production compromised by surgery and radiation in treated breast
- No increase in recurrences in women who breast fed
- Azim 2009
  - 1/10 breast feeders
  - 1/10 bottle feeders
- Gelber 2001
  - 1/27 breast feeders
  - 6/25 bottle feeders
PREGNANCY AFTER BREAST CANCER: IS THERE A RISK TO THE FETUS?
NO ADVERSE FETAL OUTCOMES

• Danish study: 216 women who became pregnant after breast cancer compared with 10,453 women without breast cancer
• Similar risks of preterm delivery, low birth weight, congenital anomalies
SWEDISH STUDY: SLIGHTLY HIGHER RISK?

- 331 women with a history of breast cancer compared to 2.8 million women without cancer
- Slightly higher risk
  - Delivery complications
  - Cesarean section
  - Preterm birth
  - Low birth weight
- Slightly higher risk of birth defects
Is Pregnancy Safe after Diagnosis and Treatment of Breast Cancer?

Probably yes, with caveats

At least 2 years after treatment

Complete treatment (not all hormonal treatment)
WHAT IS THE RISK TO FERTILITY FROM CANCER TREATMENT?
CANCER TREATMENT

• Younger age, higher stage
  • 1/3 of women less that 50 have Stage 1 disease at diagnosis
  • 2/3 have tumor > 2cm or nodes + (Stage 2 or higher)

• Who undergoes chemotherapy?
  • Stage 1 greater than 1 cm
  • Stage 2 or higher

Who undergoes hormonal therapy?
  2/3 of women under 40 have hormone receptor + tumors
CHEMOTHERAPY JEOPARDIZES OVARIAN FUNCTION

• Loss of oocytes (eggs) due to age

<table>
<thead>
<tr>
<th>AGE</th>
<th>NUMBER OF OOCYTES</th>
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<tbody>
<tr>
<td>5 months gestation</td>
<td>6-7 million</td>
</tr>
<tr>
<td>Birth</td>
<td>1-2 million</td>
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<tr>
<td>37 years old</td>
<td>25,000</td>
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<tr>
<td>51 years old</td>
<td>1000</td>
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CHEMOTHERAPY JEOPARDIZES OVARIAN FUNCTION

• Chemotherapy causes depletion of follicles (eggs) in a drug/dose/age dependent fashion

• Cyclophosphamide is the most gonadotox
c
• 20-70% of women less than 40 have ovarian failure

• AC regimens

• 0% of women less than 30, up to 96% of women over 30

• Taxanes

• Increase the risk in regimens including docetaxel, doxorubicin and cyclophosphamide but not paclitaxel
FERTILITY PRESERVATION IMPORTANT

• American Society of Clinical Oncology (ASCO) encourages prioritizing healthy survivorship

• Recognizes fertility preservation as integral part of cancer patient care

FERTILITY IS IMPORTANT TO YOUNG BREAST CANCER PATIENTS

• Interviews with breast cancer survivors 10 years after diagnosis:
  • Women desiring a child when diagnosed but who became infertile after treatment experienced significantly higher levels of distress than those who didn’t become infertile

Canada and Schover, Psychoonology, 2010.
EXPERIENCES OF YOUNG BREAST CANCER PATIENTS REGARDING FERTILITY PRESERVATION

- 88.4% received chemotherapy
- 87.2% did not receive fertility preservation (embryo cryopreservation or oocyte cryopreservation)
- 46.8% were not counseled regarding fertility preservation
WHO COUNSELED REGARDING FERTILITY PRESERVATION

![Bar chart showing percent counseled by different professionals.]

- **Primary OB/Gyn**: 10%
- **Reproductive Endocrinologist**: 20%
- **Breast Surgeons**: 30%
- **Medical Oncologist**: 40%

*Christianson et al, 2011*
DESCRIPTION OF FERTILITY PRESERVATION DISCUSSION

- Discouraged from fertility preservation: 41%
- Provider told opinion and didn't have a choice: 33%
- Felt like decision maker: 26%

Christianson et al., 2011.
REASONS FERTILITY PRESERVATION NOT CHOSEN

- Children not desired
- Not enough time
- Not a priority
- Couldn’t afford, insurance didn’t cover
- MD advised not to get pregnant

Christianson et al., 2011.
Fertility Preservation:

What Options are Available for Women with Breast Cancer?
Assisted reproductive technologies (ART) for fertility preservation can be performed 2-4 weeks after surgery, prior to chemotherapy.
EMBRYO CRYOPRESERVATION

• Widely established
• Controlled ovarian hyperstimulation, oocyte retrieval, fertilization and then cryopreservation
• Embryos thawed and transferred to patient or gestational carrier
• Pregnancy rates can be $>40\%$ per transfer
• Requires 2-4 weeks
EMBRYO CRYOPRESERVATION

**Candidates:**
- Have partner or willing to use donor sperm
- Can delay cancer treatment 2-4 wks

**Not Candidates:**
- No partner or decline donor sperm
- Can’t delay treatment
- Moral or religious objections to freezing embryos (or live in country where illegal)
CONTROLLED OVARIAN HYPERSTIMULATION – RISKY?

• Results in supraphysiologic levels of estrogen, 10-20 times normal reproductive cycles
• Theoretical concern about stimulating receptors on estrogen-responsive cells
• Estrogen may have a mitogenic effect on hormone receptor negative tumors

LETROZOLE

- 3rd generation aromatase inhibitor
- Can be used for ovarian stimulation
- Competitively inhibits aromatase enzyme activity in ER+ cells and suppresses estrogen production
LETROZOLE OVULATION INDUCTION

• No increased risk of recurrence in breast cancer patients with this protocol compared to those who declined ART
  • Mean follow-up 48 months
• Time-lapse between surgery and chemo longer (45 d vs 33 d, P=0.01)

Azim et al, J Clinic Oncol, 2008.
OOCYTE CRYOPRESERVATION

- Considered investigational
- Option for women who:
  - No partner or decline donor sperm
  - Understand success rate much lower than embryo cryopreservation
- ASRM advises live-birth rate of 2-4% per oocyte
OOCYTES EXTREMELY SENSITIVE

• Largest cell in human body
• Largest water content
• Abundant cytoplasm
• Ice crystals can damage meiotic spindle
OVARIAN TISSUE CRYOPRESERVATION

• Ovarian tissue harvested at laparoscopy or laparotomy
  • Obtain by biopsy or oophorectomy
  • Tissue then be transplanted upon completion of gonadotoxic therapy after patient is in remission
TRANSPLANTATION OF OVARIAN TISSUE

• Investigational approach with about 18 live births to date
• Option available for those who cannot delay treatment to harvest oocytes
• Rarely used for breast cancer patients

Fertility Preservation:

Are GnRH Analogs Effective at Protecting the Ovaries from Gonadotoxic Chemotherapy?
• Theorized that toxicity from chemotherapy reduced by diminishing ovarian function
• Gonadotropin-releasing hormone (GnRH) agonists diminish ovarian function
  • Since effect reversible, resumption of ovulation is possible when cytotoxic and GnRH therapies are discontinued
• Whether protective against gonadal damage is controversial
SUPPORT OF GNRH AGONISTS

• Systematic review of 9 controlled, mainly non-randomized studies found GnRH agonists during chemotherapy protective
  • Resumed menstrual cycles, premenopausal FSH:
    • 93% GnRH agonist
    • 48% No GnRH agonist
  • Pregnancy rates:
    • 22% GnRH agonist
    • 14% None GnRH agonist

Clowse et al, J Womens Health, 2009
SUPPORT OF GNRH AGONISTS

• Randomized trial: 285 breast cancer patients undergoing cyclophosphamide chemotherapy
  • GnRH agonist
  • GnRH agonist plus tamoxifen
  • Tamoxifen alone
  • Controls
• Menses up to 36 months out:
  • 36% GnRH agonist
  • 7% GnRH agonist plus tamoxifen
  • 13% Tamoxifen alone
  • 10% Controls

OTHER STUDIES DO NOT SUPPORT GNRH AGONISTS

• 3 small randomized trials reported GnRH agonist treatment ineffective in preserving fertility in patients receiving chemotherapy for lymphoma or breast cancer

• Protective role of GnRH analogues against cyclophosphamide induced ovarian damage was not demonstrated in human ovarian xenograft model

Other Assisted Reproductive Technology Options
DONOR OOCYTES

• IVF using donor oocytes is proven approach
• Success rates exceeding 60% per embryo transfer
GESTATIONAL SURROGACY

• Candidates include those who:
  • Underwent hysterectomy
  • High risk of recurrent breast cancer
  • Lifelong therapy with aromatase inhibitors
  • Do not want to wait until completion of aromatase inhibitors
What Other Gynecologic Health Concerns Face Young Women with Breast Cancer?
CHEMOTHERAPY-INDUCED AMENORRHEA

• Majority of patients will have amenorrhea
• Menses resume in 6 months for 60%
• Menses resume in 12 months for 90%
• For women younger than 40 yo, risk of permanent menopause is 15-45%

MENOPAUSAL SYMPTOMS: HOT FLASHES

• Vasomotor symptoms most common
• 20% of breast cancer patients consider stopping endocrine therapy because of symptoms.

• Possible Treatments:
  - Venlafaxine
  - Paroxetine
  - Gabapentin
  - Clonidine

MENOPAUSAL SYMPTOMS:
VAGINAL ATROPHY

• Atrophic vaginitis
  - Treatment options:
    • Replens
    • Vaginal 17β Estradiol (if oncologist approves)
    • Vaginal estriol

CONTRACEPTION

• Hormonal contraceptives contraindicated (even in hormone negative tumors)

• Current recommendations:
  • Nonhormonal alternatives such as barrier methods, sterilization, non-hormonal IUD

• Mirena IUD - controversial

Backman et al, Obstet Gynecol. 2005
Trinh et al, Fertil Steril. 2008
CONCLUSIONS

• Early referral is key!
  • Preferably before or right after surgery to allow ovarian stimulation without delaying chemotherapy
• Young women with early stage breast cancer should not be discouraged from pregnancy in the future