Gyn Care for Breast Cancer Survivors

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Disclosures- I am a Medical Advisor and on the Scientific Advisory Board of company that is developing a medical device to treat vaginal dryness

Breast Cancer Epidemiology-

- Most common invasive cancer in US women
- 252,710 new cases invasive Breast ca in US in 2017
- Median age of diagnosis is 61
- 12% diagnosed in reproductive years (ages 20-44)
- Lifetime risk is 1/8 (at age 85)
- For cancer localized to the breast, 99% 5 yr. survival rate and deaths from breast cancer have declined 40% between 1989-2015
Breast Cancer Treatments

- Breast surgery – either breast conserving lumpectomy or modified mastectomy. May also include immediate or delayed reconstructive procedures
- Radiation
- Chemotherapy
- Hormonal Therapies
- Many of these treatments have gynecologic effects

Menopausal complaints often more severe

- Surgical treatments may include oophorectomy with immediate onset of menopause
- Premenopausal women with normal menstrual functioning may get put into menopause with chemotherapy
- Postmenopausal women taking HRT tend to abruptly stop when diagnosed with breast cancer
- Vasomotor symptoms common with hormonal drugs like Tamoxifen or Aromatase Inhibitors

Is Chemotherapy-Induced Menopause Permanent?

- Incidence of chemotherapy-induced amenorrhea varies widely
- More common for women > 40 to have permanent ovarian failure post chemotherapy
- Can occasionally see menses return even 2 years post chemo
- Getting menses back does not necessarily correlate with fertility
- Long-term cytotoxic effects - women who menstruate post chemotherapy still at increased risk for premature menopause

Chemotherapy-Induced Amenorrhea and Cancer Outcome

- Recent meta-analysis showed that women having chemotherapy induced amenorrhea had better cancer outcomes - improved DFS and OS for ER+ and node+ disease
- Suggests both cytotoxic effects of chemotherapy and indirect hormonal effect mediated by damage to ovarian estrogen-producing cells – thought ? genes play a role
- More studies needed to fully understand the mechanism between CIA and breast cancer outcomes

Chemotherapy and Fertility Concerns

- Studies showing that close to 30% of patients with breast cancer make cancer treatment decisions based on fertility desires

Can Ovarian Toxicity be Prevented?

- POEMS (Prevention of Early Menopause) prospective international, phase 3, randomized trial to see whether GnRH agonist with chemotherapy would reduce the rate of ovarian failure in hormone negative breast cancer
  - Found adding ovarian suppression to chemotherapy associated with less ovarian failure, more pregnancies and more successful live births AND higher disease free survival and overall survival

What Should Gyn’s Do with this Data?

- Based on POEMS trial, showing possible prevention of ovarian toxicity with ovarian shutdown before chemotherapy ...
- And studies showing patients with breast cancer make treatment decisions based on fertility desires....
- Refer to fertility colleagues prior to breast cancer treatments if fertility desired and clinically appropriate

Breast Cancer Tumors

- Breast tumors are all sent for ER/PR status and to see whether over-expression of Her2neu
- Estrogen and Progesterone positivity tells you the tumor will benefit from drugs that manipulate the hormonal environment
- 2/3 of breast cancers are hormone positive
**HER-2 Tumors**

- The HER2 gene makes human epidermal growth factor receptor, a protein important in controlling epithelial cell growth, cell differentiation and possibly angiogenesis - basically controls how a healthy breast cell grows, divides, and repairs itself.

- HER2 tumors overexpress Her2-neu and are oncogene driven and a marker of more aggressive tumor.

- 18-20% of breast cancers over express HER2-neu.

**Drugs Used to Treat Her2-neu Breast Cancer**

- **Herceptin** - attaches to HER2 receptors on the surface of breast cancer cells and prevents them from receiving growth signals.

- **Kadcyla** (chemical name: T-DM1) - a combination of Herceptin and chemo agent emtansine. Designed to deliver emtansine to Her2 neu cancer cells in a targeted way by attaching emtansine to Herceptin.

- **Perjeta** (chemical name: pertuzumab); similar to Herceptin and works by blocking Her 2 neu cancer cells ability to receive growth signals.

- **Tykerb** (chemical name: lapatinib), works against Her 2 neu cancers by blocking certain proteins that can cause uncontrolled cell growth.

**HER-2 Tumors- What do Gyn’s need to Know?**

- New form of treatment that is biologic targeted therapy.

- These drugs are used in combination with chemotherapy agents.

- Very successful but can see cardiotoxicity so patients should be screened for cardiac side effects.

- If found to be pregnant these drugs can cause fetal toxicity and death.

**Hormonal Treatments and Breast Cancer**

- Used to reduce recurrences and overall breast cancer mortality in women with hormone receptor positive breast cancer.

- Biologic goals of hormonal therapy:
  - Block production of estrogen
  - Block action of estrogen
  - Down-regulate the estrogen receptor.
**Hormonal Treatments of Breast Cancer**

- **SERMS**: Tamoxifen (Soltamox), Raloxifene (Evista), Toremifene (Fareston)
- Estrogen Receptor Downregulators: Fulvestrant (Faslodex)
- Aromatase Inhibitors: Anastrozole (Arimidex), Letrozole (Femara), Exemestane (Aromasin)

**Benefits and Uses of Tamoxifen**

- 5 years of tamoxifen reduces breast cancer recurrence by 40%-50% in PMP women and 30%-50% in premenopausal women
- 5 years of tamoxifen reduces risk of a new contralateral breast cancer by about 50%
- 5 years of tamoxifen has shown improved overall survival for at least 15 years *(survival benefit AFTER stopping)*
- Used as neoadjuvant therapy to shrink large, hormone-receptor-positive breast cancers prior to breast cancer surgery

**Hormonal Treatments of Breast Cancer - Tamoxifen**

- Complex drug with estrogen and anti-estrogen properties
- Originally made as contraceptive then found to suppress mammary tumors in rats
- By 1992 shown to increase disease free interval and decrease contralateral breast cancer in pre and postmenopausal women

**Benefits and Uses of Tamoxifen**

- Trials looking at 10 years of tamoxifen have shown reductions in recurrence, mortality, contralateral breast cancer so some oncologists recommending 10 years of treatment
- Tamoxifen can be use to prevent breast cancer in high risk women- At 16 yr. follow up, 5 years of tamoxifen associated with a 29% reduction in the risk of developing any type of breast cancer and a 35% reduction in the risk of developing ER+ breast cancer compared with placebo-treated controls

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What do Gyn’s need to know about longer treatment?

- Tamoxifen is used primarily in premenopausal women and many may be interested in pregnancy
- Many trials have shown safety of pregnancy after breast cancer
- Given some recommendations for 10 yrs. of tamoxifen treatment more oncologists recommending stopping tamoxifen for pregnancy and then resuming post partum
- No long-term data whether this will be as beneficial for cancer outcomes as continued treatment

What do Gyn’s need to know for breast cancer patients who want to get pregnant?

- Typically recommended to do at least 2 years of tamoxifen therapy as higher risks of recurrence in first 2 years
- Stop for at least 2 mos. (wash out) prior to attempting pregnancy
- Recommended to restart post partum but Tamoxifen may slow milk production and should not be used when breastfeeding

Tamoxifen – Adverse Events

- Increased rate of venous thromboembolic events, particularly in first two years, more when used with chemotherapy
- Overall 2-3 fold increased RR for DVT and PE
- Increased risk for arterial thromboembolism (stroke)
- Most recommendations are to discontinue tamoxifen for few days before surgery or long travel

Tamoxifen – Common Side Effects

- Weight Gain - initially thought 7-10 lbs.
  - Not clear if this is true, but likely harder to lose weight

Common Side Effects:
- Hot Flashes
- Vaginal Discharge
- Vaginal Dryness
- Joint Pain
- Headaches
## Hot Flashes – Alternatives to Hormones

- **Low dose antidepressants** – Venlafaxine, Paroxetine, Fluoxetine, Citalopram, Escitalopram, Desvenlafaxine
- Antihypertensive Clonidine
- Gabapentin and Pregabalin
- Vitamin E
- Soy supplements
- Herbal Products: best studied Black Cohosh
- Tibolone (in Europe)
- Chinese Herbs
- Alternative Therapies- CBT, mindfulness, acupuncture, stellate ganglion blocks, relaxation techniques

## Non-Hormonal Pharmacologic Treatments for Hot Flashes

- Many studied: Venlafaxine (best studied) paroxetine, fluoxetine, citalopram, escitalopram, desvenlafaxine, mirtazapine, sertraline
- Much of data showing a benefit in short trials less than 12 weeks
- **Beneficial effects in days and doses typically lower than that for depression** - most effective dose of venlafaxine 75 mg per day in divided doses
- Side Effects: dry mouth, decreased appetite, fatigue, nausea, constipation and sexual disturbances

## Integrative Therapies for Menopausal Hot Flashes

- Acupuncture – data in survivors show benefits, but not clear if placebo effect
- Exercise/physical activity
- Lifestyle modifications- weight loss if obese
- Cognitive behavioral therapy (CBT)
- Yoga
- Hypnosis
- Tai Chi
- Stellate ganglion blocks
  - Small trials have shown benefits but overall limited data on effectiveness

## Clinical Pearls for Non-Hormonal Pharmacologic Treatments

- Start with lowest dose possible!
- Best studied, venlafaxine: start with low doses to avoid discontinuation – lowest is 25 mg but scored, **most effective dose 75 mg** typically in divided doses
- For pure SSRI’s start with **10 mg**
- For gabapentin – 900 mg most well studied, use at night as **SEDATION** is common side effect. Start with **100-300 mg** and increase up to a max of 2400 mg in divided doses
- Wean when stopping to avoid any rebound effects
- NCCN website Survivorship- Menopause Guideline for dosing recommendations
Tamoxifen - Biologic Effects

- Agonist and Antagonist effects
- Effects of Tamoxifen vary depending on hormonal environment

Tamoxifen and Premenopausal Women

- Induces estrogen production and ovulation - has been used for ovulation induction for IVF. If need contraception, non-hormonal formulations recommended
  - Copper IUD a great option
  - Reports of ovarian cysts in upwards of 30% women
  - Menstrual irregularities- mainly oligomenorrhea or amenorrhea (but affected by prior chemotherapy)
  - Growth of endometrial polyps, fibroids, endometriomas
  - Not thought to increase the risk of endometrial cancer

Tamoxifen and Postmenopausal Women

- Increased endometrial proliferation, cystic changes, polyp formation, adenocarcinoma and uterine sarcoma
- Frequency of cancer dependent on endometrial surveillance: TVS vs. EMB and criteria for surveillance – symptomatic vs. asymptomatic
- Reported risks of endometrial ca in Tamoxifen users range from 1.3-7.5 in RCT, and increase with longer use
- Meta-analysis of 32 RCT trials showed RR 2.7, primarily in women > 50

Tamoxifen and Endometrial Cancer

- Absolute risks - about 4 cases of endometrial cancer per 1000 women taking Tamoxifen each year
- 95% of Endometrial Cancers present with Vaginal Bleeding
- Some more aggressive subtypes but tamoxifen not thought to affect endometrial cancer survival
- Risks are thought to decrease as soon as tamoxifen is stopped
- Most women get a much greater benefit to their breast than risk to their uterus
Endometrial Surveillance with TVS – what are the concerns?

- Increased endometrial thickness, irregular echoes, cystic changes (‘Swiss-cheese appearance’), polyps and hyperplasia
- Findings do not correlate with malignant histology
- Thickened endometrium can be atrophic. Mechanism may be stromal hypertrophy, enlargement of subendometrial glands
- No prospective data on what is normal endometrial thickness for women on tamoxifen

What are the problems with routine surveillance?

- Absence of a defined endometrial thickness cut-off for the tamoxifen patients reduces ultrasound accuracy and increases the number of patients referred for unnecessary hysteroscopy
- Overtreatment with unnecessary surgeries

Ultrasound of Patient on Tamoxifen

Clinical Pearls regarding Tamoxifen

- Get baseline sono for comparison because there are many times that “things come up” – bloating, pain, bleeding that may require imaging - recommended in ACOG guidelines
- Do not get routine surveillance
- Do not use endometrial thickness as an indicator for intervention
- Endometrial effects are thought to stop once tamoxifen is stopped and risks back to baseline in about 5 years
What about levonorgestrel-releasing IUD (Mirena) for women on Tamoxifen?

- Cochrane review in 2015 looked at effectiveness and safety of levonorgestrel intrauterine system (LNG-IUS) in pre- and postmenopausal breast cancer patients taking adjuvant tamoxifen. Found IUD reduced incidence of polyps and hyperplasia but not powered enough to tell if fewer endometrial cancers or if effects on breast cancer recurrence.


San Francisco Trivia

- The multiple alley ways in the south or market area are thought to be named after......

- A. Early San Francisco politicians
- B. Prostitutes from the Gold Rush era
- C. Famous bars from the early 1900’s

And the Answer is ......

- Evidence suggests that these alleys are named for famous prostitutes from the Gold Rush era

- Broke Ass Stuart, Minna Rae Simpson, Belle Cora

Aromatase Inhibitors

- Tamoxifen competes with estrogen at receptor binding site in the breast preventing receptor activation

- Aromatase Inhibitors prevent conversion of androstenedione and testosterone into estrogens and decrease peripheral circulating estrogen

- Not useful in premenopausal women because blocking aromatase in the ovaries reduces negative feedback to the pituitary (in the short term) with increased FSH output, and increased follicular development and increased estradiol
Aromatase Inhibitors

- Third generation AIs used:
  - Anastrozole (Arimidex)
  - Letrozole (Femara)
  - Exemestane (Aromasin)

First Data: Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial

- 9000 PMP women with early stage breast ca, treated with 5 yrs. of Anastrozole vs. Tamoxifen, first interim analysis presented in 2001 with now 16 years of follow up.

  - Anastrozole had improved Disease Free Survival
  - Anastrozole had improved time to recurrence
  - Anastrozole had lower incidence of contralateral breast cancer

Aromatase Inhibitors in 2017

- Many international trials have now shown efficacy of aromatase Inhibitors in adjuvant treatment for postmenopausal women

  - FDA approved Anastrozole (Arimidex) as first-line adjuvant therapy in PMP women with hormone positive breast cancer

  - FDA approved Letrozole (Femara) for extended adjuvant use in women with early-stage, hormone-receptor-positive breast cancer after five years of tamoxifen

Aromatase Inhibitors in 2017

- Ideal length of treatment not clear - Recent trial data showed reduced recurrences with 10 years of AI treatment but no benefits on overall survival


  - Both Exemestane (Aromasin) and Anastrozole (Arimidex) have showed reduction in preventing ER-positive invasive breast cancer, but not yet FDA approved for prevention
What do Gyn’s Need to Know About Side Effects of Al’s

- Bony and joint pain - bone loss and increased fractures while taking, doesn’t continue after stopping
- Potential cardiac risks - no increased risk of MI or strokes but study showed higher dysrhythmia, valvular dysfunction, and pericarditis
- Because of shut down of all peripheral estrogen – marked vaginal dryness, dyspareunia and decreased libido, but lower risks of endometrial cancer – Al’s thought to prevent endometrial ca

How to manage all the Vaginal Dryness – OTC Options

- Vaginal Moisturizers – retain water and provide longer term relief
- Oils- penetrate thin tissue and soothing
- Topical Vitamins- D or E, liquid or suppositories
- pH balanced gels with Hyaluronic acid
- Soothing agents for vaginal or vulvar pain
- Topical anesthetics for introital discomfort
- Lubricants for sexual activity
  - None of these products are FDA approved as drugs
  - Get to market typically with little data- only takes 12 week trials to show effectiveness and safety

How to Manage Vaginal Dryness: Local vs. Systemic Estrogen

- Local estrogen therapy is generally preferred for vaginal dryness/dyspareunia
  - Targeted efficacy to vaginal tissues
  - Minimal systemic absorption, fewer adverse effects
  - Progestin component is not needed in women with uterus
- Local estrogen thought to improve lubrication, increase blood flow and sensation in vaginal tissues

Hormonal Options for Vaginal Dryness

- Vaginal Estrogens
  - Estrogen creams
  - Estradiol vaginal ring
  - Estradiol vaginal suppositories
  - Ring and suppositories thought to have minimal systemic absorption
- Vaginal Testosterone
  - Not FDA approved and need to be compounded
  - Low doses of vaginal creams typically don’t have male hormone side effects

Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer: A Randomized Clinical Trial.


**Novel Therapies for Vaginal Dryness**

Micro ablative CO2 laser
- Acts to improve collagen production in the vagina
- FDA approved in 2014
- Data based on 12 week prospective trial in 77 postmenopausal women
- Requires 3 treatments in physician office
- Not covered by insurance
- Ongoing larger trials
  - Perino, A et al. Maturitas. 2015 Mar;80(3):296-301

**Vaginal Dryness and Sexual Functioning**

- Important to treat the vaginal dryness first and libido after!
- If hurts to be touched or have penetration, desire for sex will be affected

**Newer Pharmacologic Options for Painful Sex**

- Ospemifene – a Selective Estrogen Receptor Modulator (SERM)
- Prasterone – FDA approved vaginal preparation of DHEA
- Both are contraindicated in estrogen-dependent cancers
Ovarian Suppression and Ablation

- Ovarian ablation is the oldest form of systemic treatment for breast cancer, first described in 1896.
- Methods include surgical, radiation-induced, and medical with GnRH analogs (Zoladex).
- Many studies have examined ablation as adjuvant therapy.

Overview of trials:
- Ovarian suppression (OS) and ovarian ablation (OA, via surgical oophorectomy) significantly decrease recurrence and improve survival in women < 50 with hormone-positive tumors.

Ovarian Suppression and Ablation

- Questions have been raised about whether OS provides an additive benefit to endocrine therapy in premenopausal women with hormone-positive disease.

Results from Ovarian Suppression Trials - “game changing”

- Eastern Cooperative Oncology Group trial, Suppression of Ovarian Function Trial (SOFT), Tamoxifen and Exemestane Trial (TEXT), Austrian Breast Cancer Study Group ABCSG-12.
- All showed in high risk disease (for women needing chemotherapy), OS + Tamoxifen or AI associated with fewer recurrences and improved disease-free survival (but not overall survival).
- In young women (particularly < 35) AI and OS more beneficial.
- In low risk disease, no added benefit of OS so tamoxifen alone recommended.
What’s Important for Gyn’s to Know about Ovarian Suppression?

- All trials showed ovarian suppression associated with significant increase in menopausal symptoms, sexual dysfunction, and decreased quality of life—common complaints were hot flashes, sweating, decreased libido, weight gain, anxiety, depression, somnolence, and confusion.

Should the Ovaries Come Out?

- If recurrent disease after tamoxifen and planned AI therapy – YES
- If high risk disease and long term hormonal therapy planned with minimal likelihood of remaining ovarian function – YES
- If low risk disease and likelihood of ovarian function when treatment complete – NO
- ? Counterbalancing risks of subsequent heart and osteoporosis

San Francisco Trivia

- Murphy beds were invented in San Francisco. They were popularized here because.....
  - A. More space was needed for pets to sleep in the small apartments of SF
  - B. There were frequent robberies in the Gold Rush era and people would hide in these beds with their valuables to prevent thieves from finding them
  - C. Murphy was living in a one-room apartment in SF and was trying to woo an opera singer to be his wife but customs of the day wouldn’t allow a woman to enter a man’s bedroom so he created a bed that could fold into a closet
And the Answer Is....

C. Murphy beds were invented by William Lawrence Murphy (1856-1957). San Francisco housing has always been limited and in 1918 he invented this out of urban necessity. He was living in a one-room San Francisco apartment while trying to woo his future wife, a local opera singer. The customs of the day would not permit a woman to enter a single gentleman's bedroom, but by folding his bed into a closet, they apparently felt the room constituted a parlor, allowing him to entertain her there.

Breast Cancer – What’s New in 2017

- Individualized Treatment - Advances in gene expression technologies improves predictions of prognosis and treatment benefit

- Oncotype DX/DCIS, Mammaprint, PAM50 test - genomic tests that predict risk of recurrence and for invasive ca, the likely benefit from adjuvant chemotherapy

- Targeted therapies- Drugs that target HER2, anti-angiogenesis drugs, PARP inhibitors or biologic targeted therapies being used more

Final Thoughts.....

- Common questions about breast cancer

Is it safe to get pregnant after having Breast Cancer? -

- YES

- Large population registry studies have shown no increased risks of recurrences for women who get pregnant after prior treatment for breast cancer

- Typically recommended to wait at least 2 years from diagnosis

- Pregnancies more often in women with early stage disease so possible selection bias “healthy mother effect”

- Most often unable to fully breast feed because of inadequate hypertrophy and lactation in affected breast
Can MHT be used after Breast Cancer?

- Still contraindicated
- Only 2 RCT had conflicting results – “Hormonal Replacement Therapy after Breast cancer: Is iT Safe (HABITS)” and “Stockholm Trial” so not really known
- Ok if DCIS only and bilateral mastectomies

Is Breast Imaging needed after Bilateral Mastectomies?  NO

- If complete mastectomy no need for imaging
- If skin sparing, nipple sparing procedure, some centers may still recommend screening mammography
- MRI can be helpful to establish the presence of residual breast tissue after bilateral mastectomy, and routine screening not recommended if no residual breast tissue is seen
- With saline or silicone implants or autologous reconstruction procedures imaging typically not recommended

Hopefully now, you will....

- Know more facts about breast cancer
- Understand the gyn issues related to breast ca
- Understand when Tamoxifen and Aromatase Inhibitors are used
- Understand the gyn implications of Tamoxifen and the Aromatase Inhibitors
- Know how to treat hot flashes and vaginal dryness
- Know about the role of ovarian suppression in breast cancer
- Know about safety of pregnancy and use of MHT after breast ca

- Know something new about breast cancer that you didn't know before this talk......