# An Oncologist's Perspective on the Clinical Use of Teratogenic Products

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# Overview

- Breast cancer as a paradigm: breast cancer epidemiology and treatment
- Potential teratogenicity of systemic agents
  - Chemotherapy
  - Endocrine therapy
  - Treatment of pregnancy-associated breast cancer
- Risk management in oncology clinic
- What tools and strategies are needed?

# Who am I?

- Academic breast cancer medical oncologist at Dana-Farber Cancer Institute (NCI-Designated Comprehensive Cancer Center)
  - DFCI: one of the largest breast cancer groups in the country (23 MDs)
  - Over 3000 new breast cancer patients each year

- Clinician and clinical researcher
  - Design and run clinical trials of novel agents in breast cancer
  - Maintain a busy practice; about 150 patient visits a month

- Treat women > 18 years old, all stages of breast cancer, from early stage to end of life

# Breast Cancer Epidemiology

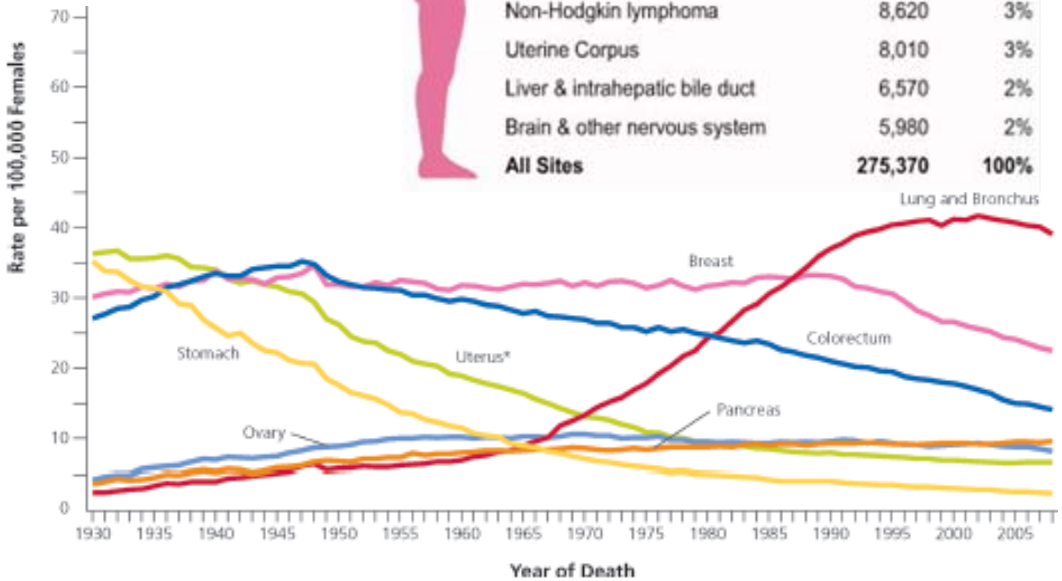
- In 2012:
  - 229,060 new cases breast cancer (invasive and non-invasive)
  - **64,670 cases in women < 50 years old**
  - 2,190 cases in men
  - 39,920 deaths
  - estimated **3 million breast cancer survivors in US**
- In general
  - New cases decreasing
    - >50 yo cohort
    - Related to less HRT
  - Deaths decreasing

**Females**

| | | |
|---|---|---|
| Breast | 226,870 | 29% |
| Lung & bronchus | 109,690 | 14% |
| Colon & rectum | 70,040 | 9% |
| Uterine corpus | 47,130 | 6% |
| Thyroid | 43,210 | 5% |
| Melanoma of the skin | 32,000 | 4% |
| Non-Hodgkin lymphoma | 31,970 | 4% |
| Kidney & renal pelvis | 24,520 | 3% |
| Ovary | 22,280 | 3% |
| Pancreas | 21,830 | 3% |
| **All Sites** | **790,740** | **100%** |

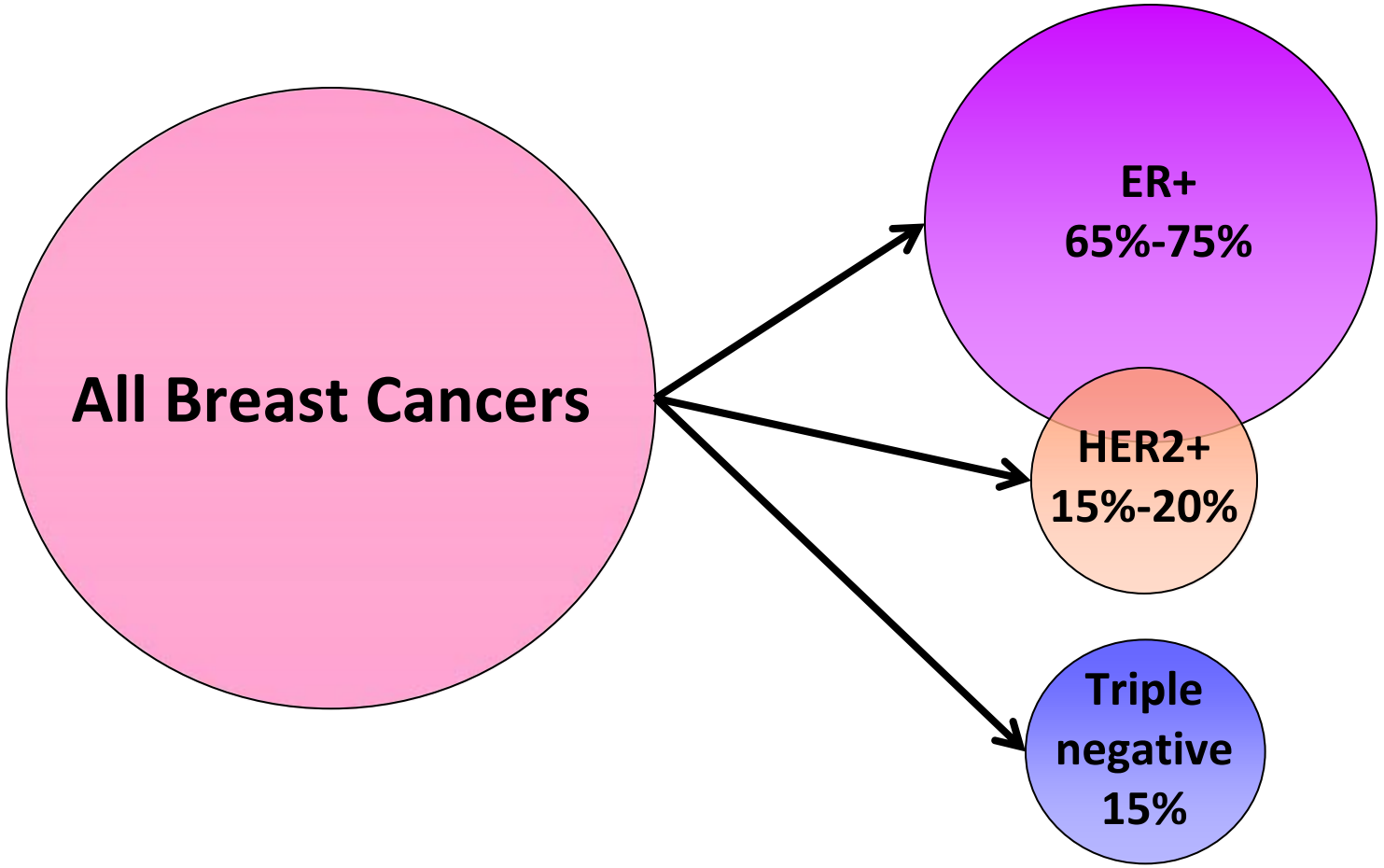
**Females**

| | | |
|---|---|---|
| Lung & bronchus | 72,590 | 26% |
| Breast | 39,510 | 14% |
| Colon & rectum | 25,220 | 9% |
| Pancreas | 18,540 | 7% |
| Ovary | 15,500 | 6% |
| Leukemia | 10,040 | 4% |
| Non-Hodgkin lymphoma | 8,620 | 3% |
| Uterine Corpus | 8,010 | 3% |
| Liver & intrahepatic bile duct | 6,570 | 2% |
| Brain & other nervous system | 5,980 | 2% |
| **All Sites** | **275,370** | **100%** |




Siegel et al, Ca J Clin 2012

# Invasive Breast Cancer Subsets Defined by IHC

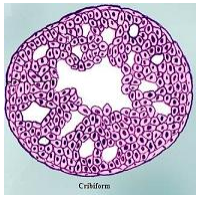


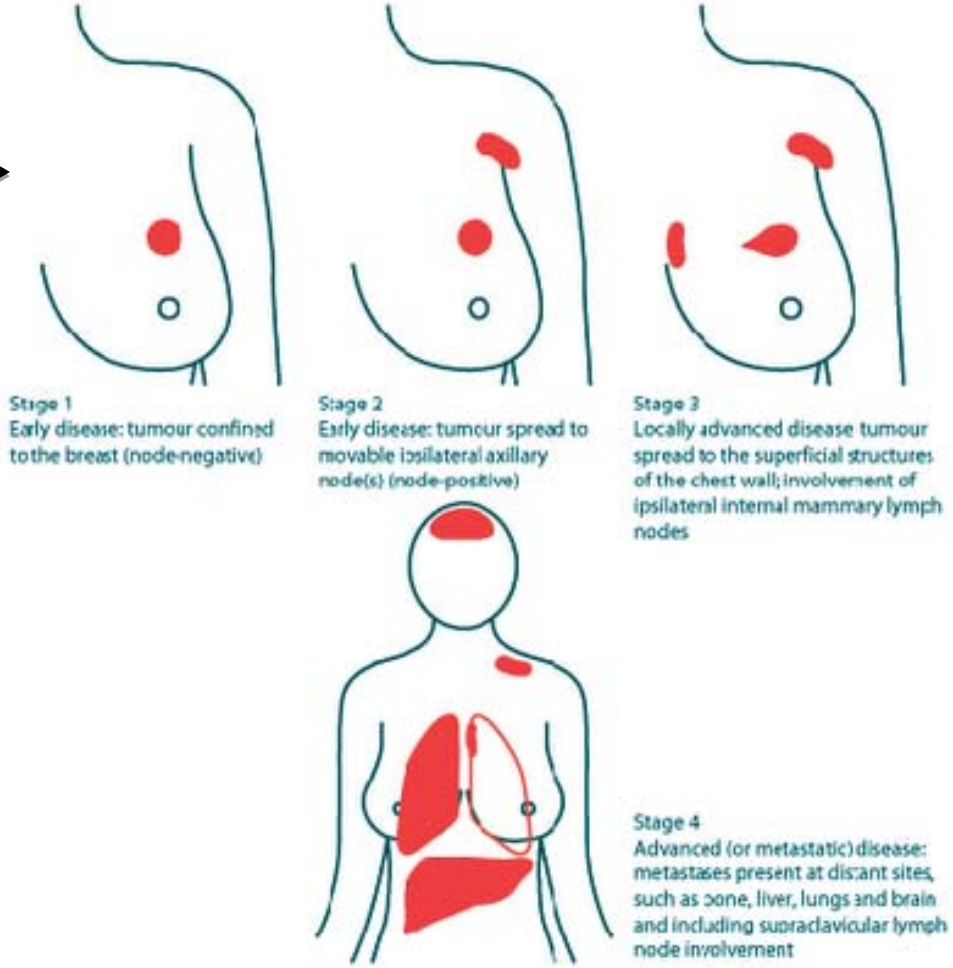



Burstein, Goldhirsch. St Gallen 2007.

# Breast Cancer Staging

DCIS





# Systemic Therapy For Breast Cancer

- Endocrine Therapy
- Chemotherapy
- Biologic Therapy

- Treatment selection is tailored to:
  - Tumor characteristics/risks of recurrence
  - Patient factors: comorbidity, preferences

- For Stage I-III breast cancer, therapy can be curative
- For Stage IV breast cancer, therapy is palliative

# Endocrine Therapy for Invasive Breast Cancer

- Standard treatment for hormone receptor-positive invasive breast cancer

- For premenopausal patients, the standard of care is 5+ years of oral tamoxifen
  - non-steroidal selective estrogen modulator (SERM)
  - tamoxifen and metabolites have potent anti-estrogen effects

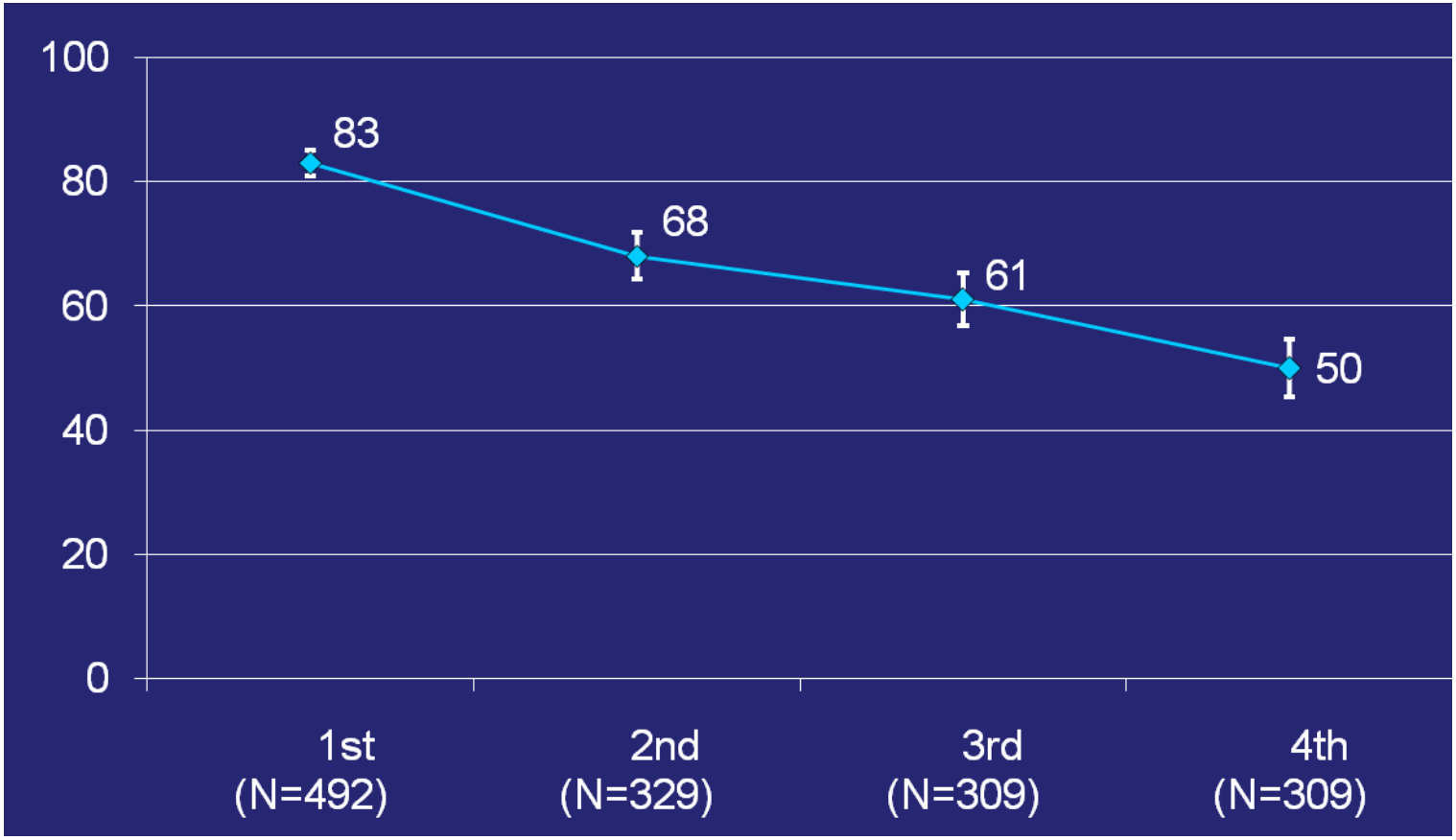
- Effective endocrine therapy provides a substantial reduction in risk of cancer recurrence
  - 40-50% reduction in risk of recurrence, 30% reduction in risk of breast cancer death

# Endocrine Therapy for DCIS/Prevention

- 5 years tamoxifen offered for DCIS (ductal carcinoma in situ) to prevent local recurrence

- Tamoxifen and aromatase inhibitors can **prevent** first diagnosis breast cancer (prescribed by PCP).
  - Despite offering 50% reduction in risk of developing breast cancer in high risk women, few decide to pursue tamoxifen

# Long-term Adherence to Adjuvant Tamoxifen in Women with Early Breast Cancer



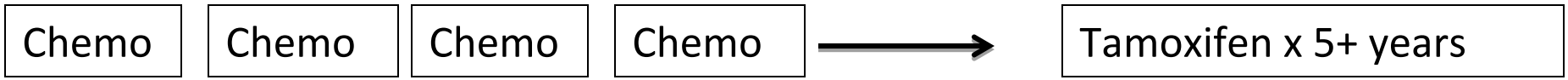

Monitoring Rx refill rates in 2,300 patients

Partridge et al., JCO 2003

# Chemotherapy for Breast Cancer

- Stage I-III Disease (Adjuvant)
  - Duration 12-24 weeks
  - Agents include adriamycin, cyclophosphamide, paclitaxel, docetaxel – all parenteral
  - Trastuzumab added for an extra year if HER2+
- Metastatic Disease (Palliative)
  - Essentially all patients post-menopausal
  - Chemotherapy may be used indefinitely
  - Many new biologics entering the field
    - Pertuzumab, TDM-1, everolimus

# Timeline of Adjuvant Breast Cancer Care




- For premenopausal women, systemic therapy may lead to exposure to potential teratogens

# How Can We Determine Safety of Systemic Cancer Therapy in Pregnancy?

- Estimated 1/1000 pregnancies complicated by cancer
- Likely to increase in the future with more women delaying childbearing
- Frequency of common malignancies observed during pregnancy:

| Type of cancer | Number of cancers diagnosed prenatally per 100,000 deliveries |
|---|---|
| Breast* | 3.7 |
| Thyroid | 3.3 |
| Cervix | 1.6 |
| Ovary | 1.5 |
| CNS | 1.2 |
| Hodgkin Lymphoma | 1.0 |
| Leukemia | 1.0 |

* The majority of published data describes breast cancer experience

Donegan, Ca Cancer J Clin, 1983; Pavlidis, Oncologist 2002; Smith et al., Am J Obstet Gynecol, 2001

# What is the Safety of Tamoxifen in Pregnancy?

- Limited data on tamoxifen exposure during pregnancy; most reports lack information about duration and timing of usage

- Early case reports noted congenital abnormalities
  - ambiguous genitalia, Goldenhar's Syndrome, Pierre Robin sequence

- Series of 85 pregnancies in women taking tamoxifen for cancer prevention
  - No fetal abnormalities reported

- Manufacturer database: 136 pregnancies
  - 17 abnormal outcome
    - 10 congenital abnormalities
    - 1 stillbirth with fetal defects
    - 6 terminations with fetal defects
  - 50 normal outcome
    - 33 live births without abnormality
    - 1 stillbirth without abnormality
    - 16 terminations without fetal defects



Braems et al, The Oncologist 2011; Clark et al, Lancet 1993

# What is the Safety of Tamoxifen in Pregnancy?

- Summary of known reports of in utero tamoxifen exposure
  - 24 with fetal defects
  - 140 without fetal defects
  - 57 unknown

- No data on long-term follow-up of children exposed to tamoxifen in utero

- Despite limited published data, relatively high frequency of reported congenital abnormalities reinforces **lack of safety of tamoxifen during pregnancy**

- **But… no guarantee of harm**



Braems et al, The Oncologist 2011; Clark et al, Lancet 1993

# Chemotherapy in Pregnancy

- Chemotherapy is a potential teratogen; risks are related to agent selection, timing of administration, dose

- Potential risks in humans include:
  - Early effects:
    - Spontaneous abortion, teratogenesis, organ toxicity, premature birth, IUGR, low birth weight
  - Labor and delivery complications:
    - Low blood counts (bleeding, anemia, infection)
  - Late effects:
    - Carcinogenesis, gonadal dysfunction, infertility, retarded physical and neuropsych development, mutagenesis of germ-line tissue and teratogenicity and carcinogenesis of subsequent generations

- *However*, chemotherapy administration is possible, with rates of congenital malformations resembling baseline population risk.
  - Potential benefits from use of the drug may make risk acceptable in some circumstances



Partridge and Garber, Seminars in Oncology, 2000, 712-726

# Chemotherapy in Pregnancy: Major Case Series

- Most standard regimens for common pregnancy-associated cancers appear to be safe to use in $2^{nd}/3^{rd}$ trimesters

- Cardonick and Iacobucci (Lancet Oncology, 2004)
  - 104 patients with PABC, self reported
  - Malformation rate 3.8%

- Ring et al. (J Clin Oncol 2005)
  - 28 women treated for PABC
  - 1 sAb after $1^{st}$ trimester exposure, all other neonates without abnormality

- Hahn et al (Cancer 2006)
  - 57 patients with PABC
  - 5% with abnormalities

- Loibl et al (Lancet Oncol 2012)
  - 413 women treated for PABC
  - 2% rate of fetal malformation

# DF/HCC Systemic Therapy

| Systemic Therapy (N=68 patients delivered live born infants, 36 received chemotherapy therapy) | Number | Percent |
|---|---|---|
| **Chemotherapy during pregnancy (N = 68)** | | |
| Yes | 36 | 52.9 |
| No | 32 | 47.1 |
| **Gestational age at initiation of treatment (N=36)** | | |
| 0-12 weeks (1st trimester) | 0 | 0.0 |
| 13-27 weeks (2nd trimester) | 29 | 80.6 |
| 28-40 weeks (3rd trimester) | 7 | 19.4 |
| **Chemotherapy regimen (N=36)** | | |
| Every-3-week AC | 29 | 80.6 |
| 4 cycles (N=29) | 21 | 72.4 |
| 3 cycles (N=29) | 2 | 6.9 |
| 2 cycles (N=29) | 5 | 17.2 |
| 1 cycle (N=29) | 1 | 3.4 |
| Dose-dense AC | 7 | 19.4 |
| 4 cycles (N=7) | 5 | 71.4 |
| 2 cycles (N=7) | 2 | 28.6 |
| AC x 4 + weekly paclitaxel (12 weeks) | 3 | 8.3 |
| Dose-dense AC (N=3) | 2 | 66.6 |
| Every-3-week AC (N=3) | 1 | 33.4 |
| **Neoadjuvant chemotherapy (N=36)** | | |
| Yes | 8 | 22.2 |
| **Growth factor support (N=36)** | | |
| Yes | 6 | 16.7 |
| Pegfilgrastim (N=6) | 4 | 66.7 |
| Filgrastim (N=6) | 2 | 33.3 |



Meisel et al, SABCS 2011

# DF/HCC Fetal Outcomes

- More than half of deliveries were < 37 weeks gestation
- Over 70% of those were planned “to expedite maternal treatment”
- Rate of fetal malformation 4.4% is not different that general population

| **Fetal Outcomes (N = 68)** | Frequency | Percent |
|---|---|---|
| **Method of delivery (N=68)** | | |
| Method of delivery known | 62 | 91.2 |
| Spontaneous onset of labor (N=62) | 8 | 12.9 |
| Induction of labor (N=62) | 38 | 61.3 |
| Caesarian section (N=62) | 21 | 33.9 |
| Method of delivery unknown | 6 | 8.8 |
| **Gestational age at delivery (N=68)** | | |
| Gestational age at delivery known | 66 | 97.1 |
| <34 weeks (N=66) | 4 | 6.7 |
| 34-36.9 weeks (N=66) | 33 | 50.0 |
| >37 weeks (N=66) | 29 | 43.9 |
| Gestational age at delivery unknown | 2 | 2.9 |
| **Weight for gestational age (N=68)** | | |
| Weight for gestational age known | 50 | 73.5 |
| SGA (<10$^{th}$ percentile) (N=50) | 4 | 8.0 |
| AGA (N=50) | 45 | 90.0 |
| LGA (>10$^{th}$ percentile) (N=50) | 1 | 2.0 |
| Weight for gestational age unknown | 18 | 26.5 |
| **Apgar scores (N=68)** | | |
| Apgar scores known | 50 | 73.5 |
| ≤7 at 5 minutes (N=50) | 0 | 0.0 |
| ≥7 at 5 minutes (N=50) | 50 | 100.0 |
| Unknown | 18 | 26.5 |
| **Complications of delivery (N=68)** | | |
| Spontaneous preterm delivery | 5 | 7.3 |
| Arrested preterm labor | 2 | 2.9 |
| PPROM | 5 | 7.4 |
| Chorioamnionitis | 1 | 1.5 |
| Cord prolapse | 1 | 1.5 |
| Uterine atony | 1 | 1.5 |
| **Fetal Abnormalities (N=68)** | | |
| Cleft palate | 1 | 1.5 |
| VSD, club foot, hypospadias | 1 | 1.5 |
| ASD | 1 | 1.5 |

Meisel et al, SABCS 2011

# Chemotherapy Agents in Pregnancy

| Agent | Generally Acceptable | Generally Unacceptable at any time | Not Enough Study to Recommend |
|---|---|---|---|
| methotrexate | | X | |
| cytarabine | | X | |
| 5-FU | X | | |
| cyclophosphamide | X | | |
| doxorubicin | X | | |
| bleomycin | X | | |
| vincristine | X | | |
| etoposide | X | | |
| platinums | | | X |
| vinorelbine | | | X |
| taxanes | | | X |

# Trastuzumab in Pregnancy

- Recombinant humanized monoclonal antibody
  - Potentially can cross placenta
  - Long half life, up to 6 weeks after infusion

- Limited experience to date:
  - 11 early case reports of use during pregnancy
  - Notable fetal effects
    - 5 oligohydramnios; 2 anhydramnios
    - 2 renal dysfunction
    - 1 newborn died from multiorgan failure at 21 weeks

- Package insert includes Boxed Warning for pregnancy

- Given findings, ***trastuzumab use discouraged in pregnancy***

As stated in the Herceptin® (trastuzumab) Package Insert, Herceptin is classified under Pregnancy Category D. Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, **use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.** Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy and provide contraception counseling to women of childbearing potential. Please refer to the Herceptin Package Insert for full prescribing information including **Boxed WARNINGS** and additional safety information.

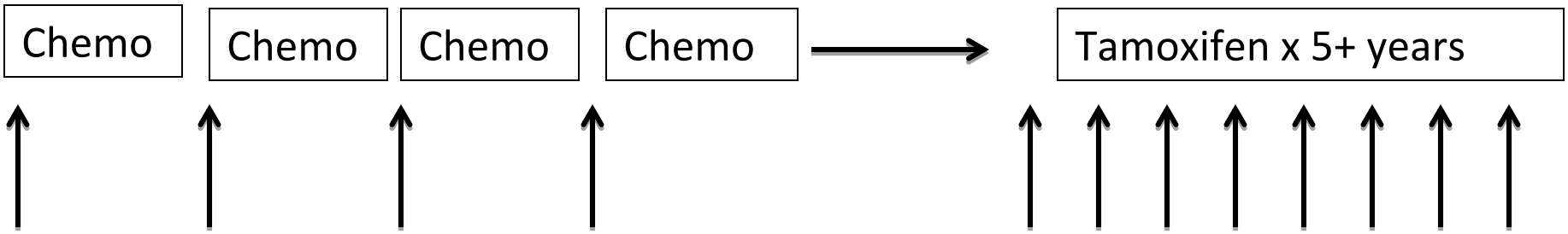


Witzel et al, Ann Oncol 2008; FDA Package Insert

# Pregnancy after breast cancer: Is it safe?

- No clear adverse effect of subsequent pregnancy on prognosis
  - (caveat: “healthy mother” bias)
- Conventional wisdom is to wait until >2 years, to get through early risk of recurrence period or receive endocrine therapy
- No data to suggest harm in pregnancy sooner
- Ultimately the decision to get pregnant is a very personal one

# Timeline of Adjuvant Breast Cancer Care




- Multiple moments in routine clinical care when pregnancy status and contraceptive choices can be discussed
- Care increasingly shared by MD and NP/PA

# How Effective are Medical Oncologists at Discussing Pregnancy and Contraception?

- Do we know these are important topics?
  - YES
- Do we try to discuss pregnancy status with patients before receiving potentially teratogenic systemic therapy?
  - YES
- Does this discussion happen every time?
  - We try; if not by MD, layers of safety with NP/RN exist
- Does a pregnancy test always get sent before potentially teratogenic therapy is provided?
  - Sometimes, typically driven by patient report

# How Do Medical Oncologists Discuss Chemotherapy with Premenopausal Patients?

- What we always discuss
  - Rationale for taking the medication
  - Side effect profile and management (fertility issues)
  - Consent for treatment
  - Emergency situations
  - Emotional reassurance

- What we try to discuss
  - “Is there a chance you could be pregnant/LMP?”
  - Appropriate contraception during chemotherapy

# DFCI Experience: Pregnancy Evaluation Before Chemotherapy

- Pregnancy and contraception **always** discussed by chemotherapy infusion nurse with the patient
  - Discussed at initial chemotherapy visits and at daily assessments
  - Example from one of my patients (40 years old, G1P1, receiving adjuvant chemotherapy)

  - *"Sexuality/Reproductive Pattern*
    - *Are you sexually active? Yes*
    - *Do you use any form of birth control? Yes*
    - *Has your disease or treatment interfered with your sexuality? No*
    - *Do you have concerns about your cancer treatment and its effects on your sexuality (e.g. infertility, impotence)? No*
    - *Women: Date of last menstrual period: 6/19/12"*

- Performed for all of our patients

# How Do Medical Oncologists Discuss Tamoxifen with Premenopausal Patients?

- What we always discuss
  - Rationale for taking the medication
  - Duration of use
  - Side effect profile
  - Survivorship care

- What we try to discuss
  - “Is there a chance you could be pregnant?”
  - Appropriate non-hormonal contraception while on tamoxifen

# What is Appropriate Non-Hormonal Contraception?

- Barrier protection
  - condoms and diaphragms
- IUD
  - Copper only, progesterone-containing LNG-IUD (Mirena)
- Permanent contraception
  - Sterilization: tubal ligation or partner vasectomy

# What About LNG-IUD (Mirena)?

- Progesterone-impregnated IUD; low level systemic hormone absorption
- Multiple population studies suggest no increased risk of new breast cancer
- Small studies in premenopausal women on tamoxifen generally do not suggest increased risk of breast cancer recurrence.
- However formally contraindicated “in a woman who has or may have breast cancer.”
- Royal College of OB/GYN Society of Family Planning: (2012)
  - "More research is needed to determine the long-term safety of the levonorgestrel IUD by women with a history of breast cancer."



Trinh et al, Fertil Steril 2008; Lyytinen et al, Int Jour Cancer 2010 ; Patel et al, Contraception 2012

## Follow-up Provider Clinical Checklist for Young Women

☐ **Prescriptions refilled, adherence issues addressed as needed**

☐ **Genetics discussed:**
- Refer to counseling, as needed _____
- Refer for testing, as needed _____

☐ **Fertility/contraception issues updated:**
- Referral to fertility specialist, as needed _____

☐ **Menopausal symptoms or sexual dysfunction addressed:**
- Referral to specialist, as needed _____

☐ **Bone health recommendations made:**
- Encourage vitamin D (400-800 IU/day) and calcium (1000 mg/day if premenopausal, 150 postmenopausal) supplementation
- Weight bearing exercise
- Baseline bone mineral density scan (DEXA scan) if at risk for osteoporosis

☐ **Psychosocial resources discussed:**
- Consider referral to social worker, counselor or other mental health professional
- Local support groups or other local programs
- One-to-one through ACS
- Young Survival Coalition: www.youngsurvival.org

☐ **Dietary and behavioral considerations discussed:**
- Encourage regular, moderate exercise
- Encourage weight reduction, if overweight
- Consider nutrition consultation, if not ideal BMI

## Key Survivorship Topics for Young Women

**Below are topics that you may want to talk about with your doctor *in long-term follow-up*:**

☐ **Prescriptions needing refills:**
- Any trouble obtaining or taking recommended medication regularly?

☐ **Menopausal symptoms, hot flashes and problems with sex:**
- What can I do to help with the symptoms I am experiencing?

☐ **Fertility after treatment:**
- If I want to try to get pregnant in the future, what are my options now?
- What are the pros and cons for these options?
- What are my options for contraception at this point?

☐ **Bone health:**
- Am I at risk for bone thinning (osteopenia/osteoporosis)?
- What should I be doing about this? (Diet? Exercise? Supplements?)
- Do I need to get a bone density evaluation?

☐ **Coping:**
- Where can I get more help if I am having difficulty emotionally?

☐ **Diet and healthy living:**
- Are there any specific things that I should be thinking about or doing related to diet, exercise and other health habits at this time?
- What can help me to get or maintain a good, healthy body weight?

# Dana-Farber Survivorship Guidelines

| | | |
|---|---|---|
| **Counseling** | **Adherence** | Patients on oral anti-neoplastics should be questioned and counseled about adherence at each medical oncology clinic visit. |
| | **Genetics** | Update family history annually and refer to genetic counselor if appears to meet criteria of >10% risk of BRCA mutation (including all male breast cancer patients) assuming patient has not been previously tested or decided against testing. |
| | **Fertility and contraception** | Address annually with potentially fertile patients; refer to reproductive endocrinologist or contraception clinic as needed. |
| | **Psychosocial** | Assess at least annually for psychosocial concerns such as fear of recurrence, depression, anxiety; consider referral to clinical social worker in the adult survivorship program or other providers as clinically indicated. |
| | **Health behaviors** | Patients should be informed at least annually about data on merits of exercise, weight loss/maintenance, avoiding excessive alcohol and smoking cessation. Consider referral(s): BWH medical weight management clinic if BMI is $\geq$ 30. Exercise- Nancy Campbell and/or Nutrition. |
| | **Sexual functioning and menopausal symptoms** | Assess symptoms and concerns around sexual function at least annually; consider referral to the sexual health clinic in the adult survivorship program to treat and manage symptoms of menopause and sexual dysfunction. |
| | **Other symptoms** | Annually, ask about fatigue, lymphedema, and cognitive dysfunction. NCCN.org recommendations may be helpful for management. |
| | **Calcium/ Vitamin D** | Patients should be advised at least annually to consider taking calcium 1000mg daily (premenopausal) or 1200mg daily (postmenopausal) in divided doses and vitamin D 600-800IU daily (over age 71 800IU) unless otherwise medically unadvisable. |

# Existing Professional Guidelines

- American College of Obstetrics and Gynecology (March 2012)
  - “Contraceptive options for patients with breast cancer include barrier methods, such as condoms and diaphragms, the copper intrauterine device, and sterilization”

- National Comprehensive Cancer Network (NCCN 2012)
  - Patients should not become pregnant during treatment with radiation therapy, chemotherapy, or endocrine therapy.
  - Although data are limited, hormone-based birth control is discouraged regardless of the hormone receptor status of the patient's cancer
  - Alternative methods of birth control include intrauterine devices (IUD), barrier methods or for patients with no intent for future pregnancies, tubal ligation or vasectomy for the partner.

# Barriers to Discussing Pregnancy Status/Contraception

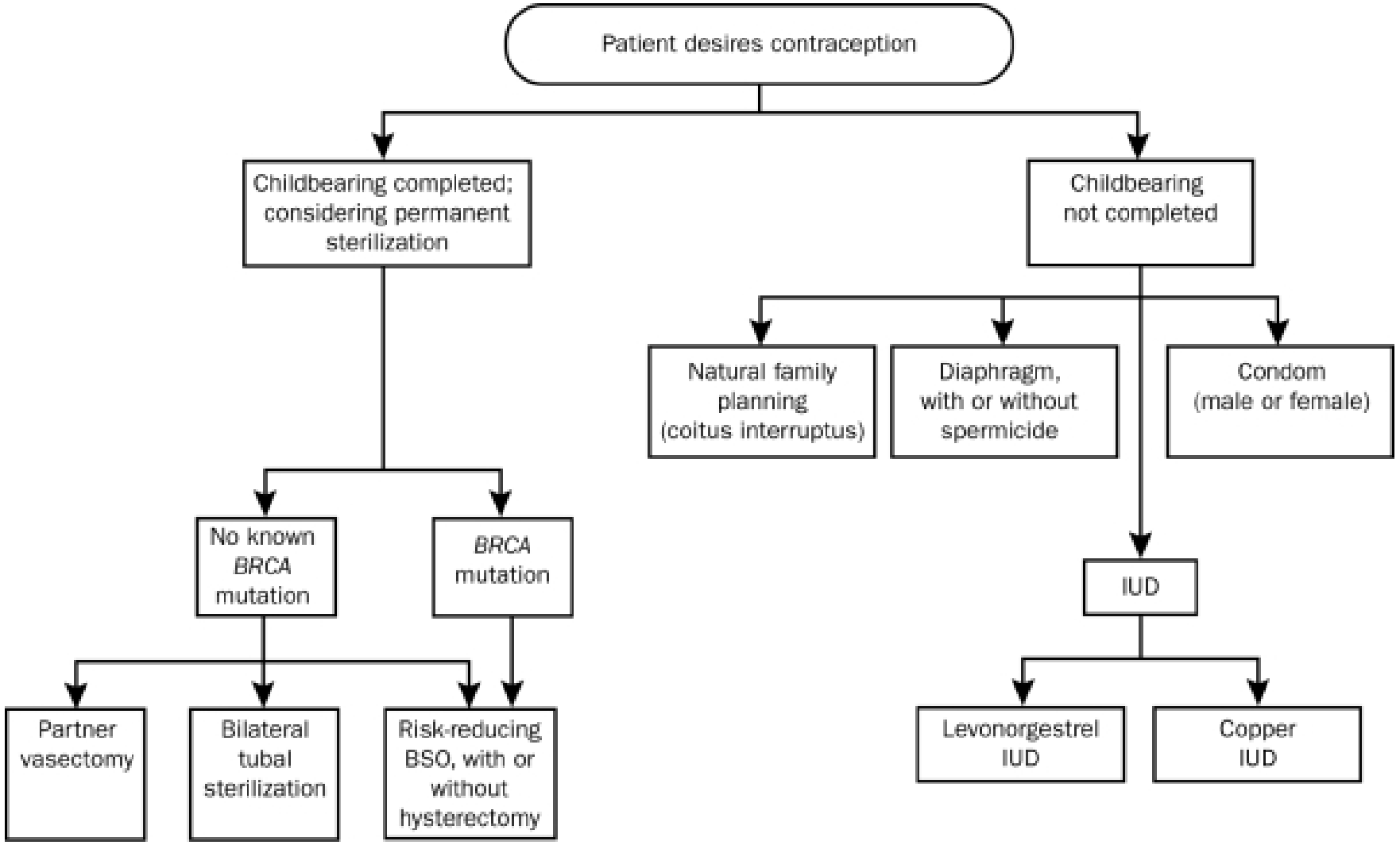
- Lack of time
  - Many topics to be discussed with breast cancer survivors regarding direct cancer care and surveillance
- Provider discomfort
  - Lack of knowledge about resources recommendations
  - Uncomfortable talking about sexuality
  - Perception of low priority
- Assumptions about the patient
  - Cancer patients “know” not to get pregnant
  - Cancer patients lack libido
  - Breast cancer patients know to avoid hormonal options

# What Would be Helpful to Overcome Barriers?

- Take advantage of the electronic medical record used by many providers
  - EMR based reminders/monitoring
    - Pop up box reminding to ask about pregnancy and contraception when provider is writing chemotherapy
  - Educational resource
    - Links to more detailed information
    - Patient-oriented interface available
  - Easy to navigate, streamlined within clinic schedule

- Referral resources for patients with questions beyond oncology score of expertise

# A Possible Algorithm?






Bakkum-Gamez et al, Mayo Clin Proc 2011

# Conclusions

- Many premenopausal patients receive potentially teratogenic therapy as part of systemic breast cancer management
- Chemotherapy can be safely administered in pregnancy; tamoxifen and trastuzumab are generally not safe at any time in pregnancy
- Medical oncologists are aware of the need to counsel patients about pregnancy and contraception; ability to do so may be limited by time constraints/knowledge deficits
- Consistent with IOM recommendations for patient-centered care, systems are in development to guide clinical care; mechanisms that **FACILIATE** but not restrict ability to provide optimal comprehensive care are ideal