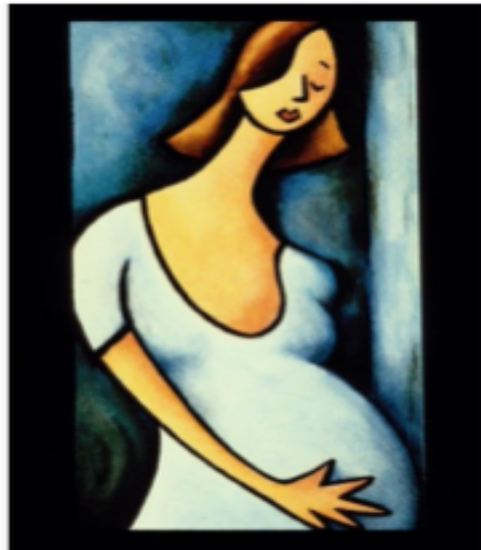


Pregnancy for Cancer Survivors



Elyce H. Cardonick, MD
Professor of Obstetrics &
Gynecology, Division of
Maternal Fetal Medicine
Cooper Medical School of
Rowan University
Camden NJ

I have no disclosures

Objectives

- ◆ **Pre-conception evaluation of a woman who had a cancer in the past, including the effect of pregnancy on the risk of recurrence, evaluation of the consequences of past surgery chemo or radiotherapy that can impact pregnancy**
- ◆ **Propose a plan of follow-up during pregnancy postpartum when appropriate, especially regarding the risk of post-chemo cardiomyopathy**

Parenting After Cancer: A Survey of Survivors

- 🎗 Survey of 89 women in tumor registry Cleveland Clinic
- 🎗 Majority felt healthy enough to be a good parent
- 🎗 Feeling healthy enough to be a good parent was the strongest predictor of emotional well being
- 🎗 Majority felt their experience of having cancer would make them a better parent
- 🎗 Less than 57% received information about pregnancy
Schover, Cancer, 1999
- 🎗 Report in Psycho-Oncology reported that the experience of having breast cancer did not hinder overall positive motivations toward childbirth, nor did it increase overall negative feelings

Parenting After Cancer: Survivor's Concerns



Chromosomal/birth defects



Offsprings' risk for cancer



Pregnancy complications



Risk of recurrent malignancy

Pregnancy dose not affect risk of recurrence of any type of cancer

LIFETIME RISKS AFTER CANCER TREATMENT

2/3 of childhood cancer survivors experience ≥ 1 chronic medical condition
1/3 develop severe or life threatening complications years later including cardiovascular events, pulmonary dysfunction or second malignancies

Jarin Repro Biol&Endo 2016

Pulmonary dysfunction risks include prior treatment with pulmonary-toxic chemotherapy; chest radiotherapy $>20\text{Gy}$; treatment before age 16years or prior allogenic stem cell transplant with h/o GVDH

Restrictive lung disease with reduced volume

- limited ability to increase minute ventilation in pregnancy

- chronic fetal hypoxia \rightarrow fetal growth restriction \rightarrow adult cardiovascular and metabolic dysfunction

Decreased diffusion capacity-more respiratory symptoms reported in pregnancy, increased fatigue compared to survivors without decreased DC

Female survivors with normal PFTs 2years post treatment still have decline in diffusion capacity compared to males or female survivors not exposed to $>20\text{Gy}$ to chest.

Armenian J Clin Onc 2015

Planning a Pregnancy for a Cancer Survivor

- ⌘ Address concerns about risks for offspring
- ⌘ Do routine surveillance preconceptionally (PET, mammogram, colonoscopy...)
- ⌘ Wait at least 3 months after stopping methotrexate
- ⌘ Discuss optimal time of delay after breast cancer (more to come)
- ⌘ If prior Hodgkin's Disease and radiation, check TSH
- ⌘ Prior anthracycline treatment or left chest radiation check echocardiogram, EKG

Childhood Cancer Survivor Study: Pregnancy After Chemotherapy/Radiation

- ⌘ Rate of live birth was not lower for patients treated with any particular chemotherapy agent
- ⌘ Trend toward higher miscarriages after radiation therapy *regardless of location*
- ⌘ Newborns of patients who received pelvic radiation were significantly more likely to weigh < 5 pounds
Green, J Clin Onc 2002
- ⌘ After abdominal radiation increased incidence of breech and earlier gestational age at delivery
Hawkins, IntJ Ca, 1989
- ⌘ Elective terminations are higher in cancer survivors (and partners of male survivors)

Pregnancy After Cancer Treatment: *Abdominal/Pelvic Irradiation*

Scarring in uterus can affect blood flow to placenta, elasticity, volume, damage to lining where pregnancy must implant

Risk depends on total dose, site irradiated, woman's age (prepuberty?)

30% of irradiated Wilm's tumor survivors had an adverse pregnancy outcome

- Increased fetal or infant loss
- Increased preterm birth
- Increased birth weight <5 pounds

Li, JAMA, 1987

- None of 6 patients carried beyond second trimester

Wallace, ClinCon 1989

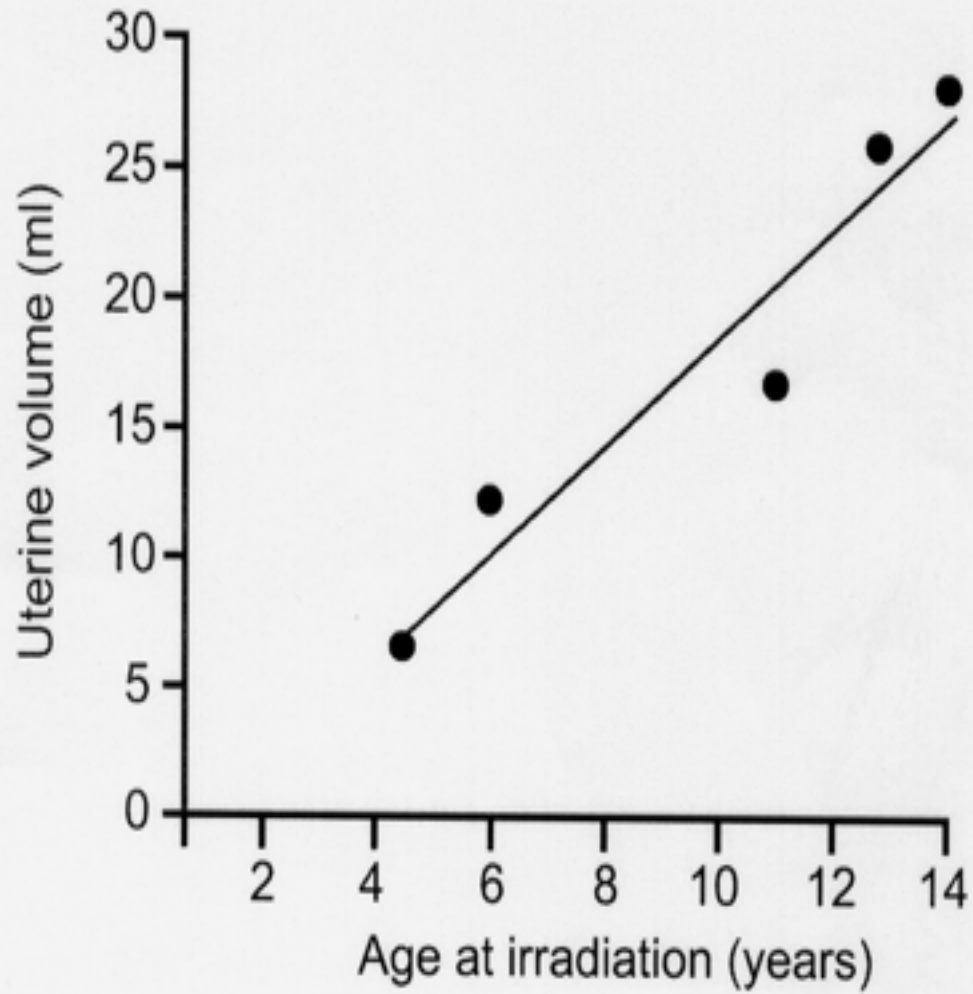
- Abnormal adherence of placenta with hemorrhage +/- or invasion into bladder reported after adolescent radiation

Norwitz, ObstetGynecol 2001

Li, JNCL, 1979;

Pridjian, AJ OG, 1990

Uterine Volume and Age at Irradiation



Prenatal care, importance of surveillance

- ⌘ Patients with Hodgkin's Disease are at risk for secondary cancers
- ⌘ Do breast exams including axillae
- ⌘ Prior radiation therapy to neck check for hypothyroidism
- ⌘ Echocardiogram, EKG if prior chest radiation or anthracycline, obtain dosage

Induction of Ovulation for Breast Cancer Survivors: Use Tamoxifen/Letrozole

- 🎀 Ovarian induction for patients with breast cancer
- 🎀 Tamoxifen and letrozole with low dose FSH can be used for ovulation induction
- 🎀 911 newborns conceived after infertility treatment with letrozole or clomiphene

Tulandi, T. Fertil Sterile 2006.85:176-65

Parenting After Cancer: *Breast Cancer* Survivors

- ⚡ Pregnancy after breast cancer does not worsen 5 year survival and some studies show a statistically improved survival

Gelber, J Clin Onc, 2001

- ⚡ 3 cancer registries in USA linked to birth certificate data:
438 women with breast cancer and subsequent pregnancies vs.
2775 controls *matched for age at dx, race, yr of dx, stage
Improved survival with pregnancy after breast cancer

Mueller, Cancer, 2003

- ⚡ Prognosis determined by **nodal status** and **stage**, not subsequent pregnancy

Ariel, IntSurg, 1989

- ⚡ Pregnancy safe even after **ER positive** breast cancer

Pregnancy Subsequent to Breast Cancer: Is there an optimal time to wait?

Time to Conception

Survival

< 6 months:

54%

1 year:

50%

1-2 years:

80%

2 years:

100%

Peters, Clark

<3 months:

RR mortality 1.7 (1.2-2.6)

4-6 months:

RR mortality 1.0 (.55-1.9)

2-3 years:

RR mortality 0.49 (0.27-0.86)

Mueller, Cancer, 2003

Risk of Mortality with Pregnancy <10months After Breast Cancer

(Information not collected on spontaneous losses)

- ⊗ <35 years at diagnosis, no difference in mortality
- ⊗ >35 years-relative risk (RR)1.8
- ⊗ Metastatic disease at diagnosis-RR 1.7
- ⊗ Positive lymph nodes at diagnosis-RR 1.8
- ⊗ No difference with tumor size \leq 2cm
- ⊗ No difference according to maternal race

Risk of Mortality with Pregnancy >10months After Breast Cancer

- ⚡ Women having children >10 months after breast cancer diagnosis had a *decreased* mortality
- ⚡ RR .54 (0.41-071) compared to women without births
- ⚡ True for women with local/metastatic disease, all maternal ages, lymph node +, tumor >2cm
- ⚡ No difference according to maternal race

Mueller, Cancer 2003

PREGNANCY AFTER BREAST CANCER SAFE EVEN FOR WOMEN WITH ER+RECEPTORS

Multicenter, retrospective cohort study of women becoming pregnant after breast cancer

Women matched for ER receptors, nodal status, adjuvant therapy, age and year of diagnosis to nonpregnant breast cancer survivor

333 pregnant patients and 874 nonpregnant

No difference in disease free survival observed for patients with and without subsequent pregnancies for either ER+ or ER- breast cancer

Azim, J Clin Oncol 2013 31:73-79.

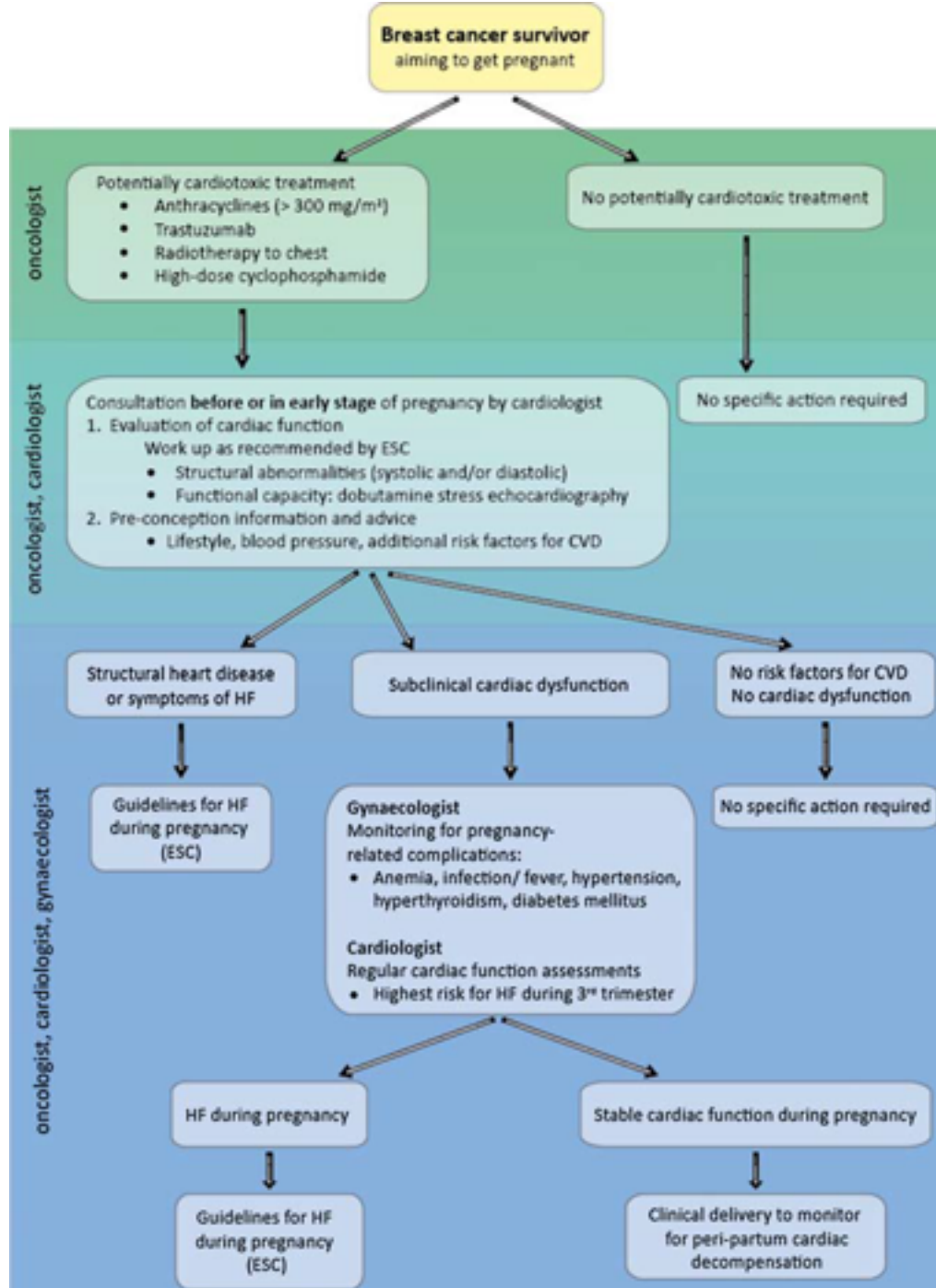
CARDIOTOXICITY ESPECIALLY A CONCERN AFTER BREAST CANCER TREATMENT WITH ANTHRACYCLINES AND HERCEPTIN

Cardiotoxicity After Trastuzumab (Herceptin) alone:

Cardiac dysfunction	2-4%
Asymptomatic cardiac dysfunction	5-10%
Congestive heart failure	1%

*Synergistic effect of anthracyclines with radiation and Herceptin

Some authors report up to 25% risk for decline in systolic function when Herceptin given concurrently with or shortly following anthracycline treatment



Flow-chart with proposed strategy for counseling of female cancer survivors in the child-bearing age, to estimate the risk for heart failure during pregnancy.

RADIATION-INDUCED CARDIOVASCULAR DISEASE

Mechanism:

- ♥ Vascular injury
- ♥ Endothelial dysfunction

Risk Factors:

- ♥ Dose > 35 Gy
- ♥ Adjuvant cardiotoxic chemotherapy
- ♥ Radiation field
- ♥ Hypertension; Smoking

Manifestations:

- ♥ Coronary artery disease
- ♥ Acute or constrictive pericarditis
- ♥ Valvular thickening/sclerosis
- ♥ ECG abnormality: AV block; long QTc; RBBB
- ♥ Myocardial- fibrosis; dysfunction; restrictive cardiomyopathy
- ♥ Carotid disease

Lee MS, et al Am J Cardiol 2013: 112: 1688-1696

Mousavi, N, et al: Curr Treatment Options in Cardiovasc Med: 2013: 15: 507-517

PERIPARTUM CARDIOMYOPATHY IN A PATIENT TREATED FOR ACUTE MYELOID LEUKEMIA

5 years after treatment for AML first pregnancy uneventful

7 months later second pregnancy, 1 week postpartum developed shortness of breath, edema, cough and fever

EKG: tachycardia, low voltage with inverted T waves V4-6

ECHO: hypokinetic LV, mitral & tricuspid regurgitation, EF <25%

Doxorubicin total dose 360mg;mitoxantrone 60mg)

Colovic, N.2016

Patient treated for Hodgkin's lymphoma 10 years before a first pregnancy

Developed pulmonary edema at 34weeks-felt to be secondary to cardiotoxicity of doxorubicin (360mg) combined with concomitant radiation which can cause valvular fibrosis

Patient with mild hypertension without superimposed preeclampsia; hypothyroidism

1 year before pregnancy echo 58% EF

Hadar, A 2004;Katz, 1997

Cardiotoxicity after Doxorubicin can be higher than the risk of cancer recurrence!

- ◆ Patients can acutely develop arrhythmias, dilated cardiomyopathy; coronary artery vasospasm; myocardial ischemia; hypertension; acute heart failure
- ◆ Late-onset ventricular dysfunction, chronic dilated cardiomyopathy
- ◆ Can occur years after treatment
- ◆ Most commonly associated with anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone)
- ◆ Risk is dose-dependent
- ◆ Increased risk if chest radiation with heart exposure (left sided breast cancer)
- ◆ Can affect quality of life and overall survival

Cardiotoxicity Risk 26% with cumulative doses of 550mg/m²-

Swain, SM. Cancer 2003 97(11) 2869-79

Risk factors:

- ♥ Cumulative dose
- ♥ Length of treatment
- ♥ Radiation to heart
- ♥ Concomitant Treatment: cyclophosphamide; bleomycin; vincristine

Clinical Risk factors:

- ♥ Female-gender
- ♥ Pre-existing cardiac risk factors/ disease
- ♥ Treatment before age 4
- ♥ Life style-cigarettes, diet, weight management

Mechanism of Cardiotoxicity

- ◆ 4.1% incidence of CHF in adult survivors of childhood/ adolescent cancer with hazard increased if dose exceeded 250mg/m²
- ◆ Toxicity secondary to :
 - ◆ Free radicals
 - ◆ Disintegration of sarcolem integrity
 - ◆ Myofibrillar loss of contractile proteins
 - ◆ Myocyte death
- ◆ Resulting in: Oxidative stress; changes in calcium metabolism; activation of apoptotic pathways

Classifications of cardiac toxicity: physiology and timing of symptoms

Pathophysiology:

- ♥ Type 1: irreversible myocardial injury, cell death of myocytes via necrosis or apoptosis of microstructure
- ♥ Type 2: reversible cardiac myocyte dysfunction without microstructural damage

Temporal:

- ♥ Acute: within two weeks of completion of chemotherapy (this less-frequent presentation includes arrhythmias, acute coronary syndrome, acute HF, pericarditis, myocarditis)
- ♥ Chronic beyond 2 weeks and further subdivided into early or late presentation (>1 year after treatment completed) and manifests as asymptomatic systolic and/or diastolic dysfunction or symptomatic congestive heart failure

Cancer therapies with known cardiac toxicity include anthracyclines, biologic agents (trastuzumab), and multikinase inhibitors (sunitinib).
Not just a concern for survivors of *childhood* cancers!

- ♥ The most frequent presentation is dilated cardiomyopathy
- ♥ Monitoring commonly performed by assessment of left ventricular (LV) ejection fraction, which requires a significant amount of myocardial damage to allow detection
- ♥ Different biomarkers have been proposed including troponin release resulting from cardiomyocyte damage and natriuretic peptides reflecting elevation in LV filling pressure/wall stress.
- ♥ Increase in the levels of troponin and natriuretic peptides have been correlated with cumulative dose of anthracycline and the degree of LV dysfunction.

Cardiotoxicity mechanisms: measuring biomarkers

- ◆ Cardiac troponins (cTn) are released after cardiomyocyte damage such as ischemia, inflammation, oxidative stress, or apoptosis.
- ◆ Absence of cTnI elevation early and 1 month after therapy associated with 1% risk; cTnI elevation transient 37% risk; persisting 1 month after therapy 84% risk of cardiotoxicity
- ◆ Anthracyclines with adjuvant Herceptin: elevated early and at 3 months is independent predictor with 17x increased risk
- ◆ NT-proBNP levels at the time of anthracycline treatment completion and at three months were *not* predictive of cardiac toxicity in contrast to cTn
- ◆ Novel biomarkers for prediction of cardiac toxicity: looking for markers of ischemia and necrosis, inflammation, endothelial dysfunction...

PERIPARTUM CARDIOMYOPATHY RISK APPROXIMATELY 10 FOLD HIGHER THAN GENERAL POPULATION

Retrospective study of female cancer survivors at least 5 years from diagnosis
Pregnancy associated cardiomyopathy defined as shortening fraction <28%;
ejection fraction <50% or treatment for cardiomyopathy during pregnancy or up to
5 months postpartum with no prior diagnosis of cardiomyopathy

847 female survivors; 1554 pregnancies

4.7% developed non pregnancy-associated cardiomyopathy

0.3% developed cardiomyopathy in pregnancy or within 5 months postpartum

all treated before age 10; none received radiation; 2 had cytoxan

Survivors with cardiomyopathy received a higher median dose of anthracyclines
compared to those who did not (321mg/m² vs 164, p<0.01)

No significant differences in current age, age at diagnosis or race

Of 26 women who had cardiac dysfunction prior to pregnancy-8 had recurrent
cardiomyopathy (3) or deterioration of cardiac function (5) including 3 who
normalized by the time of conception

Vaginal delivery recommended with pre-existing dilated cardiomyopathy

Pregnancy After Anthracyclines: Pregnancy is not a contributory factor to worsening cardiac function in patients with FS > 30%.

- ◆ 37 women treated with doxorubicin for childhood cancer (72 pregnancies)
 - ◆ All received < 500mg/m²; 4 > 450mg/m²
 - ◆ Followed for 17 years, only 1 patient treated before age 4
 - ◆ Lower birthweight in study group
 - ◆ Pregnancy outcome generally favorable in women unless baseline LV dysfunction before or during early pregnancy
 - ◆ No significant change in FS before the first pregnancy to after last delivery (p=.09)
 - ◆ 29 women with fractional shortening of > 30% before pregnancy had no change in FS
 - ◆ 22% with FS < 30%, had 19% decrease after last delivery but still not significant between pre and post pregnancy (26% to 21%, p=.08)
- 2 developed CHF, more cases maternal and neonatal ICU admissions, longer hospital stays

Preconception Evaluation

- ♥ History (location of radiation, anthracycline dosage)
- ♥ Examination
- ♥ ECG (AV block; RBBB; ischemic changes)
- ♥ Echocardiogram



CLOSE MONITORING DURING PREGNANCY

- ♥ Clinical symptoms
- ♥ Echocardiography
- ♥ BNP
- ♥ Initiate medical therapy if necessary

Labor, Delivery and the Postpartum Period

- ♥ Continue medications on schedule
- ♥ Judicious administration of fluids and salt load
- ♥ Watch for signs/symptoms of CHF/pulmonary edema
- ♥ Monitor for symptoms of arrhythmia, edema into the postpartum period
- ♥ Early ambulation
- ♥ If decompensation during pregnancy clinical follow-up continuing for the first 3-6 months postpartum
- ♥ Evaluate prior to subsequent pregnancies

Monitoring the Pregnant Patient with a History of Malignancy

Radiologic Studies

- ⌘ No contraindication to mammography, CT or MRI
- ⌘ PET delayed until postpartum

Tumor markers (CEA colon, lung, breast; CA125, CA15.3 ovarian, breast, CA 19-9 GI/adenoca/pancreas)

- ⌘ CA 125 increases in pregnancy
- ⌘ CA 15.3 increases during second trimester but most studies show still within normal range
- ⌘ 3 of 4 studies found no increase in CEA with pregnancy
- ⌘ No change in 19-9 with pregnancy

Physical Exam

- ⌘ Moles may increase in size or become darker in pregnancy but do NOT become irregular or itch or bleed due to pregnancy
- ⌘ Do not assume breast lumps are “normal changes in pregnancy”

Prenatal Evaluation of Cancer Survivors

Mother: Review type of treatment

- Chemotherapy-agents

Bleomycin, consider PFTs

Anthracyclines: Echocardiogram, EKG

Stop Tamoxifen; Herceptin

- Radiation -review doses and heart volume exposed; TFTs

- Surgery- Thyroidectomy

Watch calcium balance, especially with magnesium

- Mastectomy/Lumpectomy

Patients able to breast feed adequately from single breast

Mastitis difficult to treat in previously irradiated breast

- If necessary, can continue to perform cancer screening during pregnancy

Prenatal Evaluation of Cancer Survivors

Fetus:

- ◆ Offspring of cancer survivors are not at increased risk of malformations or genetic abnormalities
- ◆ Do not recommend CVS or amniocentesis unless other indications
- ◆ Growth ultrasound if prior radiation therapy
- ◆ Evaluate placental attachment in second trimester if prior abdominal/pelvic radiation

