Breast Cancer and Pregnancy
By William Wagner, M.D.

Cancer complicates approximately 1/1000 pregnancies and 1/118 malignancies is associated with pregnancy.¹ There is no increased incidence of malignancy in pregnant women.

Breast cancer is one of the most common cancers complicating pregnancy; as many as 15 percent of premenopausal cases occur during pregnancy. Histology of breast cancer diagnosed during pregnancy is no different from nonpregnant patients. There is no survival difference between women diagnosed with breast cancer during pregnancy and with age- and stage-matched non-pregnant women.¹,³,⁵ Pregnant women are more likely to be diagnosed with Stage II cancer and less likely to be diagnosed with early stage disease (21 vs. 54 percent).⁶ Women that are pregnant and under the age of 40 are more likely to be diagnosed with Stage II disease than women over 40, and have a statistically worse survival rate (75 vs. 55 percent). This would suggest that age may have a stronger influence on survival than pregnancy.⁶ Nodal status is a highly significant predictor, where pregnancy is not.⁵

DELAY IN DIAGNOSIS:
Delay in diagnosis is common in pregnancy and is likely related to masses found on examination that are ascribed to ‘normal breast changes’ of pregnancy and thus malignancy not suspected, leading to more advanced and large stage tumors at time of definitive diagnosis. Any delay in prognosis worsens prognosis.

DIAGNOSTIC TESTING:
Breast ultrasound is more accurate than mammography during pregnancy in evaluating palpable masses, owing to the increased density, vascularity, cellularity, and water content which leads to poor contrast for mammography. This being said, concern for fetal radiation exposure (0.4 rad) should not be of concern if mammography is contemplated.

The workup of the mass should be the same as in the nonpregnant setting: fine needle aspiration, core biopsy, and/or excision. False positive cytology is common owing to proliferative state of breast tissue under the influence of estrogen. Most tumors in pregnant women are estrogen receptor negative as in premenopausal non-pregnant individuals.⁷

EFFECT ON PREGNANCY:
Breast cancer itself does not directly influence perinatal outcome. Routine termination of pregnancy does not appear to offer survival advantage with breast cancer of any stage.⁵,⁸,⁹ Once breast cancer has been definitively diagnosed; mammography is indicated to exclude multifocal disease in the affected breast or in the contralateral breast. Chest x-ray CXR to determine pulmonary metastases (with abdominal shielding) should be done with minimal fetal exposure (0.06 mrad). MRI may be required. The risk of bone metastases in Stage I or II disease is 3-7 percent. Bone scan may be delayed in pregnancy in asymptomatic women with early stage disease. If patient is symptomatic or has evidence of advanced disease, bone scan may be performed with placement of a Foley catheter and aggressive maternal fluid hydration to promote washout from the radiopharmaceutical from the bladder. MRI alone of the skeleton will detect 80 percent of metastatic lesions.¹⁰ Abdominal MRI may be helpful if liver metastases is suspected or patient has advanced disease.

SURGICAL CONSIDERATIONS:
Breast conservation surgery or mastectomy can be safely performed at any gestational age with attention paid to uterine displacement at greater than 20 weeks. With conservation surgery, radiation therapy (RT) is standard once chemotherapy is concluded. With
modified radical procedure, RT is not usually indicated unless there is confirmed nodal disease, or large tumor size of positive margins on excision. In nonpregnant women, the delay in initiating RT following chemotherapy is relatively short. This consideration becomes important depending upon the gestational age at the time diagnosis and surgical management is being put forth. If a patient is diagnosed early in pregnancy, and would complete chemotherapy by 30 weeks (usually four cycles given two to three weeks apart), at least six weeks of delay would occur before RT would start, without iatrogenic preterm delivery before 36 weeks.

Sentinel node mapping and biopsy are commonly used for non-pregnant women to avoid complications of lymphedema following complete axillary lymphadenectomy. Sentinel node biopsy can be safely performed in pregnancy with Tc-99m sulfur colloid, which will identify the first draining node(s) relative to the site of the primary invasive lesion. The radioisotope will stay trapped at the site of injection or within the lymphatic’s until decay occurs (half-life six hours).11

CHEMOTHERAPY DURING PREGNANCY:
Majority of women today are treated with combination agents, Adriamycin (doxorubicin) and Cytoxan (cyclophosphamide), with or without 5-flourouracil. Doxorubicin is the preferred anthracycline to use during pregnancy with excellent margin of safety. Although Taxane therapy is the standard adjuvant therapy in women with positive nodes in the non-pregnant setting, in pregnancy it should be delayed if possible until pregnancy is completed.

COMPLICATIONS OF CANCER THERAPY DURING PREGNANCY:
Side effects most notably nausea and vomiting, may compound similar effects seen in an otherwise normal pregnancy. Close attention to hydration is important. Infection is always a risk due to the immunosuppression of both pregnancy and chemo agents as well as bone marrow suppression, which may produce profound neutropenia. Neupogen can be given safely in pregnancy, as well as Epogen if anemia occurs. Increasing calorie consumption and protein intake in weeks preceding and following chemotherapy is usually needed.

FETAL SURVEILLANCE AND DELIVERY TIMING:
Transient bone marrow suppression of the neonate can occur if delivery is within three to four weeks of treatment. Delivery should be avoided during this nadir period if possible. To ensure this, chemotherapy should not be given after 34 weeks, as the patient could potentially enter spontaneous labor during this time period. If additional treatment is anticipated, early induction may be considered, such that the interval between the last treatment and postpartum is not greater than six weeks.

Preterm infants cannot metabolize chemotherapeutic agents as well as term infants; therefore, iatrogenic preterm delivery should be avoided in patients receiving chemotherapy. Serial assessment of fetal growth at four to six week intervals by ultrasound should be done as well as aggressive management of preterm labor as needed. If Decadron has been given with chemotherapy to enhance the effectiveness of antiemetics, steroids (Betamethasone) may not be necessary to stimulate fetal lung maturity.

NEONATAL EVALUATION FOLLOWING CHEMOTHERAPY DURING PREGNANCY:
The placenta should be sent for pathologic examination in all cases. The Cancer and Childbirth Registry has been established to follow all children of women diagnosed with cancer during pregnancy. All information collected is kept confidential. (www.cancerinpregnancy.com;www.cancerandpregnancy.com/856-757-7876/856-342-2491)

**SUMMARY OF KEY POINTS WITH CANCER IN PREGNANCY:**
- Avoid delay in diagnosis by employing the needed diagnostic studies in a timely and adequate fashion as in non-pregnant individuals
- Avoid unnecessary radiologic investigation unless results will alter the treatment or patient decisions during pregnancy
- Avoid iatrogenic prematurity
- Chemotherapeutic regimens should be chosen based upon most experienced use and proven safety during pregnancy, if offers similar cure rate. Dose need not be adjusted for pregnancy
- Placenta should be made available for pathologic examination
- Multidisciplinary approach: medical/radiation oncologists, maternal-fetal specialists, and neonatology.

**GENERAL CHEMOTHERAPY CONSIDERATIONS:**
- Chemotherapy should NOT be delayed solely due to pregnancy if delay would decrease maternal chance of cure. During the first trimester, risk of malformations is highest as consequence of the majority of organogenesis occurs between three and eight weeks post conception. Despite the putative risk of IUGR, when controlled for gestational age, the incidence of fetal growth restriction is in fact not increased.
- Long-term follow-up of children exposed to chemotherapy is limited. Cited case series of neurodevelopmental follow-up for a mean of 18 years on 84 children exposed in utero to various types of chemotherapy for maternal hematologic malignancy showed clinical health status comparable to unexposed siblings. No cancer had been diagnosed in any of the children and 12 of the children exposed in utero have now had their own children with normal outcomes.2
References


LEVELS OF EVIDENCE (Modified method outlined by the US Preventive Services Task Force (www.ahqr.gov)
I    Evidence obtained from at least one properly designed randomized controlled trial
II-1 Evidence obtained from well-designed controlled trials without randomization
II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research groups
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
III (review) Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

William E. Wagner, MD

Dr. William E. Wagner is a specialist in Maternal Fetal Medicine with Minnesota Perinatal Physicians and board certified in Obstetrics and Gynecology. In addition to being the medical director for the Mercy Perinatal Center, he is a partner and practicing perinatologist at United Hospital, Abbott Northwestern Hospital, and North Memorial Hospital, all in the Minneapolis-St. Paul metro area. Dr. Wagner has expertise and special interest in the management of the surgical complications of pregnancy and critical care obstetrics. He is the perinatal physician consultant to the ROSE® Program through Minnesota Perinatal Physicians.

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