

Breast Cancer in Pregnancy: Avoiding Fetal Harm When Maternal Treatment Is Necessary

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■ **Abstract:** The management of breast cancer during pregnancy poses unique challenges and requires a multi-disciplinary approach. In this review, we discuss the treatment of breast cancer in pregnancy and recent updates regarding the safety of surgical and chemotherapeutic treatments, including both oncologic and fetal outcomes. The treatment of breast cancer during pregnancy mirrors that outside of pregnancy, with a few important differences dictated by the balance of maternal versus fetal health. Overall, surgical treatment, neo-adjuvant chemotherapy, and/or adjuvant chemotherapy are feasible in most women during pregnancy. Further research to determine the safety of these therapies in pregnancy-associated breast cancer is warranted. ■

Key Words: breast cancer, chemotherapy, pregnancy

Pregnancy-associated breast cancer (PABC), also referred to as gestational breast cancer, is defined as breast cancer diagnosed during pregnancy or in the first year postpartum (1). It has an incidence of 1 in 3,000 pregnancies with a median age of diagnosis of 33 years. As women delay childbearing for personal and/or professional reasons, there may be an increased incidence in PABC during pregnancy or before completion of childbearing (2). It has been reported that 80% of PABCs are infiltrating ductal carcinoma, 49–84% are estrogen receptor/progesterone receptor negative, 28–58% are HER2/neu overexpressed, and about 67% present with positive lymph nodes (2–5). Although PABC was initially thought to have a worse prognosis than non-PABC, this is not true when matched for age and stage.

Delay in diagnosis can occur because of a patient's confusion between cancer-related changes and pregnancy-related changes of the breast. Even for trained practitioners, hormonal influences of pregnancy on breast tissue affect the ability to detect a mass during pregnancy. Physical examination of the breast

becomes more difficult as the pregnancy progresses, or postpartum if lactation is established (5). Patient denial and, potentially, physician reluctance to intervene during pregnancy, may also lead to delayed diagnosis (4). Prompt evaluation of any breast mass, with or without biopsy, is warranted. Here we review current recommendations for the diagnosis and treatment of breast cancer in pregnancy. We will focus upon recent updates regarding the safety of surgical and chemotherapeutic treatments in pregnancy, including both oncologic and fetal outcomes.

Diagnosis

Ultrasound is the preferred imaging method for breast mass evaluation in pregnancy and is often the first step, allowing for ultrasound-guided biopsy if necessary (6). Sensitivity and negative predictive values for ultrasound in the detection of breast malignancy in pregnant patients have both been reported at 100% (7), although in other studies, sensitivity has been reported as low as 70% (8). In this latter study, however, images were reviewed at various institutions, and the authors noted that eight breast cancer cases were incorrectly classified as “probably benign.” (8) Mammography, if needed for further evaluation, has a low risk of radiation (estimated at 4 mGy), especially with abdominal shielding. However, mammography is

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DOI: 10.1111/tbj.12780

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The Breast Journal, Volume 23 Number 2, 2017 200–205

often not as informative because these women are often young with dense breasts (2,5,9). Mammography sensitivity for diagnosis has been reported ranging from 25% to 75% in some reports, and as high as 81–90% in others (3,8).

Although some authors suggest MRI can be considered due to the increased density of breasts during pregnancy (5), MRI with contrast potentially poses a risk to the developing fetus (6), and MRI without contrast is not helpful for breast imaging. Gadolinium should be avoided because the effect of free gadolinium ions in amniotic fluid is unknown and its use has been associated with fetal malformations in rats (5,6). Moreover, the lactational changes in breasts during the peri- and postpartum periods result in rapid enhancement after administration of IV contrast, making lactational changes and malignancy difficult to differentiate (9,10). Thus, the clinical utility of MRI in PABC is questionable. In Europe, novel MRI contrast agents gadobenate dimeglumine and gadoterate meglumine are currently both approved for use in pregnant women (6); further study regarding their efficacy and safety is necessary.

Treatment of breast cancer in pregnancy is similar to that outside of pregnancy, with modifications for fetal indications. There is no evidence that therapeutic abortion improves maternal survival, and such management is only indicated when progressive development of malignant disease is expected or fetal harm due to continued intensive adjuvant therapy is likely (11).

Surgical Treatment

Mastectomy versus Breast-Conserving Surgery

Mastectomy is generally recommended in the first and second trimesters (12,13). Breast and axillary surgery can be performed during any trimester of pregnancy with minimal risk to the fetus, especially after 12 weeks when the risk of spontaneous miscarriage is minimal (2,6,13). However, there is increased risk of miscarriage associated with surgery in the first trimester of pregnancy; hence elective surgery should be deferred to the second or third trimester if possible (14). Lumpectomy can be performed in the third trimester with delay of radiation therapy (RT) to the postpartum period. Neo-adjuvant chemotherapy or lumpectomy followed by adjuvant chemotherapy can be administered during pregnancy for oncologic indications, or patient choice, if remote from delivery.

Lumpectomy alone in the first trimester with delay of radiation to the postpartum period may have a detrimental oncologic impact if chemotherapy is not planned (13). Overall, breast-conservation versus mastectomy for stages I and II PABC has been shown to have similar survival in PABC (2). Radiation exposure during pregnancy is most likely to be detrimental before 10 weeks gestation (pre-implantation) or during organogenesis (until the end of the eighth week) (12). Nakagawa et al. (15) reported no significant risk to the fetus for radiation if fetal exposure does not exceed 100 mGy.

Several studies have aimed at estimating the fetal dose during tangential breast irradiation, using adult anthropomorphic phantom models consisting of transverse sections to which rings could be added to simulate the changing geometry of the pregnant female body. Typically, dosing for radiation exposure in these studies is based upon data from humans, which have estimated the tangential breast irradiation field dimensions to which patients are exposed during breast cancer treatment (16). Using such an anthropomorphic phantom model, studies were able to estimate the conceptus dose resulting from various field dose sizes during the three pregnancy trimesters. They report that for women receiving tangential breast irradiation, with a treatment dose of 50,000 mGy, the dose to the fetus was 21–76 mGy in the first trimester, a time period during which doses above 100 mGy are associated with severe mental retardation or fetal malformations. In the second trimester, the estimated dose was 22–246 mGy, during which doses above 10 mGy may be associated with decreased IQ, and those above 500–600 mGy associated with mental retardation, microcephaly, and growth retardation. In the third trimester, fetal dose ranged from 22 to 586 mGy, a time when fetal growth restriction may occur above 500 mGy, implying a possible detrimental effect on IQ in the second trimester, and fetal growth in the third trimester (16,17). Similarly, Martin Rincon et al. (18), administering a 50,000 mGy dose to the isocenter of their field target to the field parameters for over 300 patients, estimated a dose of 38.1 ± 1.3 mGy with wedges and 39.2 ± 2.2 mGy for open field (18). Overall, therefore, it appears the majority of radiotherapeutic regimens do not affect fetal IQ factors, but may affect fetal growth.

To date, although these studies seem to indicate the dose to the developing fetus is low, no reports on actually administering RT to the breast during

pregnancy have been reported. Of note, the literature includes a case report of radiation given to a woman before pregnancy was detected. Pregnancy was diagnosed at 3 weeks gestational age, during week two of RT, and treatment was continued until six gestational weeks. Fetal dose estimations were made at 39 mGy using phantom models, but no fetal outcomes were reported (19). Thus, whether the risk of radiation during pregnancy is worth the possible risk currently remains unknown. It is known that abdominal shielding may further decrease fetal dose by 50–75%. Some current reports seem to suggest RT should not be considered contraindicated in pregnancy (17), although some have argued that it may only be safe in the first and second trimesters (20).

Sentinel Lymph Node Biopsy The concerns of sentinel lymph node biopsy (SLNB) in pregnancy are the fetal effects of exposure to radiation and/or blue dye. Radiation dose estimates of technetium sulfur colloid are significantly less than the National Council on Radiation Protection and Measurement limits for a pregnant woman. Lymphazurin blue is generally avoided because of the risk of allergic reactions and anaphylaxis, while methylene blue is avoided because it is associated with jejunal atresia during the first trimester (20). SLNB is the standard of care for axillary staging of patients with clinically node-negative breast cancer. It decreases operative time and risk of complications, including lymphedema. Thus, it would be of benefit to offer SLNB in PABC (21).

Some data exist regarding radiation-related risks to the fetus with SLNB in PABC. Ellner et al. (22) reported that the abdomen absorbs less than 1.3×10^{-3} mGy/MBq of radiation during the use of technetium radiotracers for lymph node mapping, with a total average dose of 39 MBq. This is less than the average daily background radiation of 8.2 mGy/day (23). In accordance with this finding, a recent prospective trial on 12 patients demonstrated no adverse effects to the fetus associated with low-dose lymphoscintigraphy with 99m-Tc (13).

With respect to the use of blue dye, Pruthi et al. (24) estimated that the extrapolated estimated fetal exposure to blue dye, based upon the pharmacokinetics of methylene blue in 10 non-pregnant women and the organ distribution of methylene blue, was 0.25 mg. This value is likely further reduced by physiologic changes in pregnancy. They concluded that there is likely minimal fetal risk associated with

use of this technique (24). Additionally, Gropper et al. (21) described a 47-patient cohort with node-negative breast cancer in pregnancy, of whom 16 had SLNB with 99-Tc sulfur colloid and seven with isosulfan blue dye alone, with 24 of 25 pregnancies resulting in healthy deliveries. The authors concluded SLNB is feasible and appears safe in PABC. However, blue dyes in general (lymphazurin and isosulfan blue) are generally avoided because of the risk of anaphylaxis.

Reconstruction Reconstruction following mastectomy during PABC is usually delayed until after delivery because achieving symmetry is considered difficult due to pregnancy-associated breast engorgement (2), as well as to fetal and maternal concerns. Recently, Lohsiriwat et al. (25) described reconstruction in pregnancy in 78 patients: 22 underwent unilateral mastectomy; 13 of 22 had immediate reconstruction (12 with a tissue expander and one with an immediate implant). There was no infection, hematoma, capsular contraction, or flap necrosis, and 75% of patients completed expansion intrapartum. Eleven of 12 patients continued their pregnancy; one had a termination at 9 weeks. With median follow-up of 32 months postpartum, one patient had expander leakage after external radiation and one had a local recurrence 19 months postmastectomy. This study suggests intrapartum reconstruction is a feasible option warranting further investigation. Notably, the authors reported some difficulty related to increased breast size and an unpredictable degree of breast stiffness during pregnancy, indicating the need for appropriate patient counseling and provider understanding of breast cancers in pregnancy.

Chemotherapy and Neonatal Outcomes

Generally, chemotherapeutic treatment of PABC should be the same as those prescribed for non-pregnant patients (6). Chemotherapy administered during the first trimester—specifically, during organogenesis (weeks 4–12)—poses the highest risk of fetal teratogenesis, with an increased risk associated with multi-agent therapy (26,27) and thus, ideally, it would be administered after the first trimester. Several studies have confirmed the safety of the standard 5-fluorouracil, doxorubicin, and cyclophosphamide regimen (6). Notably, tamoxifen is associated with a 20% birth defect risk and contraindicated in pregnancy (13).

Several studies report on the maternal oncogenic and fetal outcomes of various combinations of anthracyclines and taxanes given to treat PABC. Hahn et al. (28) reports specifically on the use of the standard regimen of 5-fluorouracil, doxorubicin, and cyclophosphamide given to a 57-woman cohort in the second or third trimesters. A median number of four cycles (range 1–6) was given at an average gestational age of 23 weeks (range 11–34 weeks). After a median duration of 38.5 months, the majority of patients were disease free and delivered before 34 weeks with no stillbirths or perinatal deaths. A parent survey of children born to these women, aged 2–157 months, reported birth complications similar to population norms. The most common birth complication was difficulty breathing, reported in 10%. Among 18 school-aged children, only two required special attention in school, one with a diagnosis of attention deficit disorder. Additionally, follow-up data on 104 women with primary or recurrent breast cancer during pregnancy, treated with either adriamycin and cytoxan or one of 11 taxanes, reported recurrence in 30 and death in 21 (29). The fetal malformations rate was no greater than the general population, and the mean gestational age at delivery was 36 weeks, with some iatrogenic preterm birth cases following induction of labor to allow for initiation of postpartum chemotherapy treatment. Interestingly, patients reported more nausea and paresthesias as a result of the same chemotherapeutic agent given during versus after pregnancy (for patients who had intra- and postpartum treatment) (29).

Ring et al. (30) reported on 28 women who received various neo-adjuvant, adjuvant, or palliative chemotherapy regimens (e.g., doxorubicin and cyclophosphamide, epirubicin and cyclophosphamide, or cyclophosphamide, methotrexate, and fluorouracil) during the second or third trimesters. Seventeen patients received adjuvant chemotherapy, totaling 116 cycles for the cohort. Patients received a median of six cycles (range 4–8) of chemotherapy during and after pregnancy. The average gestational age at the start of chemotherapy was 20 weeks (range 15–33). The most significant complication reported was febrile neutropenia (three cases). Infants were delivered at a median gestational age of 37 weeks; only one patient had spontaneous preterm labor and no fetal abnormalities were reported. After follow-up of 7–159 months, 63% patients with stage I-III B cancer had disease-free survival.

With respect to taxol use in pregnancy, Cardonick et al. (31) reported on a 15-woman cohort—12 with

breast cancer—prospectively followed after intrapartum exposure to either paclitaxel or docetaxel. Median gestational age at delivery was 36.9 weeks, with two patients induced for preeclampsia. Complications at time of delivery included apnea or prematurity, GERD, neutropenia, hyperbilirubinemia, and respiratory distress syndrome. One infant had hypertrophic pyloric stenosis. Follow-up for a median 46 months showed appropriate infant growth.

One modification of chemotherapeutic treatment, which is appealing in the case of pregnancy, is that of dose-dense regimens, allowing for a shorter time period of treatment. Cardonick et al. (31) described 10 women exposed to dose-dense doxorubicin and cyclophosphamide. A dose-dense schedule allows for completion further from time of delivery, requiring only 12 weeks total. Pegfilgrastim (Neulasta) or filgrastim (granix) was used in 6 of 10 women in the dose-dense group as compared with 16 of 99 women in the conventional chemotherapy group. In this study, there were no statistically significant differences in gestational age at delivery, rates of preterm labor, intrauterine growth restriction, congenital anomalies, or neutropenia, indicating the safety of this protocol (31).

A recent meta-analysis of 18 cases using trastuzumab recommends against its use in pregnancy, as increased risk of renal and pulmonary complications were noted in newborn infants (13). In this report, trastuzumab was administered in pregnancy for metastatic (55.6%) or adjuvant chemotherapy, predominately in the second or third trimester (83%). Seventy-three percent of women exposed in the second or third trimester had apparently reversible oligo- or anhydramnios, as compared with none treated during the first trimester. One-quarter of patients died. Ten of 19 infants were healthy at birth and at 9 months follow-up; most had mild to severe pulmonary and/or renal disease, and/or infectious outcomes at birth. These authors concluded that trastuzumab should not be given during pregnancy, particularly because it is just as effective 6 months after receiving chemotherapy intrapartum (13).

CONCLUSIONS

In summary, the treatment of breast cancer in pregnancy mirrors that outside of pregnancy, with a few important differences dictated by the balance of maternal versus fetal health, and oncologic versus

obstetric outcome. In part, treatment recommendations are trimester-dependent. Breast-conserving surgery or mastectomy can be considered (with SLNB appearing feasible and safe) after first treatment. Overall, surgical treatment, possibly with neo-adjuvant and/or adjuvant chemotherapy, is often feasible. In the first trimester, the risks of possible treatment delays must be weighed against the risks to the fetus secondary to oncologic treatment. Intrapartum chemotherapy is an option to optimize oncologic outcomes if continuation of pregnancy is desired. Several authors have reported good oncologic and fetal outcomes using standard breast chemotherapeutic regimens given after the first trimester of pregnancy. Tamoxifen and trastuzumab should be avoided, and dose-dense regimens with granulocyte stimulating factors may be considered.

Additionally, there is a need for further research to determine the safety of diagnostic and therapeutic procedures that are routinely used in the non-pregnant woman as well as long-term data on the oncologic safety of these approaches. Furthermore, although existing studies on surgical and chemotherapeutic treatment of these malignancies in pregnancy report overall good fetal outcomes, long-term studies on children treated with these agents in utero are needed. In order to ensure the most timely and safe treatment to women with PABC, improved education of providers regarding the safety of various surgical and chemotherapeutic treatments in pregnancy is important. This, in conjunction with a multi-disciplinary approach, will provide patients with the best options for optimizing oncologic as well as fetal outcomes.

FUNDING

Dr. Mary L. Gemignani was funded in part by NIH/NCI Cancer Center Support Grant No. P30 CA008748.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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