Breast Cancer During Pregnancy


The care of a pregnant breast cancer patient is a challenging clinical situation that historically has placed the welfare of the mother in conflict with that of the fetus. For the woman in this situation, the emotions usually associated with pregnancy can be overshadowed by the emotions aroused by a diagnosis of breast cancer and its subsequent treatment. The majority of published information on the management of breast cancer during pregnancy has consisted of retrospective chart reviews, case reports, and anecdotes. There is a paucity of published data from the prospective study of women who are pregnant at the time of their breast cancer diagnosis. This review will endeavor to address the diagnosis, staging, and subsequent treatment of breast cancer during pregnancy. The limited information available for this group of women on the outcomes of labor, delivery, and neonatal health will also be reviewed. This review will not specifically address pregnancy that occurs after diagnosis and subsequent treatment for breast cancer. However, some data, particularly those of an epidemiologic nature, address breast cancer diagnosed during pregnancy or within the year following delivery. [ONCOLOGY 15(1):39-51, 2001]

Introduction

Although breast cancer is one of the most common cancers associated with pregnancy, it is still an uncommon event, with estimates ranging from 1 in 3,000 to 3 in 10,000 deliveries to women with breast cancer.[1-4] A review of 32 series of reports on pregnancy-associated breast cancer published between 1937 and 1982 estimated that 0.2% to 3.8% of all breast cancers coincided with pregnancy or lactation.[5] The prevalence of pregnancy at diagnosis of breast cancer has been reported to be approximately 1.5% in a large Canadian series of consecutive and unselected patients with breast cancer.[6]

In women 30 years of age or younger, the incidence of pregnancy-associated breast cancer may be quite high, as two case series—one from Memorial Sloan-Kettering Cancer Center and the other from M. D. Anderson Cancer Center—reported prevalences of 9.7% and 25.6%, respectively.[7,8] As more women delay childbearing, it has been postulated that the incidence of pregnancy-associated breast cancer will parallel the increased incidence of breast cancer with age.[9,10]

Diagnosis

The pregnant breast cancer patient usually presents with a mass or thickening in her breast.[11] The physiologic changes that occur in the pregnant woman’s breast—the engorgement and hypertrophy—are believed to contribute to the delay in diagnosis of a breast mass that is common in this unique group of patients.

A number of studies have documented delays of 3 months or longer in pregnant or lactating women.[12,13] In one study, patient-related factors created a 6- vs 4-month delay when pregnant and nonpregnant breast cancer patients were compared. Physician-related factors were responsible for 3- vs 2-month delays, respectively.[14]

Socioeconomic status, cultural background, and other psychosocial factors are thought to contribute to patient-based delays in diagnosis, while education (in particular, familiarity with pregnancy-associated breast cancer) is the key factor thought to contribute to physician-based delays in diagnosis.

Role of Mammography
Although approximately 80% of breast biopsies performed in pregnant women yield benign lesions, a breast mass that persists for 2 to 4 weeks warrants further investigation.[12] The effectiveness of mammography in diagnosing breast cancer during pregnancy is controversial. In a small series reported by Max and Klamer,[15] six of eight pregnant women with a breast mass that subsequently proved to be breast cancer were found to have normal mammograms. The false-negative mammograms were attributed to increased water content and loss of contrasting fat in the pregnant breast.

A slightly larger study of 23 women with pregnancy-associated breast cancer found abnormal mammograms in 18 women.[16] In a small Canadian study of pregnancy-associated breast cancer, five of eight women in the study had abnormal mammographic findings.[17] Although there is some debate as to the accuracy and utility of mammography in the diagnosis of a breast mass in a pregnant patient, the procedure can be performed safely with the use of abdominal shielding and may yield important information.

**Breast Ultrasonography**

The utility of breast ultrasonography during pregnancy, which may differentiate a solid mass from a cystic mass, has been evaluated in small studies. In the study by Liberman et al,[16] a focal solid mass was seen in six of the six cases examined. However, only two of the four pregnant breast cancer patients who underwent breast ultrasound had lesions that were suspicious for malignancy in the Canadian study.[17] Although these studies were small, breast ultrasound and ultrasound of nodal basins, if clinically indicated, likely play a role in the initial staging of the pregnant patient with a breast mass.

**Magnetic Resonance Imaging**

Studies evaluating the effectiveness of magnetic resonance imaging (MRI) in the diagnosis of breast masses in pregnant or lactating women have not been published. MRI has been used in pregnancy for fetal imaging, and, among studies published thus far (with limited follow-up of the infants), there do not appear to be any serious sequelae for the fetus.[18,19]

**Biopsy**

Despite the results of either the mammogram or breast ultrasound, a clinically suspicious breast mass, regardless of whether the patient is pregnant, requires biopsy for definitive diagnosis. A number of small studies have demonstrated the accuracy of fine-needle aspiration in diagnosing pregnancy-associated breast cancer.[20,21,22] The accurate interpretation of a fine-needle aspiration from a pregnant patient with a breast mass requires a pathologist skilled in the diagnosis of breast pathology coincident with the changes seen in the pregnant or lactating breast. Core biopsies allow for a diagnosis of invasion, but there are rare reports in the literature of the development of milk fistulas.[23] If necessary, either an incisional or excisional biopsy can be performed relatively safely during the first and second trimesters of pregnancy.[24] Ultimately, the nature of a breast mass in a pregnant patient should be established with the least invasive and technically most accurate method(s) available.

**Pathologic Features of Breast Cancer During Pregnancy**

Few studies have assessed or compared the pathologic features of the primary breast tumor in the pregnant patient with that of the nonpregnant patient.

**Hormone Receptors**

In their series of pregnant breast cancer patients, Tobon and Horowitz[25] reported infiltrating ductal carcinoma in 13 of 14 patients, negative or very low estrogen-receptor (ER) status in 7 patients, and positive progesterone-receptor (PR) status in 5 patients. In another study of 14 pregnant breast cancer patients, 6 women had tumors that were both ER and PR negative, 3 had ER- and PR-positive tumors, and the remaining 5 had tumors that were either ER positive and PR negative or ER negative and PR positive.[26]

A case-control study by Ishida et al[27] found that women diagnosed with breast cancer during pregnancy were significantly less likely to have ER- or PR-positive tumors, compared to nonpregnant controls. Bonnier et al[28] reported that women with pregnancy-associated breast cancer were significantly more likely to have ER- and PR-negative tumors and a diagnosis of inflammatory breast cancer.
Breast Cancer During Pregnancy
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cancer, compared to nonpregnant controls. In the M. D. Anderson prospective cohort of pregnant breast cancer patients treated with chemotherapy, 65% of tumors were negative for both receptors.[29] However, in a smaller case-control study of 15 pregnant breast cancer patients and their respective nonpregnant controls, no significant difference was seen in ER or PR status when the tumors of these two groups were compared.[30]

Some investigators believe that the ligand-binding assay used to measure ER and PR positivity may be less accurate during pregnancy. The first mechanism by which a ligand-binding assay may produce a false-negative result during pregnancy is associated with the increased estrogen and progesterone levels that downregulate ER levels to the point at which they are no longer detectable. Secondly, the accuracy of the ligand-binding assay depends on the availability of the unbound receptor, and it is possible that all binding sites in a pregnant woman could be occupied as a result of increased estrogen levels.

In the majority of published case-control studies, ER and PR positivity was primarily determined using the ligand-binding assay. In the study by Elledge et al.[30] a greater proportion of the tumors of the pregnant breast cancer patients were found to be ER and PR positive when immunohistochemistry and not the ligand-binding assay was used.

Genetic Factors

In the only published study of HER2/neu expression in pregnant breast cancer patients, 58% of tumors stained positive for HER2/neu in this patient group, compared to 16% of tumors in age-matched nonpregnant controls.[30] In this study, HER2/neu positivity was ascertained using a rabbit polyclonal antiserum generated against the carboxy-terminal synthetic peptide of HER2/neu. It is difficult to draw conclusions about the pathologic profile of tumors for this unique group of breast cancer patients, because the majority of studies are small or retrospective in nature, or use techniques that are not generally employed in the modern analysis of breast tumors.

The effect of BRCA1 and BRCA2 mutations upon the incidence of pregnancy-associated breast cancer is unclear, although a small Swedish study found that significantly more women with BRCA1 vs BRCA2 mutations had pregnancy-associated breast cancer.[31] However, another small study compared women with pregnancy-associated breast cancer and no history of familial breast cancer to women with sporadic breast cancer and found a higher rate of allelic deletion at the BRCA2 locus in women with pregnancy-associated breast cancer (88% vs 20%).[32]

Staging

For women with breast cancer, regardless of whether they are pregnant at the time of diagnosis, the tumor/node/metastasis (TNM) system is used to stage the disease. The TNM system can also be used to assess prognosis and to formulate a treatment plan. A number of case series and case-control studies have reported that, compared to nonpregnant breast cancer patients, women with pregnancy-associated breast cancer present with more advanced-stage disease, larger tumors, and an increased likelihood of positive lymph nodes and metastatic disease.[7,27,28,33,34] The patient’s stage of disease at the time of diagnosis may have significant psychosocial implications, particularly if the pregnant patient presents with metastatic disease.

Initial staging of the pregnant breast cancer patient involves a thorough physical examination of the breast and regional lymph node-bearing areas, with careful documentation of all abnormalities. Regional nodal disease that is clinically suspicious for metastases should be evaluated further using ultrasound and subsequent fine-needle aspiration for cytologic confirmation. Metastatic disease must also be ruled out, particularly in the lung, liver, or bone—the three most common sites of metastases. There are no contraindications for chest radiography in the pregnant patient, but abdominal shielding should be used. The ability to evaluate the lower lung parenchyma with chest radiography later in the pregnancy, when the gravid uterus is pressing against the diaphragm, may be more difficult. Abdominal ultrasound for the evaluation of liver metastases is obviously safe, but the results may be more difficult to interpret if the patient has developed fatty infiltration of the liver during pregnancy.

Computed tomography (CT) scanning of the abdomen and pelvis is generally not used during pregnancy because of the risk of fetal exposure to radiation. MRI may be useful when further visceral organ evaluation is required, as there have been no reports of harm to the fetus from exposure to MRI.[18,19] Although it has been reported that bone scans can be performed safely during pregnancy if there is adequate hydration and an indwelling catheter is used for 8 hours to prevent
Retention of radioactivity in the bladder, a screening MRI of the thoracic and lumbosacral spine may be a more palatable option in patients with no complaints suggestive of bony metastases outside the spine.[35]

When data from 12 studies were evaluated, a 3% and 7% true-positive yield of bone metastases was found on routine bone scans in patients with stage I and II breast cancer, respectively.[36] In patients with clinical stage III breast cancer, however, a 25% true-positive yield has been reported. Since it is not uncommon for pregnant breast cancer patients to present with later-stage disease, one should appropriately stage the patient, recognizing that some modifications need to be made to protect the fetus.

Monitoring the Pregnancy

The pregnant breast cancer patient requires careful and continuous monitoring of her pregnancy by a medical team highly skilled in the management of maternal and fetal health. This team, in conjunction with the oncologist, will assess and monitor the health of the mother and fetus. Ultrasonography should be used to determine gestational age and the expected date of delivery, as both of these dates play a significant role in treatment planning. As the pregnancy progresses, fetal maturity should be monitored by ultrasound. In some cases, amniocentesis may be necessary to determine pulmonary maturity, particularly if induction of labor is being considered. Amniocentesis may also be recommended in the initial assessment of the pregnant breast cancer patient if the patient is felt to be at higher than average risk for karyotype abnormalities or if there are abnormalities detected by ultrasound that warrant further investigation.

Treatment

The control of local and systemic disease is the treatment goal for both the pregnant and nonpregnant breast cancer patient. Treatment strategies are similar for both pregnant and nonpregnant breast cancer patients, although the impact of such decisions on the fetus and on the outcome of pregnancy must be considered in the pregnant patient.

Surgery

Mastectomy with axillary lymph node dissection can be performed with minimal risk to the developing fetus or the continuation of the pregnancy.[37-39] From a registry of 5,405 surgeries performed in pregnant patients, Mazze and Kallen[37] concluded that the incidence of congenital malformations and stillbirths did not increase in women who underwent surgery while pregnant. They did note, however, an increase in the incidence of low- and very low-birthweight infants thought to be secondary to prematurity and intrauterine growth retardation. They also noted an increase in the incidence of infants born alive but who died within 168 hours (the majority of these infants were in the very low-birthweight category).

No particular type of anesthesia or surgery was associated with an increased incidence of adverse reproductive outcomes in this study. The authors suggested that the underlying illness that necessitated the surgery may have contributed to these adverse outcomes.

Duncan et al[40] did not find an increase in congenital anomalies when they compared 2,565 pregnant women who underwent surgery to pregnant controls who did not have surgery. Thus, if the procedure is clinically indicated, the pregnant breast cancer patient can undergo definitive surgery for the malignancy with minimal risk to the fetus, but both the obstetric team and the anesthetist should be involved in the decision to proceed with surgery.

Breast-conserving surgery (lumpectomy or quadrantectomy) with axillary lymph node dissection is technically feasible in the pregnant breast cancer patient. However, the radiation therapy required to complete local therapy for the breast is contraindicated during pregnancy, secondary to the risks associated with fetal exposure to radiation.[41] A therapeutic course of 5,000 cGy to the breast could result in a first-trimester fetal dose of 10 to 15 cGy or a third-trimester dose as high as 200 cGy, with the higher dose resulting from the greater proximity of the near-term fetus to the radiation field.[42]

Data collected from the Hiroshima-Nagasaki atomic bomb detonations showed that an air dose of 1 to 9 cGy during weeks 6 to 11 of pregnancy resulted in an 11% incidence of microcephaly and mental retardation in the children, compared to a 4% incidence in the control group.[43] Therefore, breast-conserving surgery could be an option for a patient who presents in her third
Systemic Therapy

The indications for systemic therapy in the pregnant breast cancer patient are similar to those in the nonpregnant patient; ie, all women with node-positive and many with node-negative breast cancer are candidates.[44] Little information exists regarding the pharmacokinetics of the individual cytotoxic agents in the pregnant patient.

A number of physiologic changes during pregnancy, including alterations in renal and hepatic function, increases in plasma volume, and the "third space" of the amniotic sac, may influence the pharmacology of antineoplastic drugs.[45] There are no prospective studies that have reported in utero drug concentrations and/or fetal tissue drug levels. Although the placenta is thought to be a significant barrier to drug penetration, one case was reported of measurable tissue levels of anthracycline in a stillborn whose mother had received doxorubicin shortly before delivery.[46] The information on the effects of antineoplastic drugs administered during pregnancy has been derived largely from case reports, small case series, and collected reviews. In a review of 217 cases of pregnant women treated with chemotherapy between 1983 and 1995 for a variety of malignancies, 18 newborns had congenital abnormalities, 2 had chromosomal abnormalities, 4 were stillborn, and 15 spontaneous abortions occurred.[47]

The majority of stillborn infants and infants with chromosomal or congenital abnormalities had mothers who were given chemotherapy in the first trimester. Among the 14 pregnant breast cancer patients treated with a variety of systemic therapies, including 1 treated with hormonal therapy, there were 2 spontaneous abortions, 1 stillborn infant, and 3 infants born with congenital abnormalities of varying severities. Of the live-born infants with no congenital abnormalities (n = 8), 1 infant had intrauterine growth retardation and 3 were born prematurely.

First-Trimester Therapy: Doll et al.[45] reviewed a total of 139 cases of chemotherapy during the first trimester of pregnancy for a variety of malignancies and reported a 17% incidence of fetal malformations. The incidence of fetal malformations for the 150 women given chemotherapy during their second or third trimesters of pregnancy was 1.3%. Of 20 pregnant breast cancer patients treated with systemic chemotherapy who had been identified through a nationwide retrospective survey in France, there were 2 spontaneous abortions (both treated with chemotherapy in their first trimester), 1 stillbirth, and 17 live births; 1 infant died at age 8 days without apparent etiology.[48]

Second- and Third-Trimester Therapy: The only prospective cohort of pregnant breast cancer patients treated with systemic therapy during their second and/or third trimester did not report any congenital malformations, stillbirths, or spontaneous abortions.[29] The 24 women in this study were treated during the second and third trimesters with FAC (fluorouracil [5-FU], 1,000 mg/m² intravenously [IV]; doxorubicin [Adriamycin], 50 mg/m² continuous infusion over 72 hours; and cyclophosphamide [Cytoxan, Neosar], 500 mg/m² IV) for a median of four cycles. Berry et al.[29] concluded that chemotherapy could be administered during the second and third trimesters with minimal complications.

The only antepartum maternal complications noted were the hospitalization of one patient for diarrhea and suspected (but unconfirmed) pyelonephritis that resolved with symptomatic and supportive care, and one patient with a history of deep-vein thrombosis in the calf who developed another thrombus in the same calf and required hospitalization for intravenous heparin. There are no published reports on the use of taxanes in the treatment of breast cancer during pregnancy, and therefore, their use cannot be recommended at this time.

Hormonal Agents: In the series by Ebert et al.[47] one infant exposed to tamoxifen (Nolvadex) during all three trimesters was born at 26 weeks’ gestation with Goldenhar’s syndrome. The use of hormonal agents such as selective estrogen-receptor modulators (SERMs) or aromatase inhibitors cannot be recommended, as they could interfere with the hormonal milieu of a normal pregnancy.

Other Agents: Most of the published literature does not recommend the use of methotrexate in the management of breast cancer during pregnancy, because it is an abortifacient and causes severe fetal malformations when given in the first trimester.[45,47] Many of the cytotoxic drugs, especially the alkylating agents, are known or thought to be excreted in breast milk. Therefore,
women receiving systemic chemotherapy should be cautioned against breastfeeding while receiving chemotherapy. Caution should also be exercised with regard to the use of antiemetics chosen for women receiving chemotherapy for breast cancer during pregnancy, because antiemetics vary with regard to their safety profile in pregnant or nursing women.

**Radiation Therapy**

As previously mentioned, local breast irradiation required for the completion of breast-conserving treatment is contraindicated in pregnancy because of the risks associated with fetal exposure to radiation.[41] If breast cancer is diagnosed in the third trimester and breast-conserving therapy is a treatment option, breast irradiation may be delayed until after delivery. In addition, women who require neoadjuvant therapy for locally advanced breast cancer may postpone surgery until later in their pregnancy or after the birth of their child, making breast-conserving surgery an option.

**Termination of Pregnancy**

Although in the past it was believed that the termination of pregnancy improved survival in pregnant women with breast cancer, a number of reported case series do not support this hypothesis.[49,50] For example, in a series of 24 pregnant breast cancer patients treated with radical mastectomy, survival did not improve in those who had aborted their pregnancy.[49] Some studies have suggested that pregnant women who terminate their pregnancies may actually have decreased survival, compared with those who continue their pregnancies.[51,52] However, these results must be interpreted with caution as they may be biased. Because they are based on retrospective case reviews, these findings cannot account for the possibility that abortion was more likely to be recommended to those with more advanced disease or poorer prognostic features. In addition, such individuals would be more likely to have decreased survival regardless of whether they terminated their pregnancy.[53]

The decision to continue or terminate the pregnancy must be made by a woman who has been fully informed of the evidence, or lack thereof, regarding termination of pregnancy and survival in this unique group of breast cancer patients. In cases of known or suspected fetal teratogenesis or when the health of the mother is in jeopardy, termination of pregnancy may be an appropriate medical recommendation.

**Labor and Delivery Results**

The majority of relevant case reviews and case series reported in the literature have concentrated on the frequency of spontaneous abortion and congenital malformations in infants exposed to chemotherapy in utero. Few studies have actually examined the potential complications that may arise during labor and delivery when the mother is receiving chemotherapy. In a review of 14 cases of pregnancy during breast cancer compiled by Ebert et al.[47] 3 of 8 live-born children without congenital anomalies were premature, and 1 of the full-term deliveries was born with intrauterine growth retardation.

Of the 17 live births among 20 women in a French retrospective cohort of pregnant breast cancer patients, 1 newborn died 8 days after birth without any apparent etiology, 2 had transient respiratory distress likely related to prematurity, and 1 had intrauterine growth retardation.[48] One woman was anemic at the time of delivery (hemoglobin value = 9.5 g/dL), and 1 child had transient leukopenia with normal hemoglobin and platelet counts. The mean gestational age at delivery in the French series was 34.7 weeks.

In a case-control study by Zemlickis et al.[33] women with breast cancer during pregnancy were significantly more likely to have a premature infant, and their infants had a statistically lower mean birthweight, compared to controls. These differences persisted even when an adjustment was made for gestational age.

Finally, in the prospective cohort of 24 pregnant breast cancer patients reported by Berry et al.[29] the median gestational age at delivery was 38 weeks, with 3 women delivering prematurely, 1 as a consequence of preeclampsia and 2 with idiopathic premature labor. Among the infants born to this cohort, 1 had hyaline membrane disease secondary to prematurity but recovered without complications, 2 required oxygen support for transient tachypnea of the newborn (both having resolution of their symptoms within 48 hours), 1 had transient leukopenia without infectious sequelae, having been exposed to chemotherapy 2 days before delivery, and 1 had a birthweight lower than the 10th percentile for gestational age.
It is difficult to draw conclusions based on these studies since all but one are retrospective in nature, but a lower-than-average gestational age was a fairly consistent finding in all the above studies.

**Long-Term Follow-up Issues**

There are few published reports on the long-term effects of in utero chemotherapy exposure on the subsequent mental and physical health of exposed infants. In the French case series of pregnant breast cancer patients, all 16 live infants were reported to have reached normal developmental milestones.[48] The prospective cohort of Berry et al[29] did not report any known developmental abnormalities in the children. After 50 live births recorded to pregnant women undergoing chemotherapy for acute leukemia, there was normal growth and development and no evidence of malignancy in any of the 7 children who received long-term follow-up (up to 17 years).[54] The results of the aforementioned studies must be interpreted with caution, however, as formal developmental testing was not performed on these children.

Aviles and Niz[55] reported a series of 20 children exposed to chemotherapy in utero for treatment of maternal leukemia. Only 17 of these children received long-term follow-up; 1 was stillborn and 2 died in infancy—1 from septicemia at 21 days of age and 1 from gastroenteritis at 90 days of age. Of the remaining 17 children with follow-up to 22 years, there appeared to be no long-term sequelae as a result of this chemotherapeutic exposure.

In this study, the children were followed quite closely with physical examinations and blood counts every 3 months for the first 2 years of life and every 6 months thereafter. The children underwent a complete neurologic evaluation and had formal intelligence testing twice (3 years apart). Based on these limited data, one can cautiously conclude that exposure to chemotherapy for the treatment of maternal breast cancer in utero does not appear to affect the normal development of children so exposed.

**Follow-up for Breast Cancer**

Women with a history of breast cancer during pregnancy should be followed as per the guidelines published by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) for women treated for primary breast cancer.[56,57]

**Impact of Pregnancy on Recurrence and Survival**

Although initially breast cancer during pregnancy was thought to be associated with a poorer prognosis, numerous case-control series have suggested that when matched for age and stage at presentation, there is no significant difference in survival between women with pregnancy-associated breast cancer and nonpregnant breast cancer patients.[28,33,58,59] There are, however, other case-control studies in which pregnancy-associated breast cancer was reported to decrease survival, compared to controls matched for stage.[60] The majority of studies have concluded that women who become pregnant after successful treatment for breast cancer do not worsen their prognosis with respect to their cancer.[49,61-65] Other studies interpret the available data more cautiously and conclude that the effect of subsequent pregnancy on breast cancer prognosis is unclear.[34]

**Summary**

Breast cancer coincident with pregnancy is a relatively rare clinical situation that may become more frequent in the industrialized world as more women delay childbearing. The preferred surgical option for women with breast cancer during pregnancy—modified radical mastectomy—can be accomplished with minimal fetal risk. Although it may be possible to perform breast-conserving surgery, the radiation therapy required to complete local therapy to the breast must be delayed until after delivery because of concern regarding fetal radiation exposure.

The majority of information concerning the systemic therapy of breast cancer during pregnancy consists of case series and case-control studies. Nevertheless, data from one prospective cohort of pregnant women treated with FAC chemotherapy support the premise that breast cancer can be treated during the second and third trimesters with minimal complications. There are no data to support the use of taxanes or hormonal therapy to treat pregnant breast cancer patients. Methotrexate should not be used during pregnancy, as it is an abortifacient and can cause severe congenital abnormalities if administered in the first trimester. Pregnancy termination does not appear to improve survival, but situations in which maternal health is in jeopardy or fetal
anomalies are known or suspected may make this a medical option to be considered.

References:


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