34 Breast cancer and pregnancy

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EPIDEMIOLOGY

Three percent of all cases of breast carcinoma occur in women aged 35 or younger. Breast cancer is the leading cause of cancer death for women 15 to 29 years of age (1) with approximately 11,000 new cases of in situ or invasive breast cancer and 1100 breast cancer deaths in women younger than age 40 (2).

Young women with breast cancer are more likely to present with more advanced disease and have worse outcomes than older women (3). This is likely due to a variety of factors, including the biology of the disease and the challenges to early detection in young women. Young women with breast cancer are more likely to have hormone-insensitive, higher grade disease, with a higher proliferative rate (4) and a higher likelihood of bone marrow metastases (5).

Studies investigating how reproductive factors influence the development of breast cancer are increasing our understanding of possible reasons why carcinoma presents at an advanced stage among this group of women. Specifically, concurrent or recent pregnancy is associated with increased aggressiveness of the tumor and poorer survival. While the occurrence of breast cancer at the time of pregnancy or lactation is 3% or less of all women who develop breast cancer (6), the prevalence increases to over 15% among women before age 40. Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within the first 12 months postpartum. Currently, the average age of women with PABC is between 32 and 38 years (7), and the median gestational age at the time of diagnosis is 17 to 25 weeks (8). The incidence of PABC may increase as a growing number of women are choosing to postpone childbearing until their mid-to-late 30s.

ETIOLOGY

Reproductive factors such as age at menarche, parity, and age at first birth are well-established risk factors for breast cancer incidence due to their influence on the length of hormonal exposure to estrogen and progesterone (9). Epidemiologic studies confirm that pregnancy has a dual effect on breast cancer risk (10). Childbearing reduces the lifetime risk of developing breast cancer, although risk increases during the time surrounding pregnancy (11).

Women who have their first full-term pregnancy at an early age (defined variously as before 20 up to age 26) have a decreased lifetime risk of developing breast cancer. When compared with nulliparous women, the risk of breast cancer increases in women whose first full-term pregnancy occurred after 35 years of age (12). Nonetheless, for women who develop PABC, early age at first full-term pregnancy has been associated with more aggressive breast cancers. A recent study found that a woman with a first full-term pregnancy before age 20 had a 3.2 increased odds of having an aggressive tumor (13).

Studies have also shown that a diagnosis of breast cancer shortly after pregnancy is associated with reduced chance of survival (14). The transient increase in breast cancer risk for 3 to 15 years after childbirth is followed by a decrease in long-term risk (15).

The relationship between age at first full-term pregnancy and risk of breast cancer is likely related to physiologic and hormonal changes that occur during and after pregnancy (14). An early first full-term pregnancy imprints a specific genomic signature on the breast tissue, with differences in RNA expression and protein concentration compared with those with a later age at first childbirth (16). First full-term pregnancy appears to have a lasting effect on the hormonal environment of the mother and on her metabolism of estrogen (17). One of the mechanisms suggested to account for the incidence of breast cancer in general is exposure to high endogenous estrogen levels. Estrogen levels peak during pregnancy. Endogenous estradiol can initiate the transformation of premalignant to malignant breast cells or accelerate the progression of existing tumors (18). In addition to estrogen, a full-term pregnancy alters the concentration of other hormones, providing another possible way in which pregnancy might influence breast cancer risk. As a result, specific changes in the levels of hormones during and following pregnancy may affect the breast tissue by increasing the risk of mutations, by altering the tissue's susceptibility to hormones, or by modulating its levels of gene expression (19).

Studies specifically addressing the issue of breast differentiation and involution after pregnancy and lactation may shed light on the possible mechanisms of PABC, including changes in the pattern of breast lobular development and differentiation, cell growth, and gene expression (20). The mammary gland reaches full lobular development late during a woman's first full-term pregnancy in preparation for lactation. If this occurs at a young age, the chance for mutational events to have occurred in the breast epithelium prior to pregnancy are less than if a woman's first pregnancy is at an older age. It is therefore less likely that the stimulatory effects of pregnancy on the breast will drive abnormal breast epithelial cells to progress to cancer. Moreover, during weaning, breast epithelial differentiation and involution occurs leading to a long-term breast cancer risk reduction. Differentiated cells do not divide or proliferate under normal conditions and are less susceptible to carcinogenic transformation long term (21). Breast remodeling following lactation resembles the microenvironment that occurs with inflammation. The activated cells secrete proteins, growth factors, tissue-remodeling enzymes, and provisional extracellular matrix, all of which facilitate the return of the breast to the prepregnancy state. This involution microenvironment may promote the growth and development of transformed tumor cells if present in the

tissue (22). Furthermore, metastatic spread is facilitated by the increased vascularity and lymphatic drainage from the gravid and lactating breast (23). These observations suggest that women with precancerous or cancerous epithelial cells within the breast at the time of pregnancy may be at a high risk for tumor promotion and metastasis.

PATHOPHYSIOLOGY

Overall, women with PABC have similar pathologic features to age-matched controls. The most common histologic subtype is invasive ductal carcinoma, which is usually high grade (24). Tumor size, degree of nodal involvement, and stage at diagnosis are usually more advanced among women with PABC compared with age-matched nonpregnant women with breast cancer (25,26). Controlling for disease stage, tumor size, hormone receptor status, age, race, and type of surgery, PABC is associated with approximately a 14% increase in risk of death compared with nonpregnant controls (27). The reason(s) for this is not clear, since overall rates of treatment with radiation and chemotherapy are similar. Theories proposed include the relative immune suppression of pregnancy and differences in tumor biology due to elevated estrogen and progesterone levels during pregnancy (27). Other studies do not indicate that termination of pregnancy improves the prognosis of PABC (28).

Hormone receptor status in PABC tumors is commonly negative, more often than their age-matched controls with breast cancer (29). Between 54% and 80% of PABCs are ER-negative, possibly due to the downregulation of receptors in pregnancy (30). Using a variety of antibodies, HER2 positivity has been observed in 28% to 58% of PABCs. Sample sizes in these studies are too small to conclude whether the frequency of HER2 positivity is higher than that seen in age-matched controls (31).

DIAGNOSIS

Clinical examination of the breast is more difficult during pregnancy and nursing because the breasts are hypervascular, engorged, and nodular. Pregnancy-related changes can conceal otherwise palpable tumors in the breast. PABC most commonly presents as a painless mass or thickening. A discreet mass is often difficult to palpate during lactation and involution, and malignancy may be mistaken for mastitis (32).

On average, diagnosis of PABC is delayed 5 to 15 months (7). Difficulty in evaluating mass lesions in the pregnant and lactating breast, a reluctance to perform biopsy, false diagnosis as an inflammatory mass, and inadequate follow-up by patient and physician have all been reported as possible reasons for this delay (33). Mammography with abdominal shielding poses a low risk of radiation to the fetus in the second and third trimesters, but is not recommended in pregnant or postpartum women because the high density of the breast leads to a high rate of false negatives (34). Ultrasonography is a more sensitive alternative for pregnant and lactating women and can distinguish between cystic and solid lesions (35). Magnetic resonance imaging offers high sensitivity but low specificity for the diagnosis of breast cancer. This imaging technique is not recommended during the first trimester until more information becomes available (8). Gadolinium should be avoided if possible

since it crosses the placenta and its effects on the fetus are unknown (36). Available evidence indicates that fetal exposure to less than 0.05Gy ionizing radiation is not associated with a detectable increase in deleterious effects (37). CT scans to assess disease extent, especially those of the abdomen and pelvis, are generally not recommended during pregnancy due to the relatively high mean doses to the fetus of 0.0036Gy for abdominal and 0.089Gy for pelvic irradiation (38).

Since PABC often presents as a palpable mass, core or open biopsy is an effective diagnostic procedure. Lactation should be suppressed prior to biopsy in nursing women to reduce the risk of abscess and milk fistula formation (39). Fine-needle aspiration is less reliable during pregnancy and lactation due to the hyperproliferative features in the tissue of the pregnant, lactating, or involution breast (40).

MANAGEMENT

Patients with PABC should be treated as soon as possible and according to the latest clinical guidelines, carefully weighing the risk to the fetus. The first treatment for most breast cancer patients is surgery. General anesthesia is safe if precautions are taken to compensate for physiologic changes induced by pregnancy (41). During the first and second trimesters of pregnancy, modified radical mastectomy is recommended to eliminate the need for postoperative radiation therapy and chemotherapy for patients with early-stage disease. For accurate staging, axillary evaluation is necessary to determine nodal status. Nodal metastases are relatively common in PABC, and disease extent affects the need for adjuvant chemotherapy (42). For women diagnosed with PABC late in pregnancy or after delivery, lumpectomy with axillary dissection can be performed, with radiation treatment after childbirth (43). A small series that used Tc-99m and/or blue dye in women of gestational ages ranging from 4 to 32 weeks suggests that lymphatic mapping followed by sentinel lymph node biopsy is safe (44). Therapeutic radiotherapy is unsafe for the fetus and is contraindicated throughout all stages of pregnancy.

Adjuvant or neoadjuvant chemotherapy is potentially teratogenic to the fetus in the first trimester of pregnancy (45), with an estimated risk of fetal malformations of up to 17% when administered during the first trimester (8). If it is felt unsafe to delay adjuvant therapy until after delivery, chemotherapy can be considered in the second and third trimesters. The anthracyclines doxorubicin (46) and epirubicin (47), as well as taxanes (48), appear relatively safe, with the few series available reporting a 0% to 6% death rate (intrauterine, stillbirth, or neonatal) after treatment. It is postulated that placental P-glycoprotein may limit the transplacental transfer of these agents. Chemotherapy should be administered at least 3 weeks before delivery to avoid sepsis and bleeding in a mother with low red blood cell, white blood cell, and platelet counts (28). Trastuzumab use to treat HER-2-positive PABC was associated with anhydramnios in three of six women and should be avoided during pregnancy since it appears to interfere with the normal development of the fetal kidney (48). Lactation should be suppressed during chemotherapy to prevent agent transmission to the infant (49). The long-standing recommendation to avoid pregnancy for 2 years after a diagnosis of breast cancer is being questioned, since median time to relapse is more than 5 years, even for

patients with stage II node-positive disease who receive standard-of-care regimens of surgery and adjuvant therapy (50).

There are few reports documenting the long-term effects of chemotherapy. One study that assessed physical, neurologic, and psychologic development of 84 children with a median age of 18.7 years born to mothers who received chemotherapy during pregnancy found normal development, and no reports of malignancy (51). Two large prospective studies, one initiated by the German Breast Group and another by the Breast International Group (BIG-03), should provide more information on long-term sequelae after in utero exposure to chemotherapy (8).

For hormone-sensitive tumors, tamoxifen, a selective estrogen-receptor modulator, may be used as adjuvant treatment after surgery or as treatment for advanced cancer. Due to possible teratogenic effects, tamoxifen is not recommended during pregnancy (52). Bisphosphonates are often used to manage the complications of breast cancer skeletal metastases. Reports of their use during the third trimester of pregnancy suggest that postpartum, neonates of mothers treated with the bisphosphonate pamidronate were hypocalcemic but otherwise developed normally, suggesting that calcium levels should be closely monitored in neonates of mothers treated with these agents (53).

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