Pregnancy-Associated Breast Cancer

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Breast cancer is the second most common malignancy affecting pregnancy. Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or in the first postpartum year. Because PABC is a relatively rare event surrounded by multiple variables, few studies address the best management and treatment options. We present a case of PABC to illustrate and highlight some of the recommendations for treatment, obstetric care, delivery management, and cancer surveillance.

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KEY WORDS

Pregnancy • Breast cancer • PABC • Ultrasound • Chemotherapy • Fertility

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or in the first postpartum year.[1] Breast cancer affects approximately 1 in 3000 pregnant women and is the second most common malignancy affecting pregnancy.[1] The average age of women with PABC is 32 to 38 years.[2] Only 6.5% of all cases of breast cancer affect women age < 40 years.[3] As more women are delaying childbearing, and as breast cancer rates continue to rise, more diagnoses of PABC are anticipated. However, because PABC is a relatively rare event surrounded by multiple variables, few studies address the best management and treatment options. We present a case of PABC to illustrate and highlight some of the recommendations for treatment, obstetric care, delivery management, and cancer surveillance (Table 1).

Case Presentation

A healthy 28-year-old white woman with no previous pregnancies noted a breast mass while attempting to conceive. She had no family history of breast or ovarian cancer. She presented to her primary care physician who performed

TABLE 1

Managing Breast Cancer in Pregnancy

Time of Diagnosis	Surgical Treatment	Adjuvant Treatment	After Delivery
1st trimester	Modified radical mastectomy or lumpectomy with axillary node dissection	2nd trimester adjuvant chemotherapy	± Radiation ± Hormone therapy
2nd trimester/early 3rd trimester	Modified radical mastectomy or lumpectomy with axillary node dissection	± Adjuvant chemotherapy	± Radiation ± Hormone therapy ± Adjuvant chemotherapy
Late 3rd trimester	Modified radical mastectomy or lumpectomy with axillary node dissection		Adjuvant chemotherapy ± Radiation ± Hormone therapy

an examination and recommended an ultrasound. She was provided with reassurance that, at her young age, the breast mass was likely benign, and so she continued attempting to conceive.

She underwent an ultrasound and a fine needle biopsy that revealed an invasive ductal carcinoma. Three days following the biopsy results she found out she was pregnant. She was offered termination, but declined. She subsequently underwent lumpectomy and axillary node dissection, placing her at stage IIB (T2N1MX), estrogen receptor-positive (ER+), HER2 negative (HER2-). She had positive surgical margins and had to undergo a second lumpectomy. Due to her young age at diagnosis, she was offered and consented to *BRCA* testing; her *BRCA* test result was negative.

After reaching the second trimester, the patient began chemotherapy with adriamycin and cyclophosphamide. She was referred to the Maternal-Fetal Medicine service for her pregnancy care, and was also managed by her oncologist. She completed four cycles of chemotherapy. She underwent serial fetal growth ultrasounds and antepartum testing was scheduled to begin at 32 weeks of gestation.

Her obstetric course was complicated by a chronic placental abruption with multiple hospital admissions for vaginal bleeding. At 34 weeks of gestation she went into spontaneous labor. During the course of her labor, the fetal heart rate tracing became nonreassuring and she underwent a low transverse cesarean delivery. Her infant was admitted to the neonatal intensive care unit with an uncomplicated course. Due to in-utero adriamycin exposure, a neonatal echocardiogram was performed but did not show evidence of cardiac toxicity. Her infant was discharged on day of life 6 and continued to receive periodic echocardiographic evaluations to assess for damage to the heart. The patient did well postoperatively and was discharged home in stable condition on postpartum day 3. She planned to receive radiation therapy and postpartum paclitaxel injection.

Diagnosing PABC

Breast cancers in pregnancy, and most breast cancers in patients < 40 years, are diagnosed by a palpable mass (Figure 1).[2] At the first obstetric visit, it is imperative to perform a thorough breast examination and encourage patients to continue self-breast examination throughout pregnancy. Most women with PABC present with a painless mass in the breast or thickening of the skin of the breast.[4] Delays in the diagnosis of PABC are likely due to pregnancy-induced breast changes, such as engorgement, that often make it difficult to discern a concerning breast mass from a normal breast in a pregnant woman.

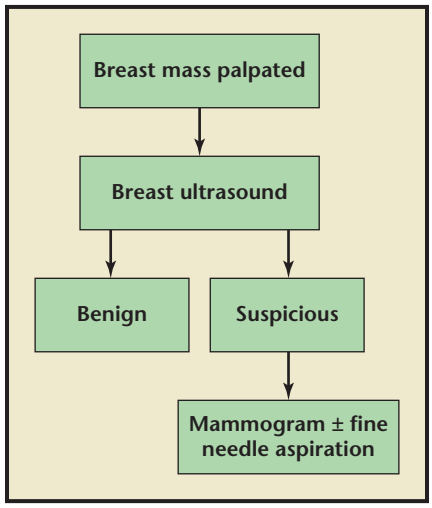

Figure 1. Work-up of breast mass.

Once a suspicious mass is identified, a breast ultrasound can help

characterize the mass and identify any concerning features. More than 80% of breast masses identified in pregnancy represent benign pathologies. Etiologies include lobular hyperplasia, fibroadenoma, cystic disease, galactocele, abscess, and lipoma.[5] Nonetheless, each mass needs to be thoroughly evaluated. Ultrasound has been noted to be 100% accurate in detecting a mass in patients with PABC.[4] If the mass is noted to be fluid filled, a fine needle aspiration can be performed to obtain fluid to send for cytology. The pathologist should be informed that the specimen is from a pregnant patient because pregnant breast tissue is rapidly dividing and can be confused with rapidly dividing cancer cells. If the ultrasound results appear suspicious, a core biopsy can be performed to obtain tissue for pathologic evaluation. If a solid mass is found, a mammogram can be performed; however, the sensitivity of mammogram in women < age 40 is low due to the increased parenchyma density of the young breast tissue.[6] Liberman and associates[7] found the sensitivity of mammogram in detecting PABC was only 78% due in large part to the increased glandularity and additional water content of the pregnant breast tissue.

Many women with breast cancer during pregnancy are in advanced stages at the time of diagnosis and thorough evaluation of possible metastasis is warranted (Table 2). Breast cancer most commonly metastasizes to lungs, liver, and bone. Chest radiographs are considered safe during pregnancy, with appropriate abdominal shielding, to evaluate for any lung metastasis.[2] Liver metastases can be evaluated with ultrasound. Outside of pregnancy, evaluation of bony metastasis is usually accomplished with a bone scan; however, in pregnancy the radioactive technetium can be harmful to the rapidly developing fetal skeleton. Therefore, evaluation for bony metastasis in pregnancy can be done with noncontrast magnetic resonance imaging.[2]

TABLE 2

Evaluation for Metastasis in Pregnancy

Chest radiograph
Liver ultrasound
Magnetic resonance imaging to evaluate bone involvement

Risk Factors for the Development of PABC

As the majority of PABCs, and pregnancies, occur in women < 40 years, BRCA mutations are over-represented in this group. In women in their 20s, approximately 33% of breast cancers will be due to genetic mutations; this number decreases to 22% in women in their 30s.[6] All women younger than 40 years who are diagnosed with breast cancer should be offered genetic testing.

There is an increased incidence of ER-negative breast cancer during pregnancy, but this increase may be artificial, due to high circulating estrogen levels competing with the binding assay.[8]

Treatment Options for PABC

Once a diagnosis of breast cancer has been made, it is important not to delay treatment. If the patient is near term, it is reasonable to proceed with delivery prior to treatment. However, if the patient is remote from term, treatment must be initiated. There has been no evidence to show that termination of pregnancy in the first or second trimester affects prognosis.[5]

Surgery is the first line of treatment for breast cancer in pregnancy, with modified radical mastectomy being the treatment of choice for operable disease.[2] The risks of surgery relative to the developing fetus are from the administration of general anesthesia, which increases the risk of spontaneous abortion in the first trimester.[2] In patients who are not pregnant, there have been multiple studies showing similar survival in women who undergo lumpectomy plus radiation when compared with mastectomy.

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Radiation therapy is, in general, contraindicated in pregnancy, due to an increased risk of fetal malformations and associated delays in neurocognitive development. Therefore, more pregnant women undergo mastectomy as a first line of treatment. However, there is a role for breast-conserving surgery and radiation following delivery if a pregnant women is near term.[2] Studies demonstrate no change in survival if radiation is given within 6 weeks of surgery.

Sentinel lymph node biopsies have become the mainstay of evaluation of lymph node involvement in breast

cancer evaluation, and studies have shown that the calculated absorbed dose is well below the minimum dose associated with adverse fetal effects.[9]

Chemotherapy as adjuvant treatment has also been shown to be beneficial in patients with high-risk breast cancer. High-risk prognostic factors include estrogen and progesterone receptor negative status, HER2 status, tumor grade, and age of the patient.[10] Chemotherapy agents are contraindicated in the first trimester of pregnancy because of the risks of teratogenicity during organogenesis.[2] After the first trimester, chemotherapeutic agents typically used for treating breast cancer have not been associated with any fetal malformations.[2] Mir and colleagues[11] performed a comprehensive review of chemotherapeutic agents used to treat breast cancer during pregnancy and found that the majority of chemotherapeutic agents, including taxanes and vinorelbine, were safe for use during the second and third trimesters. Potential risks identified include intrauterine growth restriction and possible preterm labor. If labor occurs within 3 weeks of recent chemotherapy dose, both maternal and infant leukopenia have been documented; therefore, we recommend no chemotherapy doses be given after 35 weeks of gestation to avoid delivery of a leukopenic infant.[2]

Methotrexate, trastuzumab, and tamoxifen are currently contraindicated in pregnancy. Methotrexate has been associated with central nervous system, skeletal, gastrointestinal, and cardiac malformations, and even fetal death.[12] Anhydramnios, or lack of amniotic fluid, has been reported in patients undergoing trastuzumab treatment for PABC, and currently it is not recommended in pregnancy.[11,13] Tamoxifen has been associated with spontaneous abortions, growth restriction, preterm labor, and genital tract anomalies similar to those seen with diethylstilbestrol exposure.[14]

Several ancillary medications used to decrease the side effects of chemotherapy have been shown to be safe in pregnancy. Granulocyte colony-stimulating factor was shown to be safe in pregnancy in one case series of two patients.[2] Ondansetron has not been associated with any developmental toxicities and is considered safe in pregnancy.[5] In the first trimester, corticosteroids have been associated with increased rates of cleft palate; however, in the second and third trimester they are considered safe.[5] Methylprednisolone and hydrocortisone are preferred over dexamethasone or betamethasone, as they do not cross the placenta. Repeated courses of dexamethasone or betamethasone, given for fetal lung maturity, have been associated with microcephaly and higher rates of attention deficit disorder and cerebral palsy.[15]

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A recent study looked at breast cancer in young women (age < 40 years) and despite studies showing equal survival rates of breast-conserving therapy with radiation versus mastectomy, they found that young women had a higher rate of recurrence.[3] It is theorized that the younger age of diagnosis, and hence longer lifespan, places these young women at a statistically increased risk of recurrence over time.[3] Because fewer women < 40 years are affected with breast cancer, they are underrepresented in research trials. Van Nes and van de Velde recommended mastectomy in younger patients over breast-conserving treatment.[3] The authors also showed no difference in psychological outcome in patients who had lumpectomy with radiation versus those that had mastectomy with reconstructive surgery.[3]

Fetal Surveillance

The fetal risks from in-utero chemotherapy exposure are intrauterine growth restriction, preterm delivery, low birth weight, and transient leukopenia.[5] We recommend growth scans every 4 weeks, including a detailed anatomy scan if the fetus has been exposed to medication in the first trimester (Table 3). If growth restriction is noted, we recommend shortening the interval between growth scans and adding Doppler interrogation and antenatal testing for fetal well

TABLE 3

Obstetric Recommendations

Level 2 ultrasound for anatomic evaluation
Growth scans every 4 weeks; add Doppler ultrasound if concern for growth restriction
Antepartum fetal testing at 32 weeks or sooner if growth restriction noted
Delivery at term
Send placenta for pathology

being with either biophysical profile or nonstress testing and evaluation of amniotic fluid.

There are no reported cases of metastatic disease of the breast to the fetus. Isolated reports of metastasis to the placenta have been noted.[5] It is recommended that the placenta be sent for pathologic evaluation after delivery.

Children exposed to chemotherapy in utero have shown no adverse effects.[16] The largest study looked at 84 children exposed to chemotherapy in utero for hematological malignancies and followed them for more than 18 years. They reported no congenital, neurological, or psychological abnormalities, and they did not observe any cases of cancer in children exposed to chemotherapy in utero.[16]

Timing of Delivery

Delivery should occur at term or as close to term as possible. Induction of labor is only indicated to provide a treatment to the mother that is contraindicated in pregnancy. If the patient is receiving chemotherapy, it may be useful to stop treatments prior to 36 weeks of gestation so that delivery does not occur during a period of maternal or fetal leukopenia, where the risks of chorioamnionitis and operative infections if having a cesarean delivery may lead to increased morbidity or mortality. The route of delivery should be vaginal, with cesarean delivery reserved for usual obstetric indications.

Breastfeeding With PABC

Lactation from the treated breast is not contraindicated.[8] However, there may be reduced milk volume and possibly scar tissue, limiting ability to breastfeed. It is contraindicated to breastfeed while a mother is undergoing treatment with chemotherapeutic agents or while she is undergoing radiation therapy.

Prognosis

Although most studies have indicated equal prognosis of PABC (and breast cancer in women who were not pregnant) when matched for age and stage, a recent article showed poorer survival in those with PABC.[17] Rodriguez and coworkers[17] concluded that women with PABC presented with more advanced disease, larger tumors, and an increased percentage of hormone receptor-negative tumors. When controlled for stage and hormone receptor status, PABC carried a higher risk of death.[17] It is unclear whether this is due to less aggressive therapy secondary to concern for fetal effects, a later stage at diagnosis due to the difficulties of diagnosing PABC, or physiologic changes in pregnancy that contribute to worse outcomes, or a combination of these factors. More research is needed on PABC to find the optimal treatments.

Pregnancy After Breast Cancer Treatment

All premenopausal women diagnosed with breast cancer should be counseled regarding future fertility and contraceptive options. Regardless of fertility desires, it is imperative to discuss contraceptive options that are safe to use with a history of breast cancer. In general, hormonal therapies should be avoided; intrauterine devices or barrier methods are safe options. As most recurrences of breast cancer happen within 2 years of diagnosis, most people recommend waiting at least 2 years from remission prior to conceiving.[6] Chemotherapy agents can also cause infertility. If a patient desires future fertility, referral to a fertility specialist to discuss egg or embryo freezing would be prudent.

If patients do desire to preserve fertility, options include ovarian or embryo cryopreservation. Embryo cryopreservation can be performed with natural cycle in vitro fertilization to avoid use of ovulation induction. Tamoxifen and letrozole have emerged as possible options for ovulation induction in patients with breast cancer.[18] Ovarian cryopreservation can be an option for patients without a current partner who desire to preserve fertility; however, current studies have not shown great success.

The risk of infertility with chemotherapy depends on the patient's age at initiation of chemotherapy and the chemotherapeutic agents used. Each course of chemotherapy will result in a loss of ovarian reserve, causing menopause to occur earlier.[18] Depending on the patient's age and baseline ovarian reserve, chemotherapeutic agents will affect each patient's fertility differently. Alkylating agents are the most likely cytotoxic drug to cause amenorrhea.[18] The risk is somewhat lower with anthracyclines or antimetabolites.[18] Tamoxifen itself does not cause infertility, but it is recommended that a woman not conceive while on tamoxifen due to its teratogenic effects to the fetus.[6] Cyclophosphamide-based treatments have been shown to cause amenorrhea in 18% to 61% of women age $<$ 40 years. Anthracycline-based regimens induce amenorrhea in 30% to 60% of women.[5]

Little is known about what effects a future pregnancy will have on the risks of breast cancer relapse. Fewer than 10% of women affected with PABC have become pregnant after treatment,[18] so it is difficult to assess the impact. However, the

few case series reported suggest no adverse effects on prognosis.[18]

Conclusions

With the increasing rates of breast cancer and later ages of childbearing, we will likely be faced with more cases of PABC. Awareness of the current literature on PABC, and the limitations in diagnosing and treating PABC, are imperative for all providers who care for women with this diagnosis. There is an urgent need for further research in this field. ■

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MAIN POINTS

- Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or in the first postpartum year. As more women delay childbearing, and as breast cancer rates continue to rise, more diagnoses of PABC are anticipated.
- Breast cancer in pregnancy is most often diagnosed by a palpable mass. Once a suspicious mass is identified, a breast ultrasound can help characterize the mass and identify any concerning features. Ultrasound has been noted to be 100% accurate in detecting a mass in patients with PABC.
- Surgery is the first line of treatment for breast cancer in pregnancy, with modified radical mastectomy being the treatment of choice for operable disease. Radiation therapy is, in general, contraindicated in pregnancy, due to an increased risk of fetal malformations and associated delays in neurocognitive development. Chemotherapy as adjuvant treatment has also been shown to be beneficial in patients with high-risk breast cancer; however, chemotherapy agents are contraindicated in the first trimester of pregnancy.
- A recent article concluded that women with PABC presented with more advanced disease, larger tumors, and an increased percentage of hormone receptor-negative tumors. PABC carried a higher risk of death when controlled for stage and hormone receptor status. It is unclear whether this is due to less aggressive therapy secondary to concern for fetal effects, a later stage at diagnosis due to the difficulties of diagnosing PABC, or physiologic changes in pregnancy that contribute to worse outcomes, or a combination of these factors.
- Fewer than 10% of women affected with PABC have become pregnant after treatment, and little is known about what effects a future pregnancy will have on the risks of breast cancer relapse.