



Pregnancy - Associated Breast Cancer

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Abstract

Pregnant patients should follow the same treatment protocols as non-pregnant patients, but there are certain unique factors to consider when it comes to diagnosis, staging, cancer treatment, and obstetric care. The fundamental idea is that, if possible, women should keep their pregnancies and undergo cutting-edge cancer treatment as soon as possible. Genetic testing also needs to be considered. A multidisciplinary treatment plan should be determined, while carefully considering features of the tumor, the patient and pregnancy related factors, and patient's preferences. All trimesters are safe to undergo breast cancer surgery. Beginning at 12 weeks of gestation, chemotherapy can be given to a patient without risk, but radiotherapy, endocrine and HER2 targeted therapy are contraindicated throughout the whole pregnancy. Importantly, fetal growth should be monitored, and long-term follow-up of the children is encouraged in dedicated centres [37].

Keywords: Breast cancer; PABC; Pregnancy-Associated Breast Cancer; Breast Cancer During Pregnancy; Gestational Breast Cancer; Breast Cancer and Pregnancy; Management of Breast Cancer During Pregnancy; Breast Cancer in Pregnant Women; Treatment of Breast Cancer in Pregnancy

Introduction

Pregnancy-associated breast cancer (PABC) encompasses breast cancer diagnosed during pregnancy or the first-year postpartum [39]. Although it is uncommon in general, breast cancer is the most diagnosed cancer during pregnancy [4]. It is about 4% of breast cancers of childbearing age and since more women delay childbearing and occurrence of breast cancer in young women has increased, the incidence of breast cancer in pregnancy is expected to increase. Because of the combination between the mother, fetus, and tumor, managing these tumors is challenging. The treatment of the pregnant patient with breast cancer requires a multidisciplinary team including obstetrician, maternal-fetal medicine expert, surgical oncologist, medical oncologist, geneticist, and neonatologist [39]. This review provides a comprehensive view to optimize care of this unique entity [41].

Prognosis

Large studies have shown similar stage-wise prognosis for women with PABC compared to other young women with breast

cancer, when accounting for differences in age and tumour characteristics [40].

Young age at diagnosis has a strong negative effect on survival and most PABC patients are young women.

Compared to patients identified with cancer in the second and third trimesters of pregnancy, individuals diagnosed with the disease during the first trimester of pregnancy had a considerably improved disease-free survival (DFS) [23].

It is evident that a larger tumor has a less favorable prognosis; in particular, stage III has a worse prognosis, however, only lymph node involvement and Nottingham Prognostics Index (NPI) had an independent predictive effect on OS [23].

Lymph node involvement often occurs in PABC patients in more than two-thirds of cases (50%-93.7%); this factor is considered the strongest predictor in the prognosis [23].

Patients with ER-negative tumors showed a trend toward poorer five-year survival than for those with ER-positive tumors [23].

Women with PABC are at greater risk to be detected at earlier ages with high-grade, ER- and PR-negative tumors, and advanced T/N stages [23].

Risk of preterm birth

The following risk factors could influence an increase in the risk of preterm birth: chemotherapy during pregnancy, mother's advanced age, and the trimester at diagnosis.

Most cases (77%) exposed to chemotherapy during pregnancy had a full-term pregnancy with a live birth [23].

Genetic

All women diagnosed with breast cancer under 40 years of age should be considered for genetic testing; patients with PABC are typically among these individuals.

There has not been any research done specifically on these situations, so it is unclear if genetic testing should be done before or after pregnancy. Testing prior to delivery should usually only be carried out if results alter care strategies, such as deciding for a mastectomy over breast conserving surgery or pursuing fetal testing [5].

In one study, harmful mutations of two known cancer-prone genes (BRCA1 and CHEK2) were found in 35% of PABC patients. BRCA1 pathogenic mutations were present in 30% of the patients overall. Five percent had CHEK2 gene variations. 15% of PABC patients were also found to have variations of unknown/uncertain significance (VUS) in the breast cancer predisposition genes BRCA2, CHEK2, and BRIP1 [12].

Not every patient with a germline mutation disclosed a known family history of the disease [12].

Given that PABC is strongly linked to genetic vulnerability among other predisposing variables, genetic testing should therefore be considered for these patients. Finding germline mutations may help to enhance the prognosis situation and change the PABC management strategy [39].

Diagnosis

The diagnosis of breast cancer in the pregnant woman is difficult owing to the physiologic changes of the breast that occur during pregnancy, including hypertrophy, engorgement, nodularity, and nipple discharge which are progressive until childbirth [4]. These changes also limit the sensitivity of the mammography and ultrasound. Since breast cancer in pregnant women is frequently identified with delay, it is often diagnosed in advanced stages with poorer

prognosis on presentation than nonpregnant women [39]. In one study most pregnant women aged ≤ 35 years were diagnosed at clinical stage IIIA-B (88.8%), with axillary lymph node involvement (100%) [23].

Symptoms and characteristics of PABC

A lump or a palpable thickening in the breast are the most typical signs of breast cancer. A change in the breast's size, shape, or appearance; breast pain; dimpling, redness, pitting, or other skin changes; a change in the appearance of the nipples or the skin surrounding them; inversion of the nipples; abnormal nipple discharge; axillary lumps; or symptoms of distant spread, such as bone pain, are some additional signs and symptoms.

A palpable mass or thickening in the breast is still the most typical presentation of breast cancer in pregnancy [23]; however, patients with PABC had more than twice the rate of locally advanced disease signs and symptoms, such as pain, ulcers, skin thickening and redness, nipple retraction, and discharge [4]. Any of these presentations should be evaluated further via imaging and biopsy.

Imaging

Breast cancer screening and detection are made more difficult by physiological changes in the breast that take place during pregnancy and lactation.

Despite these difficulties, postponing imaging assessment is not advisable because poorer results are associated with delayed diagnosis of pregnancy-associated breast cancer. Protocols based on age, breast cancer risk, and whether the patient is pregnant, or nursing can be used to properly do both diagnostic imaging and screening.

Imaging patterns overlap during pregnancy and lactation: whereas many benign lesions have the potential to develop, infarct, become heterogeneous, and therefore raise suspicions, PABC does not necessarily exhibit the classic malignant signs. For this reason, if the doubt still exists following the clinical and radiological evaluation, a biopsy must be done [16].

The first imaging modality that is preferred to determine whether a breast mass is solid or cystic and to define the features of the mass is ultrasound [39]. If the US findings raise suspicions about malignancy or fail to identify the etiology of the clinical complaint, mammography should be performed.

It is safe to do breast mammograms using shielding, and results have shown that the accuracy is higher than 80%. To guide a biopsy and determine the extent of the disease, ultrasound imaging of the breast and nearby lymph nodes can be employed. According to reports, up to 100% of breast tumors that arise during pregnancy have incorrect ultrasound results.

Because intravenous gadolinium-based contrast agents are used for breast MRI, it is not advised during pregnancy.

The diagnostic imaging protocol for nursing women is similar to non-pregnant, non-lactating patients; for patients under 30, ultrasound is performed first, then mammography; for patients over 30, mammography is performed first. Breastfeeding women can have MRIs for local-regional staging and high-risk screening.

A wide range of breast abnormalities, such as benign diseases, malignant neoplasms, and typical physiological changes, may be detected by the radiologist. Even though the majority of masses found are benign, if the imaging features raise suspicions of malignancy or if it fails to disappear after a brief time of clinical follow-up, a biopsy should be done. To differentiate these results from pregnancy-associated breast cancer, it is essential to distinguish the anticipated imaging appearance of physiologic changes and typical benign findings in pregnancy and lactation [25].

Staging assessment

A chest x-ray (with shielding), evaluation of hepatic and renal function, and a CBC with differential are recommended for clinically node-negative T1-T2 tumors staging.

In addition to the above, screening MRIs of the thoracic and lumbar spine without contrast and hepatic ultrasonography may be used in individuals with clinically node positive or T3 breast lesions.

Hormone receptor

It is essential to check the immunohistochemistry for HER-2neu, progesterone, and estrogen receptors. Hormone receptors more frequently are negative, and about 30% are HER2-positive [23].

Management

Initiating cancer treatment during pregnancy often decreases the risks of early delivery and prematurity [37].

A mother-fetal consultation should be part of the initial evaluation, along with a review of previous pregnancy problems, diabetes, hypertension, and other antecedent maternal risks. Fetal age and growth should also be recorded using ultrasound examination. The gestational age upon diagnosis, the disease's stage, and the patient's and family's preferences should all be considered when making personalized therapy options [39].

Consultation should include counseling regarding maintaining or terminating pregnancy, review of the surgical options, and use of systemic therapy.

Iatrogenic premature delivery leads to poor neurocognition and should be avoided [7].

Multidisciplinary specialist teams are critical for trimester dependent management. The surgical and systemic treatments according to stage are much the same as for women who are not pregnant [7-40].

Surgery

The main part of treatment is surgery. The Modified Radical Mastectomy has been the most often performed surgical surgery. Breast reconstruction is an emotive topic when a mastectomy is necessary. Most surgeons delay Breast reconstruction till delivery to reduce the risks to the unborn child. A delayed breast reconstruction (DBR) might have an impact on the result, nevertheless.

A case study described the simultaneous cesarian section and nipple-sparing mastectomy in conjunction with immediate breast reconstruction in 37-year-old patient, at the 36th week gestational age with PABC. In this case, initially, a spinal anesthetic was used during the cesarian section to reduce the baby's risks. Under general anesthesia, breast surgery including mastectomy and immediate breast reconstruction was carried out right away. The surgical treatment was completed with partial submuscular immediate breast reconstruction using an acellular porcine dermal matrix. Lactation was inhibited. So, in a single surgical session, cesarian delivery, subcutaneous mastectomy, axillary dissection, and immediate breast reconstruction were successfully carried out [24].

Breast-Conserving Surgery is also possible if radiation therapy can be delayed to the postpartum period. Breast-conserving surgery does not seem to have an adverse effect on survival when used in pregnancy.

When surgery is performed at 25 weeks of gestation or later, obstetrical, and prenatal specialists must be onsite and immediately available in the event of precipitous delivery of a viable fetus [1].

Sentinel lymph node biopsy

Sentinel lymph node biopsy should not be offered to pregnant patients under 30 weeks gestation. Only case reports and estimates of the radiation dose to the fetus resulting from the use of radioactive tracers, such as technetium 99m sulfur colloid, are available in the restricted amount of data. It is not recommended to use isosulfan blue or methylene blue dye for sentinel node biopsy operations in pregnancy.

Chemotherapy

The indications for systemic chemotherapy are same as the non-pregnant breast cancer patient, although chemotherapy should not be administered at any point during the first trimester of pregnancy. The highest risk of fetal abnormality occurs during the first trimester. Fetal malformation risks in the second and third trimester are approximately 1.3%, not different than that of fetuses not exposed to chemotherapy during pregnancy. Chemotherapy based

on anthracyclines and taxane has been proven to be safe after the first trimester. To reduce complications, frequent monitoring of the mother and fetus is necessary. Chemotherapy has a temporary myelosuppressive effect that impacts both the mother and the child [23]. Chemotherapy should stop at week 35 of pregnancy or three weeks prior to the delivery to prevent peripartum infection/bleeding [7].

Importantly, fetal growth should be monitored, and long-term follow-up of the children is encouraged in dedicated centres [37].

It should be noted that given the majority of PABC patients are younger and genetic testing is advised it may be beneficial to initiate neoadjuvant chemotherapy [39].

Anti- Her-2 targeted therapy, endocrine therapy, and radiation therapy

Anti- Her-2 targeted therapy, endocrine therapy and radiation therapy are contraindicated regardless of the trimester and should be administered post-delivery [7,8]. Only a few case reports exist regarding the usage of trastuzumab when pregnant. Among all cases, oligohydramnios or anhydramnios was the most frequently reported adverse event (58.1%) [11]. In one case, fetal renal failure happened. During the first two trimesters of pregnancy, a patient who was diagnosed with a recurrence of breast cancer was exposed to both tamoxifen and trastuzumab, according to a case study. Moreover, docetaxel was given in the second and third trimesters without causing any fetal abnormalities or obstetric problems [8].

Lifestyle modification

These women should be encouraged to have their regular exercise. Breast cancer patients who are pregnant or just gave birth must manage their cancer, their therapy, and their condition at the same time. Despite the fact that exercise has many advantages for both breast cancer survival and pregnant health, these experiences may make it difficult to engage in physical activity [42].

Psychological support

A woman must carefully remodel and rebuild her identity as she prepares for new duties and responsibilities as part of the important developmental process that is becoming a mother.

When cancer diagnosis is communicated during the pregnancy, fears, worries, and concerns emerge that specific support and multidisciplinary approach may be necessary [7].

Data suggests that support and promotion of breastfeeding might be very effective after a serious medical diagnosis [24].

Time and type of delivery

Delivery after 37 weeks is recommended, and iatrogenic preterm delivery should be avoided whenever possible. Vaginal delivery should be favored over cesarian section.

Future pregnancy:

Following treatment for pregnancy-associated breast cancer (PABC), some women want to become pregnant again in the future. A growing proportion of young women believe their families are incomplete following breast cancer treatment, as the average age of mothers rises and the prevalence of breast cancer in young women increases [1,2,26].

According to available data, long-term survival after subsequent pregnancies shows similar results, and there may even be a protective effect on survival and recurrence [39]. Additionally, there are encouraging preliminary findings that suggests it is safe for patients with PABC to become pregnant following breast cancer treatment [26].

Long-term pooled analyses are needed to develop further guidelines [26].

Conclusion

Multidisciplinary care should be provided to pregnant patients with breast cancer, and treatment plans should take the growing fetus's risks into considerations [39]. The stage-wise results are comparable to those of breast cancer patients who are not pregnant, which emphasizes the significance of early identification. International cooperation is necessary. Although there are now more publications about PABC, series are still hard to come by. To improve our understanding in this area, it is crucial to establish a worldwide database that prospectively registers each and every PABC case [22].

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