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Imaging the Breast in Pregnant or Lactating Women

Vignesh A. Arasu[1,2] · Neeta Kannan[2] · Priya M. Krishnarao[2] · Gillian Kuehner[3] · Ming C. Kuan[4] · Joseph C. Kim[1] · Bonnie N. Joe[2] · Amie Y. Lee[2]

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Abstract
Purpose of Review To describe the imaging evaluation of common benign and malignant breast lesions encountered in pregnant or lactating women.
Recent Findings There is increasing prevalence of pregnancy-associated breast cancer as the age of women during pregnancy increases. Women in the first 10 years following pregnancy demonstrate an elevated risk for breast cancer compared to the average population. MRI has been shown to be more sensitive for evaluating the extent of disease in lactating patients than mammography or ultrasound.
Summary The hormonal effects of pregnancy and lactation on the breast lead to distinct physiologic changes and pathologic lesions, which can manifest in unique imaging appearances. Most patients will undergo ultrasound for primary diagnostic evaluation. While mammography is not routinely utilized, it is not contraindicated even in pregnancy given the negligible radiation dose to the fetus. While most detected lesions are benign, pregnancy-associated breast cancer (PABC) is a rare diagnosis that must always be excluded. Women with PABC have a worse prognosis than age-matched controls partly due to delay in diagnosis. Thus prompt and accurate work-up of PABC is critical to improve outcomes.

Keywords Breast imaging · Pregnancy · Lactation · Breast cancer

Introduction

Imaging the breast in pregnant and lactating women is a unique and challenging clinical scenario. The breast undergoes distinct physiologic changes during pregnancy that consequently predispose women to unique pathology. As in any other context, the primary role of the breast imager is to promptly and accurately exclude the presence of breast cancer. Pregnancy-associated breast cancer (PABC) can be underappreciated in this population, but is often aggressive and carries a poor prognosis.

Physiology

The physiologic changes in the breast begin in the first trimester of pregnancy. Progesterone is initially produced by the corpus luteum during the first 10 weeks, followed by both estrogen and progesterone. Elevated levels of estrogen affect breast tissue by stimulating the development and arborization of the ductal system and increasing in adipose stromal tissue, both of which result in an overall increase in the breast size (Fig. 1) [1]. Enlarging breasts and breast tenderness may sometimes manifest as the first symptoms of pregnancy [2]. Progesterone works in conjunction with estrogen to contribute to ductal development, but it also affects the terminal ductal lobular unit by stimulating

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✉ Vignesh A. Arasu
varasu@gmail.com

[1] Department of Radiology, Kaiser Permanente Medical Center, 975 Sereno Dr, Vallejo, CA 94589, USA

[2] Department of Radiology and Biomedical Imaging, University of California, San Francisco, USA

[3] Department of Surgery, Kaiser Permanente Medical Center, Vallejo, CA, USA

[4] Department of Hematology-Oncology, Kaiser Permanente Medical Center, San Leandro, CA, USA

lobule development and providing secretory capability to the alveolar cells for later milk synthesis [3]. These increases in hormonal levels and subsequent breast changes occur most rapidly in the first trimester. By the second and third trimester, proliferation slows and increasing levels of prolactin secreted from the pituitary causes increased colostrum and milk synthesis in alveolar cells [4]. High levels of progesterone and estrogen inhibit actual milk release.

In the postpartum state, the absence of placental progesterone and estrogen eliminates the inhibitory effect on elevated prolactin levels, allowing for increased milk production. Simultaneously, an increase in oxytocin induces the contraction of breast myoepithelial cells to stimulate milk ejection. Biofeedback of breastfeeding leads to high levels of intermittent prolactin secretion, allowing for continued milk production, and maintains physiologic changes of the breast initiated during the first trimester of pregnancy. These changes include increased breast size, firmness, and nodularity. Approximately 3 months after cessation of breastfeeding, these physiologic changes are often reversed and the breast reverts back to its pre-gravid physiologic state [3].

Outside of pregnancy and the postpartum state, lactation changes may also be observed in patients with hyperprolactinemia, those who receive chronic hormone replacement therapy, or those taking certain non-hormonal drugs such as digitalis, phenytoin, and reserpine [5].

Imaging Evaluation

The physiologic changes to the breast described previously can be directly observed with different modalities of breast imaging. Moreover, certain imaging features are important to recognize to help differentiate between benign and malignant lesions. Prompt imaging work-up and diagnosis is critical when a pregnant or lactating woman presents with breast symptoms. While the majority of these symptoms are due to benign etiologies, patients with PABC often present with more advanced disease partly due to delay in diagnosis [6]. Following the cessation of breastfeeding, as the breast returns to its pre-gravid physiologic state, most of the associated benign imaging findings also resolve on subsequent evaluations.

Ultrasound

Ultrasound is the primary imaging modality of choice for evaluating a pregnant or lactating woman with a breast symptom [7•]. Ultrasound is highly effective for diagnosing PABC with a sensitivity of nearly 100% [8, 9]. Ultrasound is also safe to use during pregnancy and lactation due to lack of ionizing radiation.

During pregnancy, sonographic changes observed in the breast include increased vascularity and parenchymal echogenicity from lobular growth. Variable degrees of dilated, fluid-filled ducts may be seen. During the late pregnancy phase, colostrum presents as intraductal hypoechogenic material, given its decreased fat content

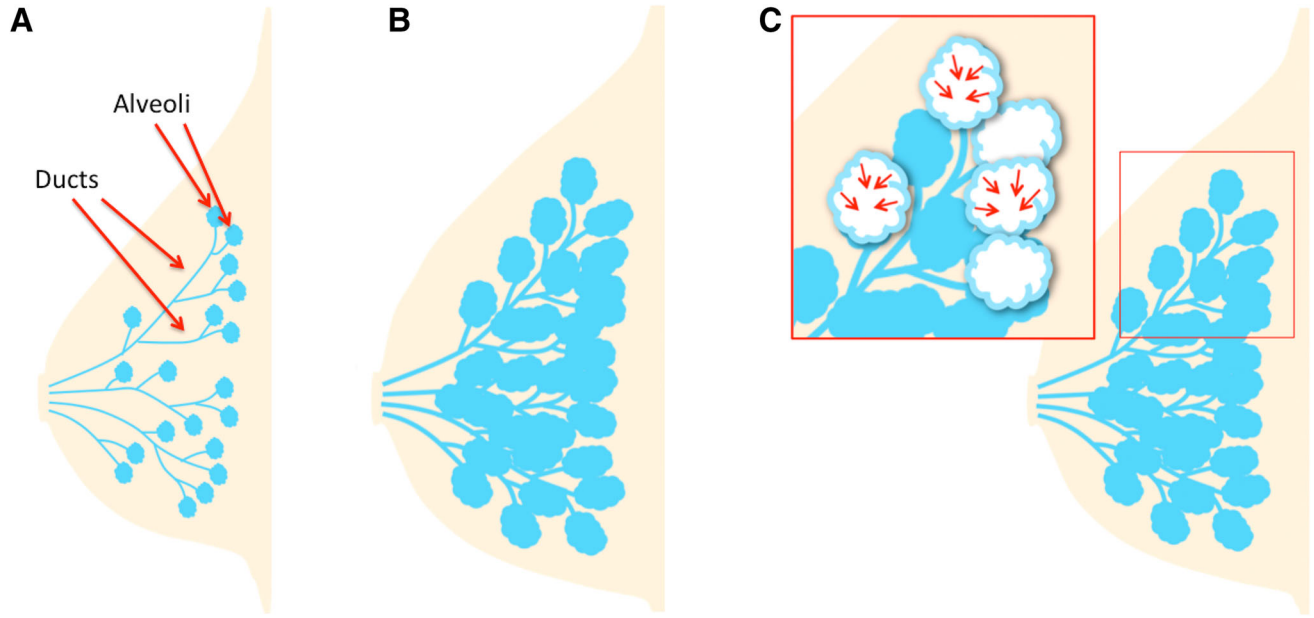

Fig. 1 Schematic illustrations of the breast show **a** the baseline appearance of the ducts and alveoli in the non-lactating breast. **b** By the third trimester of pregnancy, estrogen has caused arborization of the ductal system, increase in adipose tissue, and increase in alveolar growth/development. **c** In the postpartum breast, prolactin induces milk synthesis and oxytocin stimulates milk ejection

[10]. However, during lactation, when there is an increase in breast milk production, the parenchyma continues to appear more echogenic both from glandular enlargement and milk, which is rich in fat, filling the ducts.

Mammography

Mammography is not routinely performed for primary imaging evaluation of pregnant or lactating women, but may be helpful as an adjunct modality to better characterize certain lesions or to assess for disease extent of known or suspected cancer. Sensitivity of mammography is lower during pregnancy and lactation due to increased global bilateral parenchymal breast density. Thus diagnosing breast pathology in this population with mammography alone is limited. [11].

On mammography, the proliferative changes to the breast are most commonly seen as a global symmetric increase in breast size and density when compared to a pre-gravid study (Fig. 2). During lactation, milk within the ducts also contributes to the increased density of the breasts [3]. Therefore, in breastfeeding women, mammography should be performed after milk expression. In rare cases, women may not have dense breasts or any significant changes in mammographic breast density compared to their imaging prior to pregnancy [4].

Although the use of radiation during pregnancy raises concerns for patients and referring providers, mammography is considered safe to use during pregnancy since the radiation dose to the uterus is < 0.03 μGy, and no teratogenic fetal effects have been documented for doses < 50 mGy [12]. The use of lead apron shielding can also help decrease radiation to the uterus by approximately 50% and should be offered to pregnant patients.

Mammography is generally not recommended during the first trimester of pregnancy, the time during which the fetus is most sensitive to radiation-induced malformations and spontaneous abortion [3]. Mammography is usually performed only if underlying malignancy is suspected or has been confirmed by percutaneous biopsy. In these scenarios, mammography can be helpful to better characterize the malignancy and determine disease extent by identifying calcifications, subtle architectural distortion, or additional lesions. In cases of known or suspected malignancy, mammography is also used to screen the contralateral breast.

There is currently a lack of evidence with regard to the appropriateness of screening mammography during lactation and the appropriate time to resume screening in asymptomatic breastfeeding women. In general, given that the breast reverts to its pre-gravid physiologic state approximately 3 months following breastfeeding cessation, screening mammography is typically resumed after this time. However, screening in high-risk patients may be resumed after delivery in patients who will be breastfeeding for > 6 months postpartum [3, 13]. There is clearly a need for further research on the optimal screening approach as more women are delaying pregnancy, and thus lactation, into their 40s when they are of screening age.

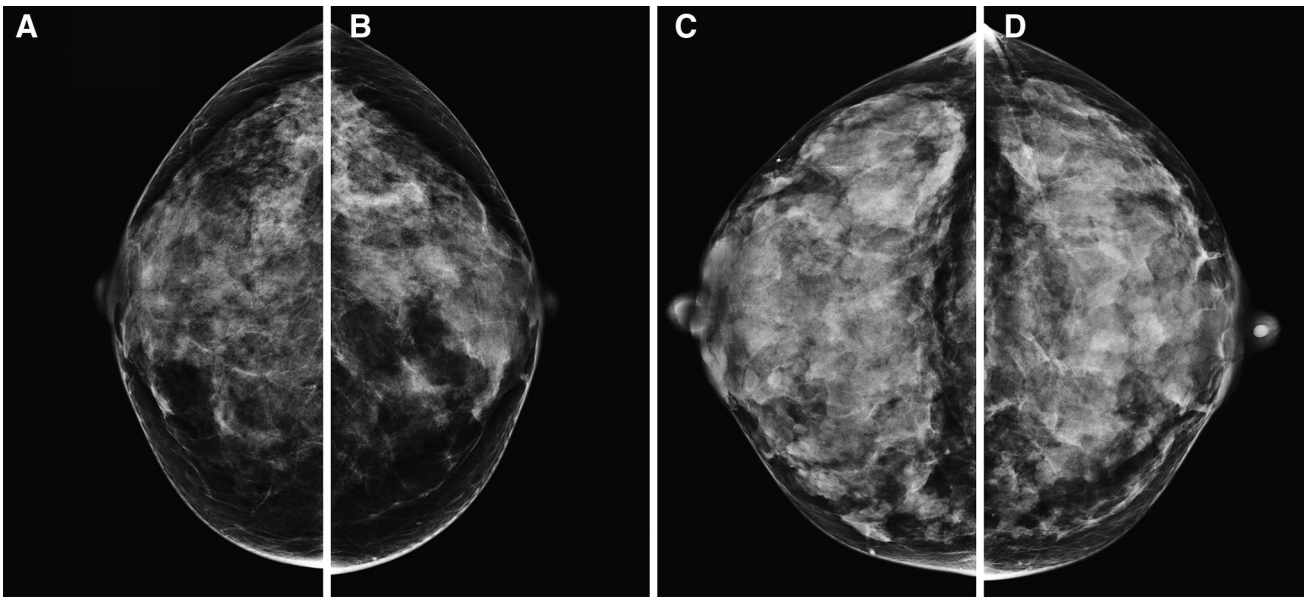

Fig. 2 **a**, **b** Craniocaudal views of the bilateral breasts show the normal appearance of non-lactating breasts at screening mammography. **c**, **d** Mammography 2 years later shows marked increased in size and density of the bilateral breasts, compatible with lactational state

MRI

Like mammography and sonography, MRI performed during lactation will reflect the physiologic breast changes described above. Background parenchymal enhancement will typically be diffusely increased bilaterally secondary to increased physiologic vascularity and hormonal effects on the breast tissue (Fig. 3). Increased parenchymal T2 signal is also observed and is thought to be due to increased milk production (Fig. 4) [14].

In pregnant women, contrast-enhanced breast MRI is contraindicated. This is due to the fact that gadolinium-based contrast agents cross the blood–placental barrier, and the effects of gadolinium on the fetus are unknown. Therefore, screening MRI for high-risk patients and diagnostic breast MRI should be delayed until after pregnancy.

In lactating women, contrast-enhanced breast MRI can be safely performed with continuation of lactation after gadolinium administration. However, patients may be advised to express and discard breast milk for the first 24 hours after gadolinium administration to ensure that the infant is not exposed to gadolinium excreted in breast milk, although this dose is minimal ($< 0.0004\%$ of the maternal dose) [15]. Screening breast MRI may be performed in high-risk lactating patients planning to breastfeed for > 6 months postpartum. However, the higher levels of background parenchymal enhancement during lactation may affect the accuracy of MRI in this population.

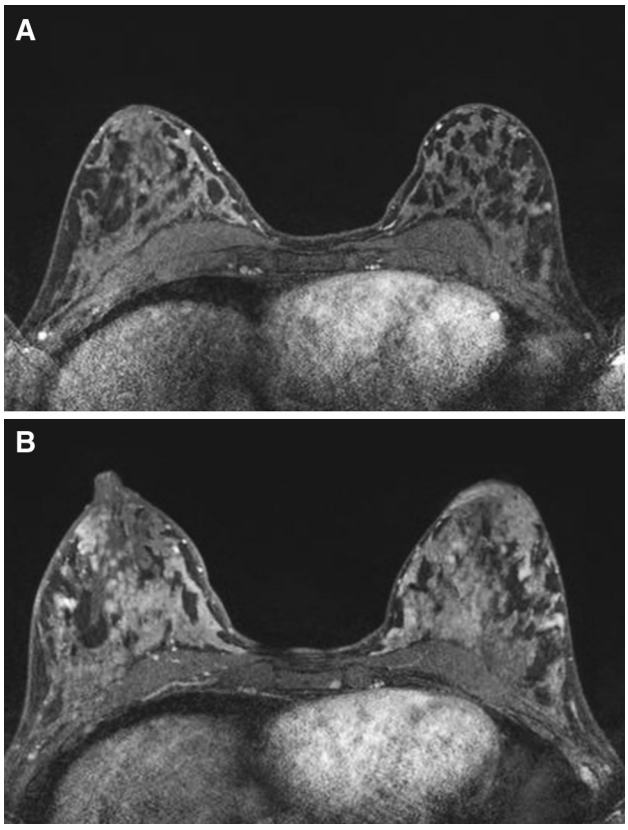

Fig. 3 **a** Axial T1-weighted post-gadolinium breast MRI shows the normal baseline appearance of the patient's bilateral breasts. **b** Axial T1-weighted post-gadolinium breast MRI 1 year later shows increased breast density and increased background parenchymal enhancement in both breasts, compatible with lactational state

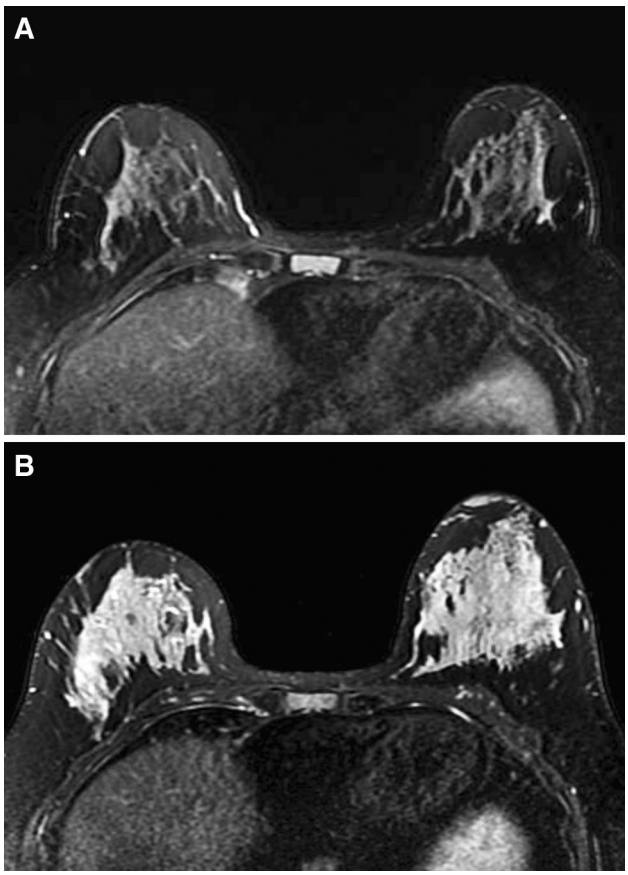

Fig. 4 **a** Axial T2-weighted breast MRI shows appearance of the patient's breast prior to lactation. **b** Axial T2-weighted MRI shows diffuse increased T2 signal throughout both breasts, compatible with lactational state

Nuclear Medicine

PET/CT for metastatic work-up of biopsy-proven cancer should be postponed until after completion of pregnancy due to high doses related to combined sources of ionizing radiation [3, 15]. If performed during pregnancy or lactation, PET/CT will show increased FDG activity in the breasts due to increased metabolic activity associated with breast changes during pregnancy and lactation [16]. It is important that this normal physiologic appearance is not misdiagnosed as hypermetabolic disease.

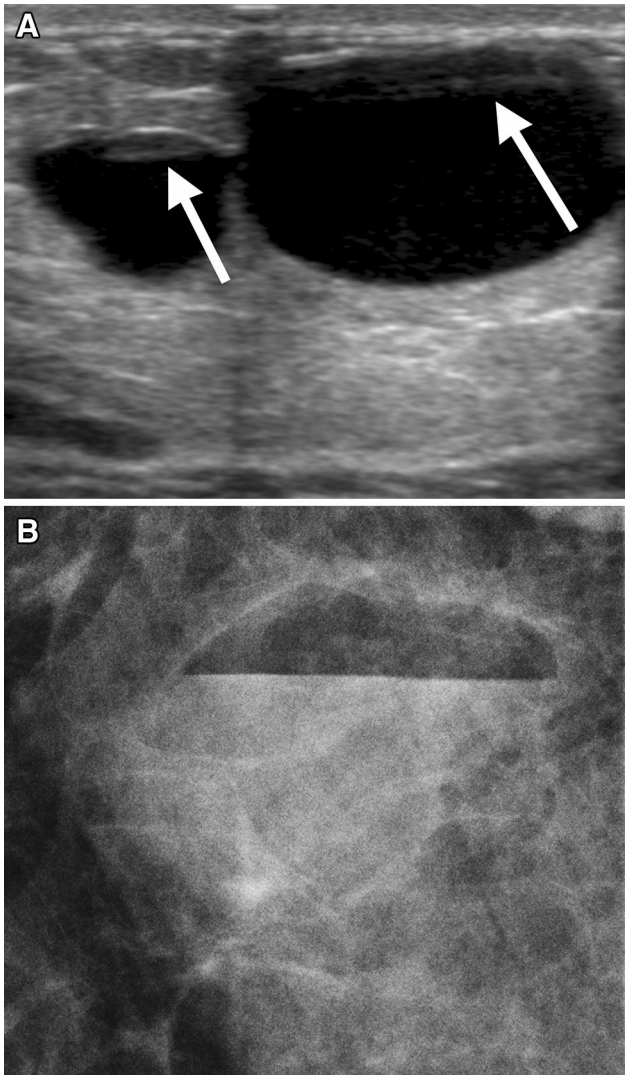

Fig. 5 A 40-year-old lactating female with a palpable right breast lump. **a** Targeted ultrasound demonstrates two adjacent cysts with fat-fluid levels. **b** Spot compression mammography at the palpable site also demonstrates a fat-fluid level. Findings are compatible with benign galactocele

Procedural Considerations

Suspicious breast masses identified on ultrasound during pregnancy and lactation can be percutaneously sampled using ultrasound guidance for pathologic analysis. Ultrasound-guided core biopsy can be easily performed and assist in making an accurate diagnosis during pregnancy and lactation. However, patients should be informed of special considerations prior to percutaneous intervention. While the use of lidocaine as a local anesthetic is considered safe in pregnancy, the risk of bleeding and post-procedural infection is greater due to the increased vascularity of the breast and prominent ductal dilatation [14].

Milk fistula formation is a reported rare complication of core needle biopsy in the third trimester of pregnancy or during lactation [17]. This results from a tract created during the procedure between a high-pressure ductal system and the skin. The risk increases with the use of smaller-gauge core biopsy needles, surgical biopsy, or with deeper central lesions. Therefore, risk may be mitigated using larger-gauge needles or fine needle aspiration for initial sampling of these masses [17]. Treatment typically involves supportive management as most fistulas will spontaneously resolve with time. For persistent non-resolving milk fistulas, cessation of breastfeeding may be necessary [18].

Benign Lesions

Galactocele

Galactoceles are retention cysts that form due to accumulation of milk within obstructed ductules [5]. The pathognomonic imaging appearance on ultrasound is a cystic mass that demonstrates a fat-fluid level, characterized by a hyperechoic superficial layer representing liquefied fat and a deeper hypoechoic layer representing fluid and sedimented proteinaceous debris (Fig. 5). The presence of multiple galactoceles is not uncommon. The contents may also be mobile and variably layer depending on the patient positioning. Thus, maneuvering the patient's position can be useful when trying to distinguish between a solid component from layering fat. Finally, galactoceles may have an indeterminate appearance as a circumscribed, uniformly hypoechoic avascular mass, depending on the stage of evolution. If mammography is performed, galactoceles may present as a partly fat density lesion, with fat-fluid level seen only on lateral projections. When the diagnosis of galactocele is certain, biopsy is not indicated. However, aspiration may be indicated if the lesion is large and painful or there is concern for superimposed infection. A milky, fatty substance will typically be seen in the aspirate.

Fibroadenoma and Lactating Adenoma

The most common breast masses encountered during pregnancy and lactation are fibroadenomas and lactating adenomas. Although pathologically distinct, the etiology of lactating adenomas lesions remains uncertain and may potentially represent a pre-existing fibroadenoma or tubular adenoma that has transformed due to hormonal alterations of pregnancy or de novo tumors [3, 19]. However, the clinical and imaging appearance of these lesions is essentially indistinguishable [20]. They most commonly present

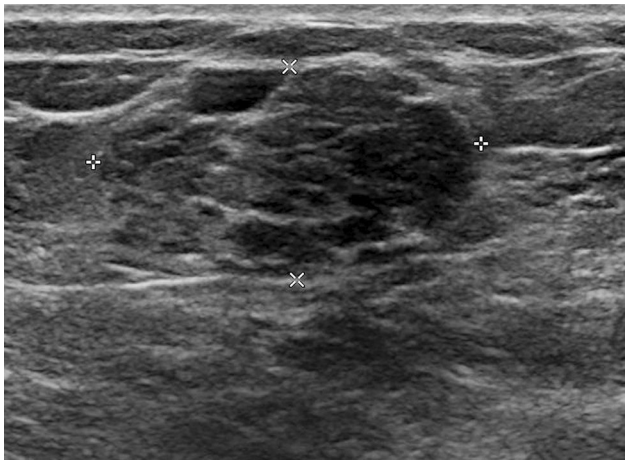

Fig. 6 A 45-year-old postpartum female with a palpable left breast lump. Targeted ultrasound demonstrates a corresponding complex solid and cystic mass. Ultrasound-guided core biopsy was recommended and pathology returned benign lactating adenoma

as painless, smooth, palpable masses, and both may rapidly grow. Both fibroadenomas and lactational adenomas are most commonly characterized on imaging as oval masses with circumscribed margins, hypoechoic echo pattern, and parallel orientation (Fig. 6). A central area of hyperechogenicity may be present in lactating adenomas, representing milk related to lactational hyperplasia. If a lesion demonstrates probably benign features (BI-RADS category 3) by imaging and biopsy is not pursued, these lesions should be followed in 6 months. After cessation of lactation, lactating adenomas will typically regress. Some lesions demonstrate more suspicious features such as irregular margins and shadowing, possibly due to a lack of capsule in lactating adenomas or the presence of infarction in 5% of lesions [11, 20]. If a lesion does not fulfill BI-RADS 3 criteria or is subjectively new or growing, malignancy should first be excluded with percutaneous biopsy. False-positive diagnosis of malignancy has been known to occur with fine needle aspiration due to lactational changes and occasional atypia [3, 20].

Mastitis/Abscess

Inflammation and infection of the breast tissue occur commonly during lactation and rarely during pregnancy. The pathophysiology is related to infection transmitted by the nursing infant via epithelial disruption of the nipple–areolar complex from skin dryness and cracking. Infection is transmitted retrograde to the milk-containing duct from pyogenic species such as *Staphylococcus aureus* and *Streptococcus* residing in the infant's nose and throat. Milk stasis and engorgement are risk factors as milk acts as a culture medium for infection [3, 21]. Women typically present with breast tenderness, swelling, erythema, fever,

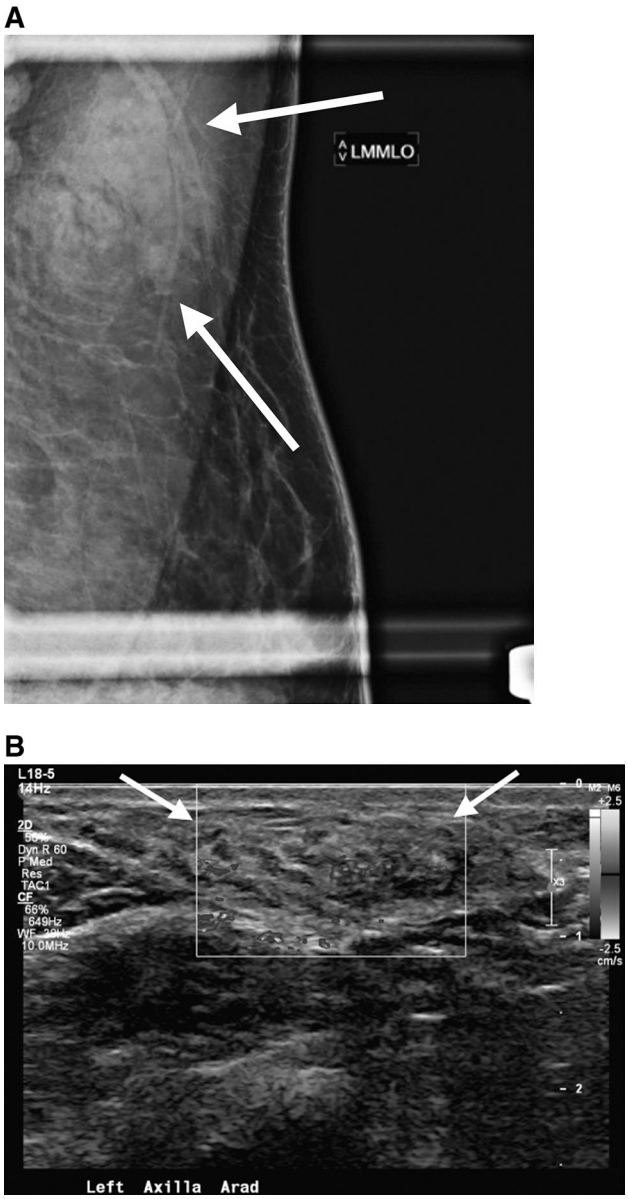

Fig. 7 Imaging appearance of benign axillary accessory breast tissue on **a** mammography and **b** targeted ultrasound in a lactating patient

and leukocytosis. *Staph* species can present as a localized infection that can quickly transform into a suppurative abscess, while *Strep* species tend to cause diffuse inflammation that progresses to abscess at a later advanced stage. Empiric antibiotics should be initiated first based on clinical suspicion. Imaging should be pursued for persistent symptoms after a full-course of antibiotics has been completed or when an abscess is suspected. An abscess will appear as an irregular hypoechoic or heterogeneous mass, sometimes containing mobile debris, with an echogenic hypervascular periphery. Percutaneous aspiration or drainage should be performed when an abscess is identified. Breastfeeding or pumping should also be continued to help promote drainage of stagnant ducts [3].

Accessory Breast Tissue

Accessory breast tissue is histologically normal breast tissue located away from primary breast, typically in the axilla. It is thought to represent tissue that fails to involute during embryogenesis and can affect up to 6% of women [22]. Accessory breast tissue can present as a palpable lump during pregnancy and lactation, as increased hormones will cause growth and development similar to primary breast tissue. The appearance is easily identified on mammography, but may also appear prominent on ultrasound due to the normal breast tissue physiologic changes in pregnancy (Fig. 7). Although typically visualized in the axilla, accessory breast tissue can occur anywhere along an embryonic line known as the mammary streak, extending between the axilla and inguinal region. Additional locations have also been reported in the face, back, and upper extremities [22].

Pregnancy-Associated Breast Cancer (PABC)

Imaging Evaluation of PABC

PABC is defined as breast cancer diagnosed during pregnancy or within 1 year of delivery. However, it is believed cancer induction leading to PABC may occur years prior to pregnancy. The incidence of PABC is 1 in 3000–10,000 pregnancies, with a prevalence of 3–4% of all breast cancers [23•]. Although pregnancy and gravidity are considered protective to a woman's overall breast cancer risk, the first 10 years following pregnancy demonstrate an increased rate of breast cancer above the average lifetime rate, peaking at year 6 [24]. Furthermore, as the maternal age of pregnancy increases, incidence of PABC will likely continue to rise.

PABC shares pathologic characteristics similar to tumors present in non-pregnant young woman under the age of 40. These tumors tend to be ER- or PR−, HER2+ , high-grade, with increased lymphovascular invasion, and increased positive lymph nodes [24]. However, PABC tends to present at more advanced stages. Women with PABC have an overall 5-year survival of 52% as compared to 80% for age-matched, non-pregnant women with breast cancer [25]. This poorer prognosis is thought to be due to a variety of factors, including delay in diagnosis, limited treatment options during pregnancy, and theoretical risk of hormonal effects of pregnancy potentiating accelerated tumor growth [6].

Breast imaging therefore plays a critical role in properly evaluating a pregnant or lactating patient to prevent delay in diagnosis. Unless undergoing high-risk screening, women will usually present with a palpable lump or, less commonly, swelling and erythema. PABC demonstrates similar imaging features to non-PABC breast cancers (Fig. 8). However, there must be a heightened awareness to the higher proportion of advanced stage disease in this population. If suspicion is raised for PABC, routine evaluation should be performed to exclude multifocal or multicentric disease and axillary lymphatic spread. Metastatic disease evaluation, typically performed in stage 3 or higher disease, is limited due to the relative contraindication of PET-CT during pregnancy.

As discussed previously, imaging evaluation usually begins with ultrasound but should include mammography in cases of high suspicion of malignancy. Ultrasound can be utilized for assessing axillary disease burden and allows for biopsy planning. Mammography is more limited in sensitivity compared to ultrasound due to increased breast density, although single-center studies have noted suspicious mammographic findings in 78–86% of PABC cases [19, 26]. However, mammography can more accurately assess for the presence of microcalcifications and architectural distortion, and acts as a complementary approach to evaluate the extent of disease involvement in both breasts (Fig. 9). Thus, mammography should always be performed in cases of known or suspected PABC.

Given the more aggressive biology of these women with PABC, MRI may be indicated in the postpartum or breastfeeding patient to evaluate extent of disease, depending on stage, tumor biology, or clinician preference. As discussed earlier, MRI is contraindicated during pregnancy but safe during lactation. Studies have demonstrated that despite limitations related to increased background parenchymal enhancement, primary lesions are visible and demonstrate similar features to non-PABC cancers [27].

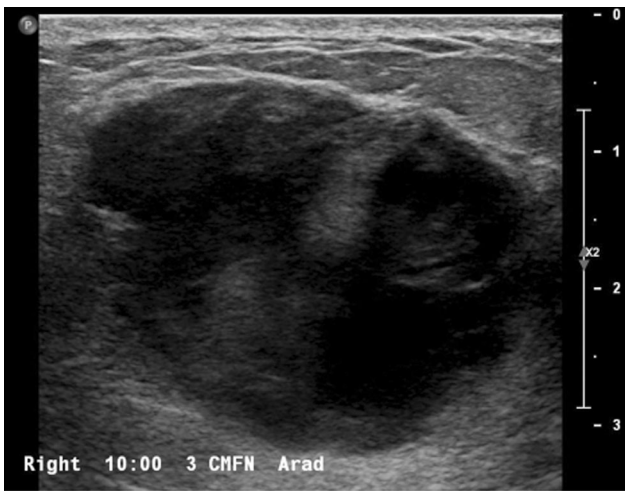

Fig. 8 A 28-year-old pregnant female with a painless palpable right breast lump. Targeted ultrasound demonstrates a corresponding complex solid and cystic mass. Ultrasound-guided core biopsy was recommended and pathology returned invasive ductal carcinoma

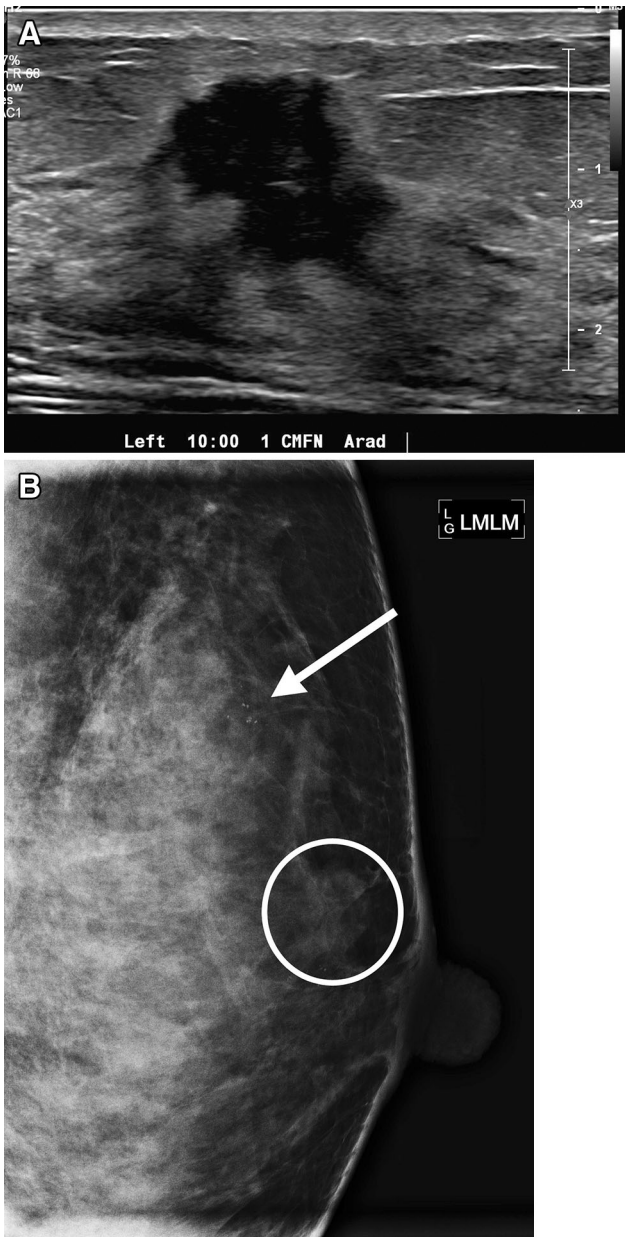

Fig. 9 A 33-year-old pregnant female with a palpable left retroareolar lump. **a** Targeted ultrasound shows a hypoechoic irregular mass with speculated margins. Given the highly suspicious sonographic finding, decision was made to pursue diagnostic mammography. **b** Left breast diagnostic mammogram shows the obscured mass (circle) corresponding to the sonographic mass. In addition, a group of fine pleomorphic calcifications were identified remote from the palpable mass. Ultrasound-guided core biopsy of the mass revealed invasive ductal carcinoma and stereotactic core biopsy of the calcifications revealed high-grade DCIS

Moreover, recent studies have demonstrated MRI was superior to ultrasound and mammography for evaluating the extent of disease in PABC. In a recent study of 53 women [28•], surgical management was changed in 28% of women with PABC, in whom 8% required a larger lumpectomy, 13% were upgraded to mastectomy, 4% had contralateral disease, and 4% were found to have metastasis. However, MRI did not detect proven disease in 2% of patients due to background parenchymal enhancement masking enhancing tumor. Another recent study of nine women found separate sites of cancer in three patients (33%) [29]. As with non-PABC, the mortality benefit preoperative MRI has not yet been proven in this patient population.

Treatment of PABC

Local and systemic control of PABC should follow the same guidelines as treatment of breast cancer in non-pregnant women, and a multi-disciplinary approach is crucial. PABC can be fully treated while a woman is pregnant without compromising the health of the mother or her fetus. Termination of pregnancy or pre-term delivery is generally not indicated, and therapeutic abortion does not improve maternal prognosis. Surgical options are similar to those for non-pregnant woman and may be performed at any time during pregnancy [30]. While there is no survival advantage for mastectomy over breast conservation, mastectomy may be preferable when PABC is diagnosed in the first trimester and there would be a significant delay in starting radiation, which is contraindicated until after delivery.

Sentinel lymph node biopsy remains controversial [31]. There is general agreement that if the lymph nodes are not abnormal on imaging, sentinel lymph node biopsy using Tc-99m sulfur colloid is acceptable, as the fetal radiation exposure is low [15]. Injection of the isotope the same day as surgery may decrease the time and dose of radiation exposure. Blue dyes should be avoided, as there is a risk of anaphylactic reaction with isosulfan blue dye and methylene blue dye [23•].

Standard neo-adjuvant and adjuvant chemotherapy can be delivered after the first trimester to avoid adverse fetal outcomes. Anthracyclines and cyclophosphamide are most commonly used. There are insufficient data to recommend general use of weekly paclitaxel, but it is acceptable if indicated by disease status [32, 33]. Anti-HER2 agents are generally not recommended during pregnancy, as they have been associated with anhydramnios, oligohydramnios, prematurity, and fetal death [34]. Chemotherapy should stop at least 3 weeks prior to delivery as myelosuppression increases the risk of peripartum bleeding and infection. Endocrine therapy and radiation are contraindicated during pregnancy, and should be administered after delivery.

Conclusion

The hormonal effects of pregnancy and lactation on the breast lead to distinct physiologic changes and pathologic lesions, which can manifest in unique imaging appearances. Most patients will undergo ultrasound for primary diagnostic evaluation. While mammography is not routinely utilized, it is not contraindicated even in pregnancy given the negligible radiation dose to the fetus. While most detected lesions are benign, pregnancy-associated breast cancer (PABC) is a rare diagnosis that must always be excluded. Women with PABC have a worse prognosis than age-matched controls partly due to delay in diagnosis. Breast imagers should maintain a high suspicion for breast cancer with a low threshold for further imaging and tissue sampling.

Compliance with Ethical Standards

Conflict of interest Vignesh A. Arasu, Neeta Kannan, Priya M. Krishnarao, Gillian Kuehner, Ming C. Kuan, Joseph C. Kim, Bonnie N. Joe, and Amie Y. Lee declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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