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Breast Imaging Considerations in Symptomatic Young, Pregnant, and Lactating Women

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Abstract

Purpose of Review Benign and malignant breast diseases in young, pregnant and lactating women including pregnancy associated breast cancers will be reviewed.

Recent Findings Compared to breast cancer in older women, poor prognostic indicators such as high nuclear grade, high Ki67 proliferation, estrogen receptor (ER) negativity, and overexpression of human epidermal growth factor 2 (HER2) may be present in young women. Even among ER + /HER2 cancers, young patients have a poorer prognosis. For pregnant women, the timing of care may be personalized based on gestational age, tumor subtype, clinical stage, and family planning considerations, including induction of labor and preservation of fertility for future pregnancies. Neoadjuvant chemotherapy can be safely administered during the second and third trimesters, and if necessary, radiation therapy can be given after birth.

Summary Symptomatic concerns warrant prompt imaging evaluation with biopsy to distinguish benign from malignant causes of breast disease in young, pregnant, and lactating women.

Keywords Young patients · Pregnant patients · Lactating patients · Breast Cancer · Mammography · Ultrasound · MRI · Gadolinium

Introduction

Because screening mammography is not performed in young women (< 40 years) with an average risk of developing breast cancer [1], breast imaging is usually performed when a clinical problem is identified. Even in the presence of a clinical problem, young women are more likely to have dense breasts, which can obscure both clinical and imaging findings. As a result, breast cancers in young women often present with a more advanced tumor size or with lymph node metastases. Breast cancer in young women is often higher grade and often consists of biologically aggressive cancer subtypes [2•, 3•]. Compared to

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older women, the risk of recurrence is not insignificant, with 40–50% recurring within 5 years [4] with a moderately high risk of developing contralateral breast cancer [5]. Even with estrogen receptor (ER)-positive luminal cancer, young women have poorer outcomes with an increased risk of breast cancer mortality compared to older women with stage-matched breast cancers [2•, 6, 7]. When a woman is pregnant or breastfeeding, physiological changes in the breast can cause both the woman and her doctor to dismiss concerns without considering an imaging test.

Imaging Considerations

Breast density decreases with age and with higher body mass index. Young women tend to have greater amounts of fibroglandular tissue because they are younger and leaner [8]. During pregnancy and lactation, high levels of estrogen, progesterone, and prolactin are present to support pregnancy and milk production, which further increase breast density. Due to the masking effect of dense fibroglandular tissue, digital breast tomosynthesis (DBT) mammography is particularly advantageous over conventional digital mammography.

In DBT mammography, a moving x-ray beam follows an arc over the breast and acquires multiple thin slices of the breast, separating the overlapping components that comprise a conventional non-DBT digital mammogram image. As such, DBT mammography has advantages over conventional digital mammography [9, 10] which exist across both screening and diagnostic settings [11]. Regardless of whether DBT or conventional digital mammography is used, the primary goal of mammography is to evaluate for suspicious microcalcifications that other imaging tests demonstrate suboptimally. Despite the limitations of mammography in dense breasts, many studies have shown that mammographic sensitivity remains high during pregnancy, ranging from 74 to 100% [12–16]. Therefore, even if ultrasound is performed first and demonstrates a finding suspected to represent malignancy, mammography can be used to further define the extent of disease.

In women under the age of 30, ultrasound is recommended for the initial evaluation of a palpable abnormality or other symptomatic concerns. Both mammography and ultrasound may be utilized as the initial evaluation in women between the ages of 30–39 [17]. The main advantages of ultrasound are that it is readily available, does not use radiation, and has high diagnostic performance even in women with dense breasts. On ultrasound, dense fibroglandular tissue provides a hyperechoic background within which hypoechoic masses may be readily detected. With pregnant women, ultrasound is used as the initial evaluation, regardless of age [18]. Even though pregnancy increases breast stroma and density, ultrasound has close to 100% sensitivity and 100% negative predictive value for breast cancer detection in pregnant women [12–15, 19].

Indications for gadolinium enhanced MRI (Gd-MRI) of the breast include high risk screening in women with a >20% lifetime risk for developing breast cancer and for the initial staging of a new breast cancer diagnosis [20]. In pregnant women, Gd-MRI is contraindicated due to theoretical risks of heart deposition to the fetus, injury to developing auditory nerves due to high acoustic noise, fetal growth retardation, and possible neurotoxic effects of chelated gadolinium [21, 22]. Exposure to gadolinium has been described as a potential cause of inflammation in the developing baby with the potential to cause neonatal death [23]. Despite evidence suggesting there are no teratogenic effects of gadolinium at doses used in clinical practice [24], the American College of Radiology's official stance has been that the use of gadolinium is contraindicated in pregnant women. Alternatively, MRI may be performed when the patient is postpartum or iodinated contrast enhanced mammography (CEM) may be considered in lieu of Gd-MRI of the breast.

The *as low as reasonably achievable* (ALARA) principal dictates radiologists consider the necessity and the benefit versus risk associated with radiation to a young woman's breasts and to the developing fetus. Low dose mammography is considered safe because a conventional 4-view mammogram delivers a radiation dose < 3 mGy to the breast. This exposure is equivalent 4 to 7 weeks' background radiation [13, 24], and teratogenic effects have not been observed below 50 mGy. Abdominal shielding may be used to further decrease exposure to the fetus, though most of the radiation is dispersed due to scatter.

In lactating women, breastfeeding or pumping before imaging evaluation can help reduce breast density and tenderness, thereby helping to achieve better mammographic compression and minimizing ductal secretions and dilatation that may be seen by ultrasound and MRI. Finally, if there is a suspicious imaging finding, though there may be increased vascularity and dilated ducts due to lactational changes, percutaneous biopsy is generally considered safe with only minimally increased risk of infection or milk fistula. Additional measures to minimize the risk of milk fistula include breastfeeding or pumping immediately before the biopsy, using the smallest possible needle, selecting the shortest distance to the target, and avoiding crossing of ducts during the biopsy [25]. Studies show the amount of lidocaine and post biopsy hemorrhage content in breast milk after a percutaneous needle biopsy are minimal [26, 27]. Some women may choose to discard the breast milk in the short duration (12- 24 h) immediately after biopsy. Percutaneous needle biopsy helps establish a definitive diagnosis in cases where benign entities appear suspicious and when breast cancers may appear deceptively benign.

Breast Diseases in Young, Pregnant, and Lactating Women (Table 1)

Fibrocystic Change Fibrocystic change is a spectrum of normal physiologic changes characterized by increased nodularity of the breast and breast tenderness that may

fluctuate with changes in the hormonal levels throughout a menstrual cycle. Imaging may show dense breasts, dilated ducts, and cysts.

Fibroepithelial Tumors This group of breast tumors includes tubular adenomas, lactating adenomas, fibroadenomas, and phyllodes tumors. Both tubular and lactating adenomas occur in young women and may be radiologically indistinguishable from fibroadenomas. Histologically, tubular adenomas, lactating adenomas are distinguished from fibroadenomas by the predominance of the epithelium and relative lack of stroma (Fig. 1). A lactating adenoma is comprised of aggregates of lobules with secretory hyperplasia and occurs during the third trimester or during the postpartum state (Fig. 2). Most lactating adenomas resolve spontaneously, however, some may persist or even increase in size requiring surgical excision [28]. Up to 30% of tubular adenomas and 50% of lactating adenomas may demonstrate suspicious imaging features of an irregular shape, non-circumscribed margins, or nonparallel orientation [29]. Fibroadenomas are the most common type of breast masses in young women. They are firm, rubbery, mobile masses composed of stromal elements. Phyllodes tumors are stromal tumors with variable malignant potential. At the benign spectrum, phyllodes may be radiologically and

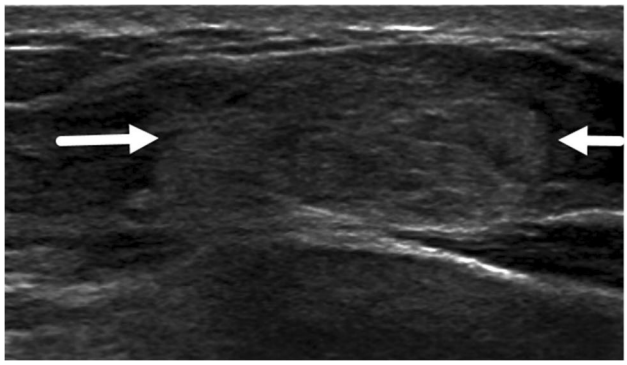

Fig. 2 37-year-old with a lactating adenoma at 6 weeks postpartum. The lactating adenoma is oval in shape, heterogeneous in echogenicity, and parallel in orientation

Table 1 Breast Disease in the Young, Pregnant, and Lactating Women

Breast Disease	Typical Clinical Presentation	Pathophysiology	Imaging Findings
Fibrocystic change	Increased nodularity and tenderness	Spectrum of normal-fibrous tissue intermixed with cysts	Dense tissue, dilated ducts, cysts
Tubular adenoma	Palpable	Epithelium without stroma	Similar to a fibroadenoma
Lactating adenoma	Palpable	Secretory changes of lactation	With lactational changes
Fibroadenoma	Palpable	Stromal tumor	Oval, circumscribed mass
Phyllodes	Palpable	Stromal tumor with cellularity	Enlarging lobulated mass
Papilloma	Nipple discharge	Frondlike intraductal tumor	Intraductal mass
Galactocele	Palpable	Accumulation of milk behind a blocked duct	Cystic mass, Fat-fluid level
Puerperal mastitis	Redness, pain	Bacterial infection due to skin abrasions or cracks in the nipple	Edema, skin thickening, fluid collections
Idiopathic granulomatous mastitis	Recurrent inflammatory change	Granulomatous, noninfectious inflammation	Tubular hypoechoic structures, fluid collections
Breast cancer in young women	Palpable, breast enlargement	Associations with genetic mutations	Variable based on molecular subtype

Fig. 1 19-year-old with a tubular adenoma. The mass is oval in shape with circumscribed margins, homogeneously hypoechoic, and parallel in orientation. It is radiologically indistinguishable from a fibroadenoma

pathologically indistinguishable from a fibroadenoma [30] (Fig. 3). At the malignant spectrum, malignant phyllodes may demonstrate hematogenous metastasis with biologic behavior similar to a breast sarcoma. Due to higher hormonal levels during pregnancy, fibroepithelial tumors may grow. If a mass grows rapidly, infarction within the mass may result in cystic areas which contribute to a heterogeneous appearance with non-circumscribed margins.

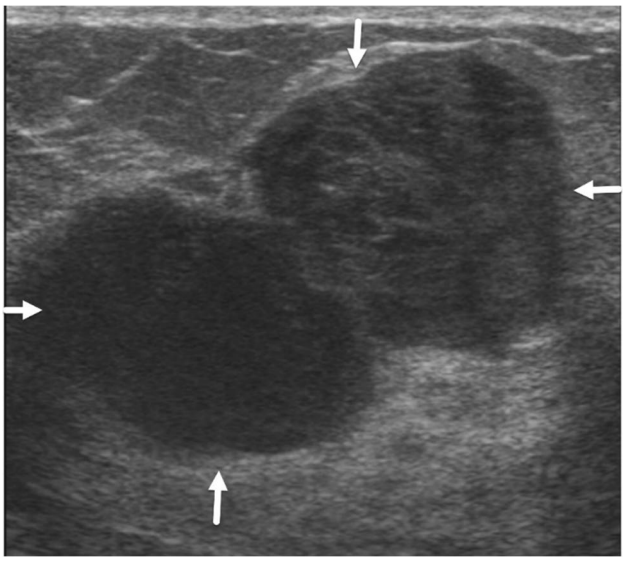

Fig. 3 21-year-old with a benign phyllodes tumor with increased stromal cellularity, presents with a rapidly growing bilobed heterogeneous mass (arrows) measuring 3.3 × 2.8 × 2.1 cm. Over 7 months, the volume of the mass had increased 66% from previous measurements of 2.3 × 1.9 × 1.5 cm

Intraductal Papillomas Nipple discharge is common among all women and is especially common in pregnant and lactating women. In this latter group, discharge is usually physiologic, and imaging is not indicated. Intraductal papillomas account for 22.2% of breast imaging cases evaluated for pathologic discharge [31•]. Intraductal papillomas are frondlike tumors arising within a duct (Fig. 4). Multiple peripheral papillomas have a higher likelihood of malignancy than single central duct papillomas. The need for surgical excision is predicated by the presence of atypia or not.

Galactoceles Galactoceles are the result of milk stagnation secondary to an obstructed terminal ductal lobular unit. The sonographic appearance of galactoceles is variable, ranging from an oval or round hypoechoic mass with low-level echoes, a hyperechoic mass, or a complicated cystic mass with thin septations, often with posterior acoustic enhancement (Fig. 5). Galactoceles may rarely manifest with irregular shape and indistinct margins and may mimic the appearance of a solid mass. The imaging feature of a fat fluid level is pathognomonic for a galactocele. When fat-fluid levels are not present, aspiration may be both therapeutic and diagnostic if milk is returned on aspiration.

Puerperal Mastitis Puerperal mastitis refers to infection related inflammation occurring during childbirth or the immediate postpartum period. Skin flora bacteria such as Staphylococcus or Streptococcus may enter the breast via skin abrasions and cracks in the nipple. Mammography may show skin thickening or trabecular thickening secondary to edema. Ultrasound may show hypoechoic areas due to edema with intervening ill-defined hyperechoic areas due to inflamed fat lobules. If

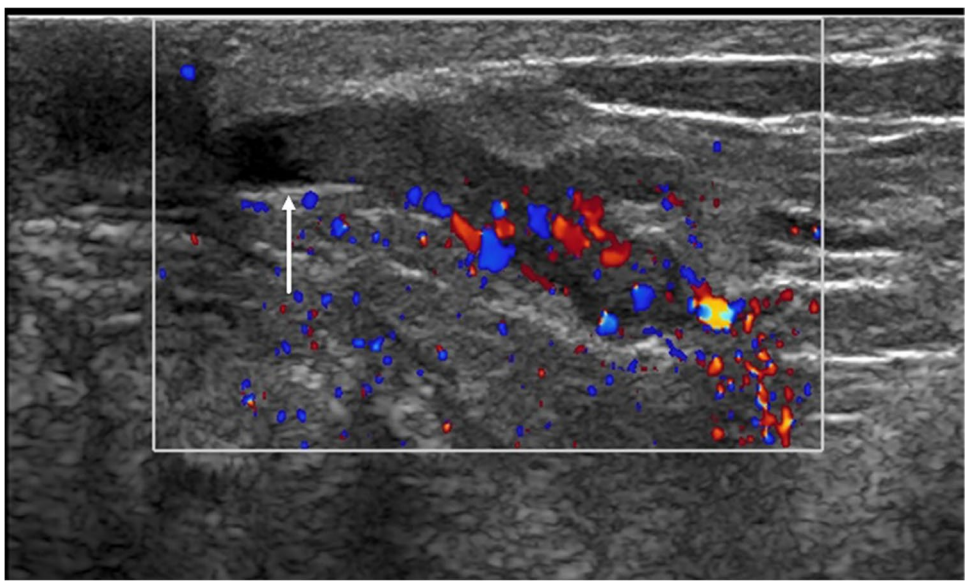

Fig. 4 30-year-old with an intraductal papilloma presents with a history of a single orifice, bloody nipple discharge. Color doppler ultrasound shows an intraductal mass with internal blood flow. Arrow shows the interface of the mass that fills the branching duct with the adjacent anechoic duct

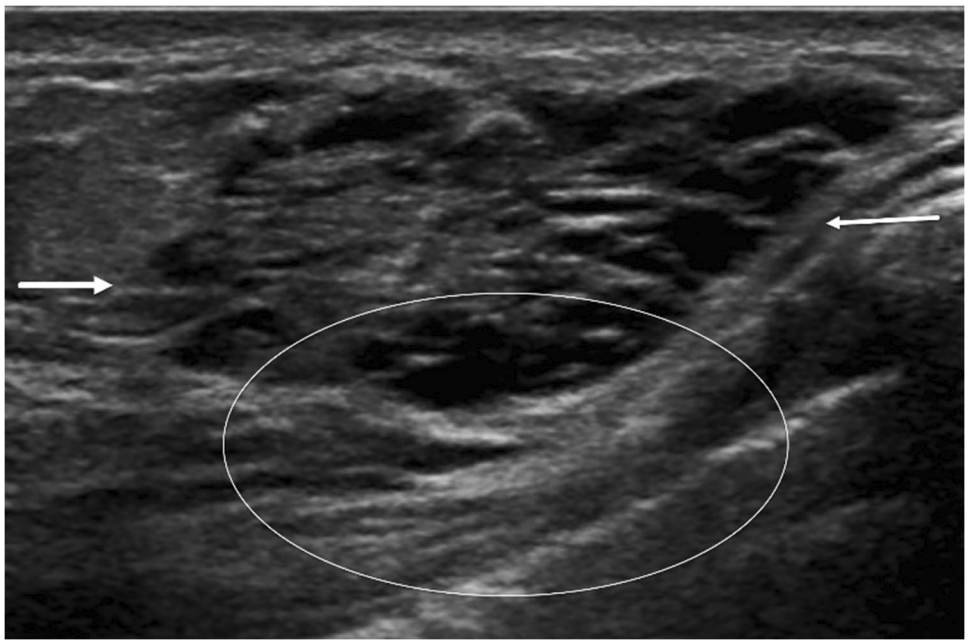

Fig. 5 31-year-old with a galactocele, initially detected on palpation during the third trimester of pregnancy and diagnosed at 6 weeks postpartum. Upon placement of the needle, milky fluid was returned. Transverse ultrasound shows a complicated cystic mass (arrows) with posterior acoustic enhancement (circle)

mastitis progresses to abscess formation, a complicated cystic mass may become evident and require incision and drainage.

Idiopathic Granulomatous Mastitis (IGM) IGM is a rare, benign, noninfectious, inflammatory disease of the breast. Though the etiology of IGM is unknown, a popular hypothesis revolves around breast feeding-induced secretions that can stimulate a local inflammatory response in the breast lobules [32]. Imaging features include a hypoechoic mass with tubular extensions and peripheral hypervascularity (Fig. 6). Treatment consists of steroids, immunosuppressants such as methotrexate, and bromocriptine to suppress prolactin production [33, 34].

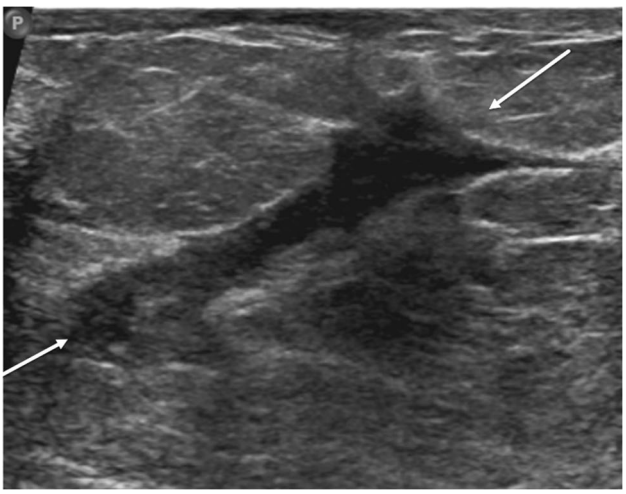

Fig. 6 25-year-old with history of recurrent left breast abscesses that were resistant to incision and drainage and antibiotic treatment. Additional history included breastfeeding 2 years prior. Ultrasound shows tubular hypoechoic extensions (arrows). Pathology yielded acute and chronic granulomatous inflammation with giant cells consistent with granulomatous mastitis

Breast Cancers in Young Women Breast cancers in young women (< 40 years of age) and the very young women (< 30 years of age) comprise an estimated 4–7% of all breast cancers [35]. According to the United States Surveillance, Epidemiology, and End Results (SEER) Program data, up to 10.3% of breast cancers are diagnosed in women less than or equal to 45 years of age [36]. A significant subset of breast cancers in this age group includes pregnancy-associated breast cancer (PABC), defined as a breast cancer diagnosed during pregnancy or within one year postpartum. The incidence of PABC is 1 in 3,000 to 10,000 pregnancies [13]. PABC accounts for 3% of all breast cancers and may be seen in association with genetic mutations. Because of the special circumstance of pregnancy, imaging and treatment considerations need modifications that consider multiple interdependent variables.

Multiple reasons exist for the observed poor prognosis of breast cancers in young patients. These include delays in diagnosis, which contribute to potentially larger tumors, lymphovascular invasion, lymph node metastases, as well as the more frequent occurrence of biologically aggressive cancer subtypes such as triple-negative breast cancers (TNBC) and human epidermal growth factor 2 (HER2) positive breast cancers [37]. Even among luminal cancers, young patients have a poor prognosis compared to stage-matched older patients [38].

Breast cancers demonstrate variable imaging appearances based on the molecular subtype [39]. The classic features of an irregular mass with spiculated margins describe the ER

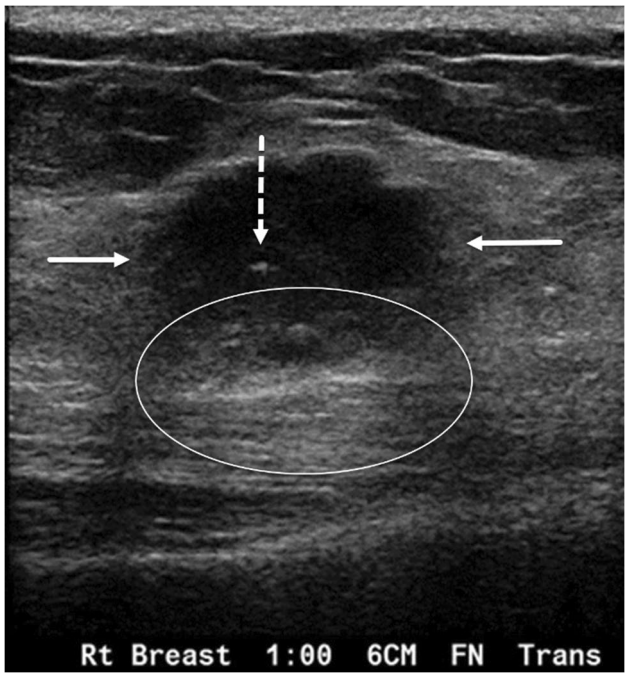

Fig. 7 32-year-old with BRCA 1 mutation presented at 38 weeks gestation with a triple-negative breast cancer with lymph node metastasis. Three months earlier while pregnant, the patient had a negative screening ultrasound, however a 2.1 cm lobulated, hypoechoic mass (arrows) with posterior acoustic enhancement (circle) and internal calcifications (vertical dotted arrow) had developed during pregnancy

positive/HER2 negative luminal cancers. In contrast, TNBCs may have a relatively benign appearance compared to luminal cancers [40] (Fig. 7). A heterogeneous, complex cystic mass with posterior acoustic enhancement may result from necrosis in rapidly enlarging tumors and may mimic breast abscesses or galactoceles (Fig. 8). The ultrasound descriptive terminology of parallel orientation has been described in 58% of PABC patients [41]. Depending on the presentation, there may be associated architectural distortion, nipple retraction, skin thickening, increased trabecular density and breast enlargement, or lymphadenopathy. As these imaging findings are encountered, an image-guided biopsy helps expedite a diagnosis, thereby allowing for initiation of treatment without delays in care.

Unique imaging and treatment considerations revolve around optimizing health outcomes for both the pregnant woman and her unborn child, including future fertility preservation goals [42, 43]. As with non-PABC breast cancers, treatment is multidisciplinary and may include neoadjuvant chemotherapy, surgery, adjuvant radiation or chemotherapy, targeted antibodies to HER2 receptors, and endocrine therapy after delivery. Particularly for TNBC, inflammatory breast cancers, large cancers, and those with lymph node metastases, neoadjuvant chemotherapies are commonly employed in current breast cancer treatment models.

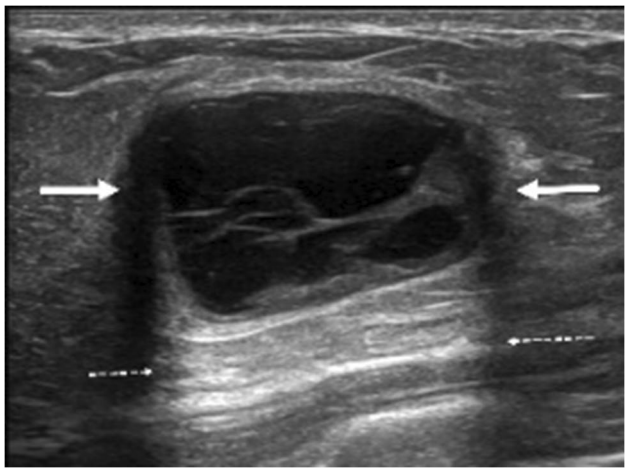

Fig. 8 32-year-old presented for delayed evaluation of a palpable mass related to a triple-negative breast cancer, manifesting as a 3.1 cm oval, circumscribed, partially cystic mass (arrows) with posterior acoustic enhancement (dashed arrows). Because this was first noted during breastfeeding, differential consideration included a galactocele, however, when aspiration yielded bloody aspirate, a core biopsy was next performed and yielded her malignant diagnosis

Chemotherapy may be safely administered during the second and third trimesters of pregnancy [44, 45]. Surgery is often deferred until the late second and third trimester. Trastuzumab, tamoxifen, and radiation therapy are contraindicated during pregnancy and lactation and therefore are reserved until postpartum after a deliberate decision is made to not nurse the newborn.

Conclusions

Because young women (< 40 years of age) are below the age at which routine annual screening is recommended, breast imaging is generally only performed upon presentation of a clinical concern. While most breast pathologies are benign, when breast cancers occur in young women, they are often associated with a poor prognosis. Reasons for this are multifactorial but appear to be related to aggressive cancer subtypes, advanced stage at presentation, as well as due to the young age. Pregnancy-associated breast cancers are a special subset of breast cancers occurring in young women. Imaging and treatment considerations often need to be modified and personalized due to the pregnancy. The multidisciplinary treatment of breast cancers in young women encompasses considerations of future family planning goals as well as the imminent concerns related to the health outcomes for the pregnant woman as well as her unborn child. In general, young women may be less compliant with endocrine therapies for ER-positive cancers, and systemic treatments must

be tailored to the individual based on the pregnancy status and gestational age. Accordingly, the timing of breast surgery and labor induction may require coordination of care.

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Declarations

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

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