The breast during pregnancy and lactation

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Learning objectives

During pregnancy and lactation, the breast can be affected by a variety of specific disorders, including benign disorders closely related to physiologic changes, inflammatory and infectious diseases, benign and malignant tumors. Pregnancy and lactation represent unique physiologic states that induce notable changes in the mammary glands in response to hormonal stimulation. Tumors or disorders affecting the breasts in pregnant or lactating women are usually the same as those observed in nonpregnant women (1). However, some breast disorders are specific to pregnancy and lactation. Most breast tumors diagnosed during pregnancy and lactation existed beforehand but manifest during this time due to changes or growth that take place in some of them in this setting. Unfortunately, the assessment of breast disorders related to pregnancy and lactation has received scant attention in the radiology literature (1).

Although most disorders related to pregnancy and lactation are benign, so-called pregnancy associated breast carcinoma (PABC) represents up to 3% of all breast malignancies (1). PABC constitutes a particularly dramatic situation that deserves special consideration because it involves both the mother and the fetus. The diagnosis of breast cancer during pregnancy and lactation is difficult both clinically and radiologically due to the striking hormone-induced changes that occur in breast tissue (1). A delay in diagnosis secondary to these intrinsic difficulties or to a lack of awareness of the possibility of breast cancer in this setting has been postulated as the major factor responsible for the advanced stage and poor prognosis that, unfortunately, are associated with PABC. Therefore, it is crucial that both gynecologists and radiologists be aware of this possible diagnosis.

Purposes

1. Recognize breast disorders related to pregnancy and lactation and the radiologic-pathologic changes that can occur in these disorders in this setting.

2. Describe the most common radiologic manifestations of each disorder and the value of different diagnostic procedures.

3. Discuss the most common and relevant clinical and radiologic manifestations of pregnancy-associated breast carcinoma.
Background

It is not infrequent for women to present to their physicians with a breast problem during pregnancy or within 1 year of delivery. Changes occurring in the breast during these physiological states make clinical and radiological evaluation of these patients challenging. Improving understanding of varied breast problems and their imaging appearance on multiple modalities is essential to ensure optimal management of these patients. In the first and second trimester, there is proliferation and differentiation of the lobules, alveoli and lactiferous ducts, the alveolar epithelium becomes secretory. With rising serum prolactin during the third trimester, the milk-producing cells continue to differentiate and colostrum eventually fills the alveoli and milk ducts prior to delivery. These proliferative changes result in bilateral breast enlargement and increased overall density of the breast tissue on imaging. Following delivery, the lactogenic effect of prolactin results in a substantial increase in milk production. All of these physiological changes directly impact the imaging appearance of the breast on mammography, ultrasound and magnetic resonance imaging (MRI) thereby complicating evaluation of pregnant and/or lactating patients, presenting with a breast problem (2).
Findings and procedure details

Imaging protocols and challenges

Radiological evaluation varies depending upon the age of the woman, her pregnancy and lactational status. Subsequent to a clinical history and thorough physical examination, patients are frequently imaged to determine whether there is an underlying abnormality to account for the patient's symptoms. For pregnant and lactating women under the age of 30 years, ultrasound is the initial imaging test of choice given the lack of radiation exposure. Mammogram could be considered in these patients if ultrasound is negative or it reveals indeterminate, suspicious or no findings (3). Lactating women over 30 years of age are typically imaged using both mammography and ultrasound. In an effort to reduce the overall breast density, lactating patients are encouraged to express milk immediately prior to imaging. In a pregnant patient, mammography should be performed, if ultrasound reveals a suspicious finding or if biopsy of a solid lesion reveals malignancy. A complete evaluation of a pregnant patient with a lump should not be delayed until after delivery, because of fear of radiation. Without shielding the abdomen, the dose to the fetus from a four-view mammogram is 0.4 mrad, much less than background, and with shielding, the risk is not significant and safe to the fetus (1, 3). Fetal malformations are known to occur at a dose exceeding 10 rads (3).

Normal imaging appearance of the breast in pregnancy and lactation

The imaging appearance on mammography, ultrasound and MRI is variable depending upon the duration of pregnancy and/or lactating state. An overall diffuse increase in breast density accompanied by breast enlargement is commonly seen on mammography. Given increased density of the breast the sensitivity of mammography is low (30 % for dense breast compared with 80 % for fatty breast), and cancer detection may be somewhat difficult (4). Murphy et al (5) evaluated patients with false-negative mammograms and symptomatic cancer, and found that 78 % of the mammographically occult lesions were in women with heterogeneously or extremely dense tissue.

Breast diseases in the pregnant and lactating patient

A wide variety of benign and malignant breast problems may be encountered in these patients. Due to physiological changes, the most commonly encountered problems are lactational change/lobular hyperplasia, lactational adenoma and lactational calcifications. Benign entities include galactocele, fibroadenoma, obstructed milk duct, mastitis with or without abscess, hyperplastic intramammary and/or axillary lymph nodes, and granulomatous mastitis. Malignant diseases include pregnancy-associated breast cancer and metastatic disease (6, 7).

Gestational and secretory Hyperplasia (Fig 1)
Microcalcifications secondary to gestational hyperplasia (related to pregnancy) or secretory hyperplasia (related to lactation) may be depicted mammographically. Two different mammographic manifestations have been reported. Microcalcifications are most commonly round, with a diffuse or focal distribution. Less commonly, they have an irregular appearance, a linear distribution, and a branching pattern closely resembling malignancy. The two manifestations can coexist: Round punctate calcifications represent hyperplasia in the lobular acini, whereas linear calcifications correspond to ductal hyperplasia. Microcalcifications secondary to gestational or secretory hyperplasia must be distinguished clinically from a different entity known as pregnancy-like hyperplasia or pseudolactational hyperplasia, which manifests with the same radiologic-pathologic findings in nonpregnant, nonlactating women. Carcinomas arising from preexisting pregnancy-like hyperplastic lesions have been described; to date, however, malignant potentiality has not been described in secretory or lactational hyperplasia (8, 9, 10).

Galactoceles

Galactoceles are the most common benign breast lesions in lactating women, although they more frequently occur after cessation of breast-feeding, when milk is retained and becomes stagnant within the breast. Galactoceles are cysts composed of cuboidal or flat epithelium containing fluid that resembles milk. They are often accompanied by inflammatory or necrotic debris. Biochemical analysis of the material aspirated from galactoceles shows wide variation in the proportions of proteins, fat, and lactose. The cysts form as a result of duct dilatation and are frequently encompassed by a fibrous wall of varying thickness that can be associated with an inflammatory component. Chronic inflammation and fat necrosis can be seen due to cyst leakage. Aspiration is both diagnostic and therapeutic, yielding fluid milk when performed during lactation and more thickened milk fluid when obtained from older lesions after lactation has ended. The mammographic appearance of galactocele depends on the amount of fat and proteinaceous material present and the density and viscosity of the fluid (11, 12, 13).

Puerperal Mastitis

Infection is uncommon during pregnancy but occurs relatively often during breast-feeding. The organism that most commonly causes infection is *Staphylococcus aureus*, followed by *Streptococcus*. The source is the nursing infant's nose and throat. The infection is due to disruption of the epithelial interface of the nipple-areola complex with retrograde dissemination of the organisms. Usually, the patient has a history of a cracked nipple or a skin abrasion. Milk stasis is an important risk factor, since stagnated milk is an excellent culture medium. *S aureus* infections tend to be more localized and invasive from the onset, so that abscesses tend to occur more frequently, even with prompt antibiotic therapy. Conversely, *Streptococcus* infections often manifest as diffuse mastitis, with focal abscess formation in advanced stages. These organisms can nearly always be cultured from milk. Antibiotic therapy given at an early stage usually controls the infection and stops abscess formation. The administration of amoxicillin-clavulanate or cloxacillin is almost always effective. The aforementioned infections correspond to
the endemic or sporadic type of puerperal mastitis, which in fact accounts for the great majority of cases of mastitis. Conversely, the epidemic type of puerperal mastitis is much less common but can be life threatening and is usually related to virulent methicillin-resistant \textit{S aureus}. Mammography is not usually required in lactational mastitis unless malignancy is suspected. No significant abnormalities are usually found, although in severe mastitis, skin and trabecular thickening from breast edema can be depicted. Abscesses can manifest as suspect, ill-defined masses. US plays an important role in the diagnosis and treatment of mastitis if abscess formation is suspected (14, 15, 16).

**Lactating adenoma**

Lactating adenoma is a benign breast lesion that is thought to occur in response to the physiologic changes that characterize pregnancy and lactation. The true nature of the tumor remains controversial. Some authors suggest that lactating adenoma is simply a variant of fibroadenoma, tubular adenoma, or lobular hyperplasia that has undergone certain histologic changes owing to the physiologic state. At histologic analysis, lactating adenomas are composed of compact aggregates of lobules that exhibit secretory hyperplasia and are separated by delicate connective tissue. At gross examination, they are well circumscribed but noncapsulated. Secretory hyperplasia in the lesion is histologically similar to the physiologic changes found in the surrounding parenchyma. Lactating adenomas characteristically regress spontaneously after pregnancy and lactation. Like fibroadenomas, lactating adenomas are prone to develop infarction. Curiously, the coexistence of lactating adenoma and malignancy has recently been reported. Lactating adenomas usually manifest radiologically as benign masses that are indistinguishable from fibroadenomas. Radiolucent or hyperechogenic areas representing the fat content of the milk secondary to lactational hyperplasia can be seen at mammography and US, respectively, and constitute a particularly useful diagnostic sign. However, a few tumors can show features that can mislead from a diagnosis of malignancy, such as irregular masses, microlobulated margins, posterior acoustic shadowing, pronounced hypoechogenicity, and structural heteroechochogenicity. Some of these confusing patterns may be due to infarction, as occurs in fibroadenomas (17, 18, 19).

**Pseudoangiomatous Stromal Hyperplasia (Fig 2)**

Pseudoangiomatous stromal hyperplasia (PASH) is a benign lesion that is classified as a mesenchymal tumor of the breast. This lesion is likely related to hormone levels, since it is most commonly seen in premenopausal women or women receiving hormonal therapy. However, it also has occurred, albeit rarely, in males and in elderly females who were not undergoing hormonal therapy. The clinical spectrum varies from insignificant incidental microscopic changes in the breast to focal palpable or nonpalpable masslike nodules (nodular PASH) (20) to diffuse breast involvement. Nodular PASH is uncommon (21). Nodular PASH usually manifests as a painless, mobile, circumscribed, palpable mass (22, 23). On radiologic images, nodular PASH may be indistinguishable from
fibroadenoma (21). Mammographically, these lesions are usually well defined with a smooth border (24, 25) and do not contain calcifications. However, their margins may be ill defined or partially defined. At US, the lesions are usually seen as well-defined solid masses with hypoechoogenicity or heterogeneous echogenicity and with sound attenuation characteristics varying from posterior enhancement to mild posterior shadowing (24, 26). At US, some large lesions contain numerous lacelike reticular areas with scattered cystic changes (27). Although these linear areas were described previously as echogenic, in some cases the masses contained linear areas that appeared relatively hypoechoic. Similar bright reticular spaces and cystic changes may be seen on T2-weighted MR images. The lesion may have signal that is isointense to that of the surrounding parenchyma on T1-weighted images and may show rapid and persistent or progressive contrast enhancement (27).

**Lactational calcifications**

Benign calcifications are sometimes seen in lactating patients undergoing imaging for a breast problem or for screening. In general, calcifications are not a common mammographic feature of lactational or post-lactational breast. On mammography, these are usually diffuse or regional, predominantly punctate calcifications, and could be bilateral or unilateral. Rarely, the calcifications may be grouped, and in those cases, stereotactic biopsy may be indicated to exclude malignancy. In a series of case reports, all cases had bilateral and diffuse distribution with focal groups, of which some had a linear branching pattern, some had a casting pattern (28) and some diffuse with regional distribution (29). On histology, the calcifications are seen in both ducts and lobules. The small rounded microcalcifications in the lobular acini likely reflect the granular pattern as seen as focal groups, whereas larger calcifications in dilated ducts correspond to the casting pattern on mammography (30). These are possibly related to milk stasis or apoptosis associated with lactation (31).

**Breast abscess (Fig 3)**

Acute bacterial mastitis will either resolve with antibiotic therapy or evolve into an abscess if treatment is delayed or inadequate. Approximately 4.8-11 % of lactation-related mastitis is complicated by breast abscesses (32). Infection is most commonly due to S. aureus (with increasing cases of methicillin-resistant S. aureus MRSA) and Streptococcus. The patient presents with fever, chills, tenderness and breast erythema. Imaging with ultrasound can confirm the diagnosis, provide a means to drain the collection to tailor antibiotic therapy and can be safely used for regular follow-up of abscess. Ultrasound is the modality of choice and typically reveals a complex hypoechoic cystic mass of varied shape, commonly multiloculated with indistinct margins, peripheral vascularity and posterior acoustic enhancement however, there should be no vascularity within the fluid collection (33). Mammography is performed only if unclear of diagnosis and may show signs such as mass, distortion, asymmetric density and skin thickening, which are not specific to cancer. Presence of suspicious calcifications is more specific for cancer (33). Percutaneous drainage combined with antibiotic therapy provides effective treatment.
In some cases multiples drainages are required (33). Warm compresses and frequent breast feeding also help to shorten the duration of symptoms. The presence of mastitis and/or abscess poses no risk to the breast feeding infant. Cessation of breast-feeding is necessary only when treatment with an antibiotic contraindicated for the newborn is prescribed (34). Due to overlap of radiological findings in infection and inflammatory breast cancer, if there is clinical suspicion, strong family history or atypical course breast biopsy or skin punch biopsy should be considered.

**Fibroadenoma (Fig 4, 5)**

It is the most common benign breast tumour in young women. Women typically present with a firm mobile mass. These tumours are hormone sensitive; hence they often enlarge during pregnancy and/or lactation in response to elevated circulating hormones. If during pregnancy the fibroadenoma outgrows its blood supply, it may undergo infarction, in which case patients may present with painful mass. On mammography, fibroadenomas appear well circumscribed, have round or oval shape and may be smoothly lobulated. Coarse popcorn-like calcifications may be seen if the tumour underwent infarction; otherwise, calcifications are quite rare as patients tend to be young in age. On ultrasound, the typical features of a fibroadenomas is round or oval shape, may show homogeneous internal echoes, well-circumscribed margins, pseudo-capsule, absence of posterior acoustic shadowing and normal adjacent breast tissue (17, 19). However, during pregnancy, the appearance can be somewhat atypical with cystic changes, increased vascularity and/or prominent ducts. The presence of atypical features such as microlobulations, irregular margins, heterogeneous echotexture, posterior acoustic shadowing and extensive hypoechogenicity, should lead to percutaneous core biopsy to confirm the diagnosis.

**Malignant Tumors**

**Pregnancy-associated Breast Carcinoma (Fig 6, 7)**

PABC is defined as breast cancer that occurs during pregnancy or within 1 year of delivery. PABC occurs in one out of every 3000-10,000 pregnancies and represents up to 3% of all breast malignancies. The prevalence of this malignancy during pregnancy is exceeded only by that of carcinoma of the uterine cervix. The prevalence of PABC is expected to increase as large numbers of women defer childbearing into the 4th and 5th decades of life (11). Patients with PABC tend to have larger, more advanced neoplasms at diagnosis and a poorer outcome than do other women of the same age with breast carcinoma. More than 50% of patients present with high-grade tumors (35). High rates of inflammatory tumors have also been reported. In addition, more than 50% of patients present with lymph node involvement. The high prevalence of hormone-receptor-negative and HER2/neu-positive tumors supports their aggressive biologic growth pattern (11). Prognosis is poor, a fact that is thought to be partly explained by a tendency of pregnant patients to present at a more advanced stage
than nonpregnant women. However, certain studies have found that pregnancy itself may be an independent predictor of worse prognosis. Worse prognosis likely results from a combination of delayed diagnosis and a more aggressive growth pattern due to the biologic effects of pregnancy. Recurrences are common and usually appear within 2-3 years of diagnosis (11). Patients with PABC almost always present with a palpable mass. Swelling, erythema, and diffuse breast enlargement are less common features that suggest locally advanced carcinoma (35). The radiologic features of PABC do not differ from those of non-PABC. Mammographic sensitivity for PABC is lower in pregnant or lactating patients due to increased glandular density. As previously stated, US constitutes the most appropriate radiologic method for assessing PABC (35). US is also useful in assessing axillary nodes and monitoring the response to neoadjuvant chemotherapy (35). Nevertheless, mammography plays a complementary role in the evaluation of these patients and must always be performed if cancer is suspected, since it can demonstrate features such as malignant microcalcifications, multifocality, multicentricity, or bilaterality that may not be suspected at US alone (35).

Metastatic disease

With a reported incidence of 1.7-6.6 %, metastasis to the breast most commonly occurs from the contralateral breast cancer, lymphoma/leukaemia, melanoma and lung carcinoma (36). Though, any tumour can metastasise to the breast, nonmammary metastatic lesions are rare. Imaging entails targeted ultrasound and diagnostic mammography. Most metastases appear as well-circumscribed masses which lack calcifications, although psammomatous calcifications may be seen if the primary is of ovarian or thyroid origin. Metastatic lesions are more likely multiple and bilateral and are often found in the subcutaneous fat, whereas primary breast cancers develop in glandular tissue. Percutaneous core biopsy permits diagnosis when clinically needed to guide management. Conclusion Substantial physiological changes during pregnancy and lactation make it challenging to evaluate patients presenting with a breast problem. Most findings in pregnant and lactating patients are benign. Ultrasound is the first-line imaging modality for all pregnant women and for lactating women less than 30 years of age. Mammography is indicated in lactating women over 30 years of age and in pregnant women with suspicious findings on the initial ultrasound or with a biopsy diagnosis of breast cancer. An awareness of the imaging features of the various benign and malignant diseases during these physiological states, permits optimal management (36).
Fig. 1: 28-year-old lactating woman presented with palpable mass. Ultrasound shows corresponding solid oval hyper echoic mass. Ultra-sound guided microbiopsy confirmed hyperplastic lobules containing dilated ducts.

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Fig. 2: A 27 weeks pregnant women who presented with left gynecomastia and circumscribed palpable mass (a). (b): Mammography shows asymmetric density with left large circumscribed mass. (c) Ultrasound shows expanded stroma with patchy areas of reduced echogenicity and loss of normal architecture within the affected area of the left
breast. Core biopsy (arrow) was performed and revealed pseudoangiomatous stromal hyperplasia (PASH).

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**Fig. 3:** A 33-year-old lactating woman presenting with inflammation and palpable mass. Corresponding ultrasound shows irregular hypo echoic abscess. Palpation-guided core needle biopsy revealed inflammation consistent. Ultrasound showing hypo echoic irregular abscess

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Fig. 4: A 38 weeks pregnant women who presented with palpable mass. Ultrasound shows corresponding solid irregular hypo echoic mass. Ultra-sound guided micro biopsy was performed and revealed fibroadenoma.

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Fig. 5: Fibroadenoma presenting as palpable mass in 28-year-old lactating woman. Ultrasound shows corresponding solid oval iso echoic heterogeneous mass. Ultra-sound guided microbiopsy confirmed diagnosis of fibroadenoma

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Fig. 6: A 30 year old lactating woman 6 months after delivery was referred to our department for left breast mass diagnosed with invasive ductal cancer. (a): Mammography shows well limited dense opacity in upper lateral quadrant of the left breast (arrow). (b): Ultrasonography: a well defined heterogeneous mass with cystic area (asterix).

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Fig. 7: A 37 year old pregnant woman, G4P3, was diagnosed with invasive ductal cancer of the right breast in the 16 weeks. (a): Mammography revealed a speculated mass (arrow).(b) Ultrasonography shows an unregulated hypoechoic mass (asterix).

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Conclusion

Substantial physiological changes during pregnancy and lactation make it challenging to evaluate patients presenting with a breast problem. Most findings in pregnant and lactating patients are benign. Ultrasound is the first-line imaging modality for all pregnant women and for lactating women less than 30 years of age. Mammography is indicated in lactating women over 30 years of age and in pregnant women with suspicious findings on the initial ultrasound or with a biopsy diagnosis of breast cancer. An awareness of the imaging features of the various benign and malignant diseases during these physiological states, permits optimal management.
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