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REVIEW

Breast cancer screening of pregnant and breastfeeding women with BRCA mutations

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Abstract Screening recommendations for women with *BRCA* mutations include annual breast MRI starting at age 25, with annual mammogram added at age 30. The median age of childbearing in the US is age 28, therefore many *BRCA* mutation carriers will be pregnant or breastfeeding during the time when intensive screening is most important to manage their increased breast cancer risk. Despite this critical overlap, there is little evidence to guide clinicians on the appropriate screening for women with *BRCA* mutations during pregnancy or breastfeeding. Hormonal shifts that occur during pregnancy, the postpartum period, and breastfeeding result in changes to the breasts that may further complicate the sensitivity and specificity of screening modalities. We explore the safety and efficacy of available breast cancer screening modalities, including clinical breast exam, mammogram, breast MRI, and ultrasound among women with *BRCA* mutations who are pregnant or breastfeeding, providing recommendations from the most current published literature and expert opinion.

Keywords PABC · BRCA · Breast cancer screening · Pregnant · Breastfeeding · Breast MRI · Ultrasound · Mammogram · Clinical breast exam

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Introduction

Breast cancer diagnosed during pregnancy or during the postpartum year is categorized as pregnancy-associated breast cancer (PABC). This diagnosis is rare and historically has presented at an advanced stage with poor histologic and prognostic features [1–4]. There is sparse literature concerning PABC with incidence reported at 1 in 3000 births, however there are concerns the incidence of PABC is increasing due to the delayed age of childbearing [2–5]. According to some studies, women with *BRCA* mutations are at an increased risk of PABC, with one study reporting that 25% of women with PABC harbored a *BRCA* mutation [4, 6].

Recent studies have indicated that women with *BRCA* mutations have an average lifetime risk of breast cancer of about 60% [7]. While the breast cancer risk varies throughout a woman's lifetime, the excess risk related to mutations in these genes is most evident during the reproductive years, with *BRCA1* mutations associated with a 3.8% annual risk between ages 25 and 40 and the average of breast cancer diagnosis being 40 [8, 9]. Current imaging guidelines for *BRCA* mutation carriers recommend screening with annual breast MRI starting at age 25, with annual mammogram added at age 30 [10]. This intensive breast cancer screening among women with *BRCA* mutations allows for diagnosis of breast cancer at an earlier stage and there is mounting evidence that it improves overall survival [11, 12].

Given the median age of childbearing in the US is age 28, many women with *BRCA* mutations will be pregnant or breastfeeding during the time that intensive screening is initiated and this period of intensive screening is an important component to the management of their increased cancer risk [13]. There is evidence for the safety and efficacy of breast screening modalities among young women with

BRCA mutations [10, 14, 15], however, decisions regarding screening among women with *BRCA* mutations who are pregnant or breastfeeding remain a difficult clinical challenge with little evidence for guidance.

In addition to the difficulties faced in screening *BRCA* mutation carriers, the augmented breast tissue and accompanying changes in vascular flow associated with pregnancy and breastfeeding cause increased mammographic density and MRI background parenchyma enhancement. These changes in the breast cause difficulty in interpreting standard breast screening techniques [16].

Performing clinical trials of breast screening modalities among pregnant or breastfeeding women with BRCA mutations is difficult because of safety and feasibility, thus clinicians must extrapolate from little existing data and utilize expert opinion. We explore the safety and efficacy of breast cancer screening modalities among women with *BRCA* mutations who are pregnant or breastfeeding and offer our clinical recommendations for this population.

Case report

A 32 year-old woman, Katie, is seen for genetic counseling and reports that her maternal aunt had breast cancer at age 45 and Katie's mother was recently diagnosed with ovarian cancer at age 50. Her mother tested positive for a *BRCA1* mutation. Katie and her two sisters are tested for the familial mutation. All of them are found to carry the mutation and none have had breast cancer screening to date. When Katie's genetic test results return, she is 14 weeks pregnant with her second child, with plans to breastfeed for up to a year postpartum, and then plans to have at least one more child as soon as possible. Given her fertility plans, there could be little opportunity for breast cancer screening between pregnancies and breastfeeding.

Clinical breast exam

Clinical breast exam (CBE) is safe to use for evaluation of high-risk women during pregnancy or breastfeeding, or at any time during a woman's lifespan. There are no dedicated studies of CBE among high-risk women who are pregnant or breastfeeding, but in one study among high-risk women the sensitivity of CBE was reported to be low at 17.8% [17]. However, the specificity of CBE among high-risk women was reported to be 98.1% [17], thus an abnormal CBE should be promptly acted upon [18, 19]. Although there are no direct studies to assess CBE techniques, CBE is likely to be more sensitive in breastfeeding women if they breastfeed or pump prior to the examination. We recommend that high-risk women undergo CBE every 6 months during pregnancy and breastfeeding.

Mammogram

Among (non-pregnant) women at high risk for breast cancer, screening mammography alone has a diminished sensitivity compared to the average risk population, and has been reported to be as low as 25–50% [15, 17, 20, 21]. In the general population, there is a small risk of radiation-induced breast cancer from screening mammogram, estimated to be found in about 1 woman with fatal breast cancer per every 100,000 screening mammograms [22]. The risk that radiation exposure during mammogram may increase the risk of breast cancer among young women with *BRCA* mutations, due to the diminished ability to repair DNA damage, has led to the recommendation that screening mammograms no longer will be performed in women with *BRCA* mutations under age 30 [23]. Further, the risk from radiation could theoretically be greater during pregnancy and breastfeeding because of increased breast epithelial proliferation.

There is little data regarding the use of mammogram as a screening tool for either average- or high-risk women who are pregnant or breastfeeding. Given the alterations in breast density and vascular flow during pregnancy and breastfeeding, the radiographic interpretation is more difficult [16], which raises the concern for an increase in false positives with routine screening. However, clinical experience among our group suggests that in some patients, especially during extended breastfeeding, the mammographic density may not be greatly increased compared to baseline. Additionally, there is risk to the developing fetus posed by radiation from mammogram, although difficult to quantify [18]. Given the radiation risks to the mother and the fetus, and the potential for false positives, in the absence of a palpable mass, the risks from screening mammogram during pregnancy outweigh the benefits.

Although mammography is not advised as a screening tool during pregnancy, when a woman has a palpable mass, the benefits of mammogram then outweigh the risks and it has excellent utility even in a pregnant or breastfeeding woman. In a retrospective review, Robbins et al. described that among 155 pregnant, breastfeeding, and postpartum women with suspicious breast lesions, the sensitivity of mammography was 100% with specificity noted at 93%, with a positive predictive value of 40% [24]. If PABC is clinically suspected, mammogram is advised even in the pregnant or breastfeeding mother [18, 25]. The ability of modern mammogram to visualize abnormalities in heterogeneously or extremely dense breast tissue during

breastfeeding [18, 24] may lead to an evolution of its use as a screening tool during breastfeeding.

Although all studies available in our literature search were conducted with standard four view mammography, there are new techniques that could prove to be more useful among young high-risk women. New techniques, such as 3D/tomosynthesis mammography, may provide increased benefit for high-risk women, however, this approach may come at the cost of increased radiation exposure, and the safety and efficacy of these techniques must be investigated before clear recommendations can be given.

Based on extrapolations from existing literature and expert opinion, our recommendation is that high-risk women should not undergo routine screening mammogram during pregnancy for safety concerns regarding additional radiation exposure to the fetus. However, in breastfeeding women above age 30, mammogram screening may be resumed, especially in women with plans to breastfeed for more than 6 months postpartum, with the understanding that the positive predictive value may be decreased relative to the patient's baseline. If a woman elects to undergo screening mammogram while still breastfeeding, we recommend that the woman breastfeed or pump immediately before obtaining the mammogram in an effort to reduce the mammographic density. Alternatively, if the patient is planning to breastfeed for less than 6 months postpartum, or is planning to discontinue breastfeeding imminently, it may be reasonable to wait 6–8 weeks after cessation of breastfeeding to re-initiate mammogram screening to allow improved breast visualization.

Breast MRI

Breast MRI is the most accurate screening tool among women at increased risk for breast cancer with a sensitivity of 71.1–100% and specificity of 89% [15, 17, 20, 21]. Breast MRI also has an excellent safety profile among non-pregnant and breastfeeding women because it does not utilize ionizing radiation, acknowledging the requisite use of IV gadolinium administration [18]. During pregnancy, however, both the US Food and Drug Administration and the European Society of Urogenital Radiology recommend against the routine use of gadolinium, unless essential diagnostic information is required, and after informed consent is obtained, due to animal studies demonstrating teratogenic effect, albeit at high and repeated doses [26–28]. Thus, although no human studies have ever demonstrated harm from fetal exposure to gadolinium, breast MRI during pregnancy is not recommended for screening.

In the breastfeeding woman, a negligible amount of gadolinium is excreted in the breast milk and further a minimal amount is absorbed by the child's gut, [29–32] thus the American College of Radiology recommends continued and uninterrupted breastfeeding after gadolinium exposure [33]. Breast MRI presents little safety concern for the breastfeeding woman or her child. There are diagnostic challenges of using this modality to image the lactating breast (changes in vascular flow, increased fibroglandular tissue, T2 hyperintensity, and dilation of the milk ducts), and no studies have evaluated the efficacy of MRI as a screening modality among high-risk women who are breastfeeding [16, 34]. However, in a series of seven breastfeeding patients, five of whom had known invasive carcinomas, who underwent breast MRI, all five of the known malignancies were visible as a contrast-enhancing mass or rim-enhancing mass on MRI, despite the physiologic changes of breastfeeding that are known to limit sensitivity [35].

We recommend that women not undergo screening breast MRI during pregnancy. However, in the postpartum period, breast MRI with gadolinium is safe, and does not require interruption to breastfeeding. If a woman plans to breastfeed more than 6 months postpartum a screening breast MRI is a reasonable option in this time period. If a woman plans to breastfeed for less than 6 months postpartum, or plans to discontinue imminently, then it is our opinion that it is reasonable to wait 6–8 weeks after cessation of breastfeeding to resume screening.

Ultrasound

Of the breast imaging modalities, ultrasound is the safest due to its lack of ionizing radiation or use of contrast. However, breast ultrasound is limited by its dependent nature upon the skill and experience of the technician, creating interoperator variability. In addition to its safety profile in the pregnant and breastfeeding woman, ultrasound is excellent at detecting PABC. When a palpable mass is noted, ultrasound sensitivity is reported at 100% with specificity at 86% [24, 36]. However, among the general population, ultrasound is a poor screening tool with a sensitivity of 29–52% [15, 21, 37]. There is little data about the sensitivity of screening ultrasound among women at high risk of breast cancer, but it can be extrapolated that the sensitivity of ultrasound is inferior to either mammogram or breast MRI. Breast ultrasound for screening of high-risk women also has the lowest specificity of the breast imaging modalities, at 90.5% [21]. Furthermore, ultrasound does not improve the sensitivity of breast cancer detection when combined with MRI in the screening of high-risk women [15, 21]. Many clinicians reasonably consider ultrasound for

breast cancer screening among high-risk women during pregnancy or breastfeeding because of its excellent safety profile. However, we feel that the minimal benefit of screening ultrasound among high-risk women (with a positive predictive value of 17.6) and the increased false positives cause the risks of screening ultrasound during pregnancy and breastfeeding to outweigh the benefits. We urge further investigation into screening breast ultrasound among pregnant and breastfeeding women before this approach is adopted widely [21, 24].

Other breast cancer predisposing mutations

For women who are considered at high risk of breast cancer because of other genetic mutations, such as *TP53, PTEN, CDH1*, and *PALB2* or because of a significant early family history of breast cancer without an identified genetic mutation, we recommend a similar approach to breast imaging during pregnancy and breastfeeding as we have for women with *BRCA* mutations, except beginning screening at the appropriate age commensurate with the risk increase for each mutation [10, 38–40]. For women at high risk, breast imaging with mammogram or breast MRI should be avoided during pregnancy, however during breastfeeding, depending on the expected duration of breastfeeding as detailed above, mammogram and breast MRI should be considered, especially if the woman has never undergone breast imaging.

Moderate risk genetic mutations, such as *ATM, CHEK2*, and *NBN*, cause an increase in breast cancer risk when women are older (with screening recommended to begin at age 40) [10, 38, 41], thus these women are less commonly pregnant or breastfeeding during the time period breast screening is most important. However, if a woman with a moderate risk mutation was pregnant or breastfeeding during a time that breast cancer screening is important, we would recommend that breast imaging with mammogram or breast MRI be avoided while she is pregnant but could be considered while she was breastfeeding, depending on the expected duration of breastfeeding and the clinical scenario.

Case report recommendations

Katie, with a *BRCA1* mutation, is 14 weeks pregnant and plans to be either pregnant or breastfeeding for several years.

We recommend that she maintain breast awareness, continue with CBE every 6 months, and if she plans to breastfeed for six or more months, we would offer either mammogram or breast MRI at about 6 months postpartum, immediately after emptying her breasts by either pumping or breastfeeding to allow better breast tissue visualization. Alternatively, if she plans to breastfeed for less than 6 months or presents to her visit with plans to imminently discontinue breastfeeding, we recommend waiting until 6–8 weeks after cessation of breastfeeding, and then offer either mammogram or breast MRI.

Conclusions

Before pregnancy

When a woman with a *BRCA* mutation is considering or actively trying to become pregnant, ensuring her breast cancer screening is important, since it will be a year or more before she can obtain breast imaging if she becomes pregnant. We recommend that if her breast cancer screening is up to date then she need not undergo additional screening. However, if she fails to become pregnant in the ensuing months and it has been 6 months since her prior breast imaging, she should undergo either breast MRI or mammogram, whichever of the breast imaging modalities she is due for. If a woman is planning to become pregnant during, or soon after cessation of breastfeeding, for whom there will not be a long window of time between breastfeeding and pregnancy, we suggest obtaining both mammogram and breast MRI toward the end of breastfeeding and before the next pregnancy. If there is likely to be a longer window of time with no pregnancy or breastfeeding, we suggest breast MRI initially followed by mammogram 6 months later. Importantly, any woman who is not using a regular and reliable method of contraception should be at least questioned if she could be pregnant at the time of breast imaging, and if there is any uncertainty about her pregnancy status, a pregnancy test should be obtained before breast imaging is performed.

Pregnancy

For women with *BRCA* mutations who are pregnant, we recommend breast awareness and CBE every 6 months and to defer screening with mammogram or breast MRI due to mostly theoretical risks to the fetus, but also due to poor visualization of the breast during pregnancy, placing women at risk for false positives. Breast ultrasound and mammogram have a clear role in the evaluation of a palpable mass detected in a pregnant woman, with biopsy of suitably identified lesions for the detection of cancer.

Breastfeeding

In general, we encourage all women to breastfeed since it may reduce their risk of breast cancer [42, 43] and offers many health benefits for the infant. For women with *BRCA* mutations who are breastfeeding, we recommend breast awareness and CBE every 6 months. There is no clear evidence of the efficacy of mammogram or breast MRI as screening tools during this time period. However, if a woman has never had breast screening, or is outside the recommended screening interval, we recommend obtaining a breast MRI if the woman plans to continue breastfeeding. Alternatively, if the woman plans to breastfeed less than 6 months postpartum, or has imminent plans to discontinue breastfeeding, it is reasonable to wait 6–8 weeks after weaning to re-initiate breast imaging with either mammogram or breast MRI.

More data about the use breast imaging modalities during pregnancy and breastfeeding to guide clinical care among this growing population of unaffected women with *BRCA* mutations are needed. We propose that performing a clinical trial to examine the use of screening breast MRI or mammogram among high-risk women of appropriate age during breastfeeding is both safe and warranted.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. All authors have submitted signed documentation to this effect.

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