Effect of the Menstrual Cycle on Background Parenchymal Enhancement in Breast MR Imaging

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Purpose: We assessed the influence of the menstrual cycle on background parenchymal enhancement (BPE) of the breast in the early and delayed phases of dynamic magnetic resonance (MR) imaging and the optimal timing of MR imaging of the breast in Japanese women.

Material and Methods: We reviewed dynamic MR images of 165 consecutive women with regular menstrual cycles and divided the women into 4 groups by week of the menstrual cycle: 32 in Week One (Days 1 through 4 of the menstrual cycle); 46 in Week 2 (Days 5 through 12); 49 in Week 3 (Days 13 through 20); and 38 in Week 4 (Days 21 through 30). We qualitatively evaluated BPE of the whole breast in the early and delayed phases of MR imaging; categorized enhancement as minimal, mild, moderate, or marked; and calculated the rate at which signal intensity increased (\(\frac{SI_{\text{post}}}{SI_{\text{pre}}}/SI_{\text{pre}}\)) in regions of interest from the early and delayed phase to the before contrast administration phase to assess BPE quantitatively.

Results: In both the early and delayed dynamic MR phases, BPE was significantly more extensive and stronger in Week 4 than Week 2 (\(P<0.01\)). Throughout the menstrual cycle, BPE was significantly stronger in the delayed phase than in the early phase in both qualitative (Week One, \(P=0.0002\); Weeks 2 through 4, \(P<0.0001\)) and quantitative (Weeks One through 4, \(P<0.0001\)) assessments.

Conclusion: The optimal time to perform dynamic breast MR imaging in premenopausal Japanese women was during Days 5 through 12 of the menstrual cycle.

Keywords: background parenchymal enhancement, breast, dynamic contrast-enhanced magnetic resonance imaging, menstrual cycle

Introduction

Magnetic resonance (MR) imaging has become increasingly important in breast imaging in the past decade, concomitant with technical and instrumental improvements.1–4 Dynamic MR imaging depicts most malignant lesions as well enhanced lesions.2,3 However, uptake of contrast medium is found in benign lesions and normal parenchymal tissue as well as malignant lesions. Strong background parenchymal enhancement (BPE) in the breast would make interpretation of MR imaging difficult.1,4–6

The phase of the menstrual cycle is well known to affect uptake of contrast medium,7–9 and the recent European Society of Breast Imaging (EUSOBI) guideline recommends the optimal timing of breast imaging for premenopausal women as between the fifth and twelfth day after the start of the menstrual cycle.10 However, there has been no precise study to validate the EUSOBI guideline. In Japan, nearly half of patients with newly diagnosed breast cancer

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are premenopausal women, and the optimal timing of breast MR imaging in these women is important.

In addition, previous studies primarily assessed the BPE of dynamic MR imaging using the delayed dynamic phase because of the limitations of MR units and techniques. Detailed assessment of BPE, especially in the early dynamic phase, seems very important in evaluating the effect of BPE on the detection and staging of breast cancer.

We evaluated the effect of the menstrual cycle on the uptake of contrast medium by breast parenchymal tissue and sought to validate the recommended EUSOBI breast MR imaging guidelines using dynamic MR imaging in both the early and delayed phases for Japanese women.

Materials and Methods

Patients

Between September 2009 and December 2010, 780 women underwent breast MR imaging in our institution after they completed questionnaires about their past history of breast disease, hormonal medication, and menstrual cycle status. Of the 780 women, we enrolled 165 consecutive premenopausal women in this study. Exclusion criteria included past history of breast surgery, hormonal therapy at the time of breast MR imaging, irregular menstrual cycle, or postmenopausal status. In accordance with our institutional review board guidelines, all patients provided their written, informed consent prior to MR examination.

All 165 patients (aged 24 to 51 years, mean age 39.2) had regular menstrual cycles (26 to 30 days, average 28.3 days) and underwent MR examination before biopsy to evaluate the nature and extent of lesions detected on diagnostic mammography (n = 76) and/or ultrasonography (n = 109). All breast MR imaging findings were reported according to the level of suspicion of malignancy based on the lexicon of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). In the 165 patients, 16 lesions of 16 patients were classified as BI-RADS category 5 on MR imaging and biopsied, and 15 (94%) were malignant; 22 lesions of 22 patients were classified as BI-RADS category 4, 14 were biopsied, and four (18%) were malignant; 63 lesions of 63 patients were classified as BI-RADS category 3, 35 were biopsied because of abnormalities on mammography and/or ultrasonography, and one (2%) was malignant. Lesions of the other 64 patients were considered benign and monitored for at least one year.

The 165 patients were divided into 4 subgroups according to the week of their menstrual cycle based on the EUSOBI MR imaging guideline: 32 in Week One (Days one through 4), average age 39.4 years; 46 in Week 2 (Days 5 through 12), average age 39.4 years; 49 in Week 3 (Days 13 through 20), average age 39.2 years; and 38 in Week 4 (Days 21 through 30), average age 38.6 years.

MR imaging

MR imaging was performed with a 1.5-tesla system (Avanto; Siemens Medical Solutions, Erlangen, Germany). All patients were imaged in the prone position with both breasts placed into the 4-channel, phased array dedicated breast coil.

Dynamic MR imaging using a 3-dimensional, fat-suppressed, volumetric interpolated breath-hold examination (VIBE) sequence with parallel acquisition was obtained before and 3 times after bolus injection of gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) (0.1 mmol/kg at 2 mL/s) followed by 20-mL saline flush using an automatic injector (Spectris Solaris; Nihon Medrad, Osaka, Japan). Bilateral breasts were examined in the transverse plane on first-phase dynamic images acquired at 60 s, second-phase dynamic images acquired at 130 s, and third-phase dynamic images acquired at 360 s. The dynamic MR imaging parameters were: repetition time (TR)/echo time (TE), 4.67/2.38 ms; flip angle, 15°; field of view, 320 mm; matrix, 384×384; receiver bandwidth, 540 Hz/Px; slice thickness, 0.8 mm; and time of acquisition, 70 s.

Image interpretation

For qualitative assessment of dynamic MR imaging, 2 experts in breast imaging, a radiologist (G. M.) with 8 years’ experience in breast MR diagnosis and a radiological technologist (K. M.) with 10 years’ experience in breast imaging, who were blinded to information about the patients’ menstrual cycles, independently reviewed all MR images.

The ratio of enhanced area to volume of normal parenchymal tissue was classified in the global assessment of BPE and categorized on the basis of the proposed BI-RADS criteria as minimal (<25% enhanced normal tissue), mild (25 to 50%), moderate (50 to 75%), or marked (>75%) (Fig. 1). For each patient, second-phase images (early, acquired 130 s after injection of contrast medium) and third-phase images (delayed, acquired 360 s after contrast injection) were assessed. The 2 reviewers resolved any difference in analysis results by consensus reading.

For the quantitative assessment of BPE, the most enhanced part of the normal parenchymal tissue
was chosen as a region of interest (ROI) on the coronal section, which was reconstructed from the dynamic transverse images on an interactive workstation (Aquarius; TeraRecon Inc., San Mateo, CA, USA). The ROI was placed carefully using information from clinical, mammography, ultrasonography, and MR examinations to avoid defined enhancing breast lesions. The mean ROI size was 6.3 pixels (range, 3 to 15 pixels).

The increasing rate of signal intensity (SI) of the ROI was calculated on the early and delayed phases using the equation (SI post – SI pre)/SI pre, where SI pre is the signal intensity before contrast administration and SI post, intensity after contrast administration.

**Statistical analysis**

BPE of the early and delayed phases of dynamic MR imaging in each menstrual cycle was compared using the Mann-Whitney U test on both qualitative and quantitative assessments. To compare BPE among the 4 weeks of the menstrual cycle for each early and each delayed phase of dynamic MR imaging, Kruskal-Wallis and Steel-Dwass tests were used on both qualitative and quantitative assessments. All statistical analyses were performed using Microsoft Excel 2010 spreadsheets. \( P<0.05 \) was considered significant difference.

**Results**

**Comparison of BPE between the early and delayed phases of dynamic MR imaging**

Figure 2 summarizes the results of qualitative assessment of BPE on early and delayed dynamic MR phases in each week of the menstrual cycle. Throughout all menstrual cycle weeks, BPE was significantly more extensive in the delayed than early phase (Week One, \( P=0.0002 \); Weeks 2, 3, and 4, \( P<0.0001 \)). In the quantitative assessment, the increasing rate of SI of BPE was significantly greater in the delayed than early phase throughout all men-
Fig. 2. Qualitative assessment of background parenchymal enhancement: comparison between early and delayed dynamic magnetic resonance (MR) imaging phases in each week of the menstrual cycle. (a) Week One, Days 1 through 4 of the menstrual cycle. (b) Week 2, Days 5 through 12. (c) Week 3, Days 13 through 20. (d) Week 4, Days 21 through 30. All P values were calculated using the Mann-Whitney U test.

Table. Increasing rate of signal intensity at early and delayed phase by menstrual cycle week

| Menstrual cycle | Early phase (%) | Delayed phase (%) | P value |
|----------------|-----------------|-------------------|---------|
| Week 1 (n = 32) | 38.28 ± 24.99   | 71.95 ± 36.60     | <0.0001 |
| Week 2 (n = 46) | 39.52 ± 26.03   | 70.88 ± 40.26     | <0.0001 |
| Week 3 (n = 49) | 54.92 ± 34.68   | 78.77 ± 40.89     | <0.0001 |
| Week 4 (n = 38) | 69.70 ± 40.57   | 99.94 ± 47.73     | <0.0001 |

The corresponding mean values and standard deviations of the signal intensity (SI) increasing rate of background parenchymal enhancement (BPE) are given for comparison at the early and delayed phases in each week of the menstrual cycle. All P values were calculated using Mann-Whitney U test.

The results of qualitative assessment of BPE differed significantly among the respective weeks (One to 4) of the menstrual cycle (P<0.0001). During Week 2, no cases were classified as having marked enhancement, and 24 (52%) of 46 patients showed minimal enhancement. In contrast, during Week 4, many cases showed marked (2 of 38, 5%) or moderate (13 of 38, 34%) enhancement. BPE was significantly weaker in Week 2 than Weeks 3 (P<0.05) and 4 (P<0.01) (Fig. 3a, continuous line). There was also significant difference between Weeks One and 4 (P<0.01, Fig. 3a, dashed line). Delayed phase (Fig. 3b)
The results of qualitative assessment of BPE also differed significantly among the respective weeks (One to 4) of the menstrual cycle ($P=0.0112$) in the delayed phase.

During Week 4, enhancement was classified as moderate or marked in 28 of 38 patients (74%); in particular, 18 of 38 (47%) showed marked enhancement. BPE differed significantly between Weeks 2 and 4 ($P<0.01$; Fig. 3b, continuous line) but not between other weeks of the menstrual cycle.

**Quantitative assessment**

**Early phase (Fig. 4a)**

The results of quantitative analysis of the increasing rate of SI of BPE among weeks of the menstrual cycle differed significantly ($P<0.0001$).

BPE was significantly weaker in Week 2 than Weeks 3 ($P<0.05$) and 4 ($P<0.01$) (Fig. 4a, continuous line) and in Week One than in Weeks 3 ($P<0.05$) and 4 ($P<0.01$) (Fig. 4a, dashed line), and there was no significant difference between Weeks One and 2. Therefore, BPE was significantly weaker in the first half of the menstrual cycle (Weeks One and 2) than in the second half of the menstrual cycle (Weeks 3 and 4).

**Delayed phase (Fig. 4b)**

The results of quantitative analysis of the increasing rate of SI of BPE among weeks of the menstrual cycle differed significantly ($P<0.0001$).
creased rate of SI of BPE among the weeks of menstrual cycle weeks differed significantly ($P < 0.0001$).

Week 4 showed a significantly higher increasing rate of SI than any other menstrual cycle week (Weeks One and 4, $P < 0.01$; Weeks 2 and 4, $P < 0.01$; Weeks 3 and 4, $P < 0.05$; Fig. 4b, continuous line).

**Discussion**

We classified patients into 4 subgroups according to the week of their menstrual cycle following the EUSOBI MR imaging guideline. In Week 2 (Days 5 through 12 of the menstrual cycle, the recommended optimal timing for breast MR imaging), both qualitative and quantitative assessment showed the weakest BPE compared to BPE in the other 3 weeks of the cycle in both the early and delayed phases. Inversely, BPE was extensive and strong during the second half of the menstrual cycle. Especially in Week 4 (Days 21 through 30), BPE showed the most prominent enhancement, with significant difference. BPE was stronger on delayed than early phase of dynamic MR imaging in all weeks of the menstrual cycle on both qualitative and quantitative assessments.

A few reports have described the effect of the menstrual cycle on dynamic MR imaging of the breast, and greater contrast medium uptake is reported during the second half of the menstrual cycle. These findings match ours here. The precise mechanism of BPE change during the menstrual cycle remains unclear, but it has been related to hormonal status, particularly estrogen levels.

Estrogen is known to cause vascular changes, such as hyperemia, with vasodilatation in the breast parenchyma. Estrogen blood levels show 2 peaks during the menstrual cycle, a preovulatory spike and a gradual peak in the second half of the cycle. In the present study, BPE on early dynamic phase tended to be stronger in the second half of the menstrual cycle. This phenomenon can be explained by the action of estrogen on the vascular system of the breast tissue.

It has been suggested that increasing estrogen levels affect more than vascular changes, that pathologic changes of the breast parenchyma also occur during the menstrual cycle. The breast parenchyma has shown histologically dense cellular stroma in the first half of the menstrual cycle; permeability and fluid leakage from capillary vessels to the breast stroma gradually increase from the first to the second half of the cycle; and stromal edema is most prominent in the secretory phase (Week 4). On MR imaging, Fowler and colleagues noted that breast parenchymal volume, $T_1$ relaxation time, and water content rose sharply between Days 16 and 28 and peaked after Day 25. In the present study, BPE was most prominent on the delayed dynamic phase in Week 4 and stronger on delayed than early phase in all weeks of the menstrual cycle. We believe that stromal edema caused by fluid leakage from the vascular space contributes to contrast medium uptake on delayed dynamic MR phase in Week 4.

In general, typical invasive breast cancer tends to exhibit fast and strong enhancement with a peak one to 3 minutes after injection of contrast medium. Fast and strong BPE in the early phase may cause misinterpretation of enhanced lesions. In Week 2, many patients showed “minimal” enhancement, and BPE tended to show a lower increasing rate of SI on early phase. BPE was significantly weaker in Week 2 than in the second half of the menstrual cycle on both qualitative and quantitative assessments. Accordingly, the acquisition of breast dynamic MR imaging should be performed within Week 2 of the menstrual cycle.

Candidates for breast-preserving surgery also undergo MR imaging to evaluate the precise extent of invasive cancer and intraductal spread. Some cases of ductal carcinoma in situ (DCIS) show persistent contrast kinetics similar to those of benign lesions and are difficult to be distinguished from them. Significantly lower accuracy in the assessment of extent of breast cancer is reported in patients with moderate/marked BPE than those with minimal/mild BPE, especially on delayed phase. In Week 4, marked BPE was most common, and the increasing rate of SI was significantly higher than in any other week of the menstrual cycle on delayed phase. BPE is confusing and disadvantageous during evaluation for breast-preserving surgery, so dynamic MR imaging of the breast should be avoided during Week 4 of the menstrual cycle.

The histological background of BPE is unclear. However, increased BPE is recently reported as strongly predictive of breast cancer risk. Therefore, BPE may be a surrogate marker for the risk of breast cancer. Further research is needed to compare the incidence of breast cancer in patients with strong and weak BPE.

Our study had several limitations. First, it was not designed to evaluate BPE change in the same patient, which could have caused inter-patient bias. Second, patient age may affect BPE. Müller and associates correlated contrast enhancement of the breast parenchyma and age, noting stronger enhancement in patients aged 35 to 50 years than in
patients younger than 35 years or older than 50 years. Our patients were 24 to 51 years of age, and mean age did not differ significantly among our 4 subgroups. So, we do not believe age was the reason for difference in BPE. Third, we did not study the relationship between BPE and histological change during the menstrual cycle. Some patients in the study underwent breast tissue biopsies to diagnose breast lesions suspected to be malignant. Comparison of BPE change and histological findings, such as peripheral vasculature, interstitial edema, and adenosis, may give some insight into the precise mechanisms of BPE change during the menstrual cycle.

Conclusion
We examined the effect of the menstrual cycle on BPE of the breast in MR imaging and found that the optimal time to perform dynamic MR imaging of the breast in premenopausal Japanese women was during Days 5 through 12 after the start of the menstrual cycle, when BPE was minimal. This result confirms the recommendation of the EUSOBI guideline.

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