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Effect of menstrual cycle phase on background parenchymal uptake on molecular breast imaging

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Abstract

Rationale and Objectives—The level of Tc-99m sestamibi uptake within normal fibroglandular tissue on molecular breast imaging (MBI), termed background parenchymal uptake (BPU), has been anecdotally observed to fluctuate with menstrual cycle. Our objective was to assess the impact of menstrual cycle phase on BPU appearance.

Materials and Methods—Premenopausal volunteers who reported regular menstrual cycles and no exogenous hormone use were recruited to undergo serial MBI exams during the follicular and luteal phase. A study radiologist, blinded to cycle phase, categorized BPU as either photopenic, minimal-mild, moderate, or marked. Change in BPU with cycle phase was determined as well as correlations of BPU with mammographic density and hormone levels.

Results—Among 42 analyzable participants, high BPU (moderate or marked) was observed more often in luteal phase compared to follicular ($p = 0.016$). BPU did not change with phase in 30 of 42 (71%) and increased in the luteal phase compared to follicular in 12 (29%). High BPU was more frequent in dense breasts compared to non-dense breasts at both the luteal phase (58% [15/26] vs. 13% [2/16], $p = 0.004$) and follicular phase (35% [9/26] vs. 6% [1/16], $p = 0.061$). Spearman's correlation coefficients did not show any correlation of BPU with hormone levels measured at either cycle phase, and suggested a weak correlation between change in BPU and changes in estrone and estradiol between phases.

Conclusion—We observed variable effects of menstrual cycle on BPU among our cohort of premenopausal women, however, when high BPU was observed, it was most frequently seen

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during the luteal phase compared to follicular phase, and in women with dense breasts compared to non-dense breasts.

Keywords

molecular breast imaging; menstrual cycle; background parenchymal uptake; hormones

INTRODUCTION

Changes in radiologic appearance of the breast due to changes in hormonal milieu across phases of the menstrual cycle have been described for multiple imaging modalities, including mammography, magnetic imaging resonance (MRI), ultrasound, optical imaging, and nuclear medicine technologies (1-17). These menstrual-cycle effects have important clinical implications. Timing imaging during the follicular phase of the menstrual cycle has been shown to improve diagnostic performance for both mammography and breast MRI (1, 5-7). In addition, variation in the magnitude of cyclic changes on breast radiologic appearance between women is thought to reflect differences in hormonal responsiveness of breast tissue, which in turn has been hypothesized as a potential differentiator of breast cancer risk (18-20). By this theory, the more variant the appearance of the breast on imaging at different stages of the menstrual cycle, the more hormonally responsive the breast tissue, and the higher the breast cancer risk.

Molecular breast imaging (MBI) is a functional imaging technique that uses a dedicated gamma camera to image preferential uptake of Tc-99m sestamibi in cells with elevated metabolic activity. MBI and similar techniques using Tc-99m sestamibi have been shown to detect breast tumors, particularly those occult on mammography due to radiographically dense tissue (21-23). MBI can also demonstrate uptake in normal parenchyma, which has been termed background parenchymal uptake (BPU) (24, 25). In the screening setting, we have observed variability in BPU among women with similar mammographic densities, ranging from photopenic (less intense uptake within fibroglandular tissue compared to that in subcutaneous fat) to marked (uptake in fibroglandular tissue more than twice as intense as that in fat), suggesting that MBI depicts properties of breast parenchymal function that are not readily appreciated by the anatomical depiction of fibroglandular tissue on mammography.

In a recent retrospective analysis of over 1100 women who had undergone screening MBI, we observed that high BPU (either moderate or marked) was more frequent in premenopausal women than postmenopausal women, and among postmenopausal women, high BPU was more frequent in those using hormone therapy, indicating BPU is influenced by both exogenous and endogenous hormones (17). However, an association of BPU with phase of menstrual cycle was not found in that analysis (17). Several factors may have affected these results: first, BPU at follicular and luteal phases were not compared within the same woman; second, the cohort included peri-menopausal as well as premenopausal women, in whom cycle regularity was not confirmed; and last, a substantial portion of women (25%) were taking hormonal contraceptives at the time of MBI, resulting in disruption of the normal hormonal milieu.

To address these issues and further investigate effects of menstrual cycle on BPU seen on MBI exams, we designed a prospective study to perform serial follicular- and luteal-phase MBI exams in premenopausal volunteers who reported regular menstrual cycles and were not using exogenous hormones. The objective of this work was to assess the impact of menstrual cycle phase on BPU appearance, and examine the influence of mammographic density and serum hormone levels on BPU across the menstrual cycle

MATERIALS AND METHODS

Participants

A total of 50 female volunteers were prospectively recruited for the study, through an advertisement posted on our institution's research volunteer webpage. The study protocol was approved by the [blinded for review] Institutional Review Board. Informed written consent was obtained from all participants. Participants were required to be between age 35 – 45 years, premenopausal with uterus and both ovaries intact, and to have regular menstrual cycles defined as cycle length of 21 to 35 days, with menstrual flow of 2-7 days, and no intermenstrual spotting or bleeding. Participants were asked to report the commencement of their menstrual period (date of onset of bleeding) for at least three months prior to study imaging to determine cycle regularity and allow scheduling of MBI exams at appropriate times to coincide with anticipated follicular and luteal phases of cycle.

All participants were required to have had a mammogram performed within one year prior to enrollment that demonstrated negative or benign findings and have no signs or symptoms of breast cancer, such as a new palpable mass or nipple discharge. Because, by definition, BPU describes relative uptake in fibroglandular tissue compared to fat, the BI-RADS breast density score was obtained from this mammogram report as an indicator of the quantity of fibroglandular breast tissue (26). Exclusion criteria were the following: current use of hormonal contraceptives or other sex steroid hormones; breast implants; personal history of any cancer, except non-melanomatous skin cancer; and pregnancy or lactation.

Molecular Breast Imaging Procedure

Each participant underwent two MBI exams - one during the follicular phase and one during the luteal phase of the menstrual cycle. The follicular phase MBI was targeted for day 7 of the menstrual cycle (mid-follicular), but allowed to be performed between days 4-13 to accommodate scheduling availability while ensuring timing within the follicular phase. Similarly, luteal phase MBI was targeted for day 21 (mid-luteal), but allowed to be performed between days 19-31.

MBI was performed on one of two similar MBI systems, Discovery NM 750b (GE Healthcare, Haifa, Israel) or LumaGem (Gamma Medica, Salem, NH). Each MBI system comprises a dual-head cadmium zinc telluride (CZT) gamma camera mounted on a mammographic-type gantry that allows imaging of the breasts in planar projections analogous to those used in mammography.

At each MBI procedure, 370 MBq (10 mCi) Tc-99m sestamibi was administered through an arm vein. Imaging commenced approximately 5 min after injection. The patient was seated

at the MBI gamma camera, with the breast positioned between the dual-head detectors. Gentle stabilization, with compression force of approximately 15 lb-force, was applied to limit motion. One acquisition of each breast was performed in mediolateral oblique (MLO) projection for 10 min per view. The same technologist performed all MBI exams and used standard breast positioning techniques, similar to mammographic positioning, to ensure inclusion of the pectoralis muscle and intramammary fold. Compressed breast thickness for each breast was recorded such that similar breast compression could be used at both follicular phase and luteal phase MBI exams.

Serum Hormone Measurements

Hormone levels were measured in serum collected from a blood draw at the time of each MBI procedure. All analyses were conducted by the Immunochemical Core Laboratory, [blinded for review]. Blood was allowed to stand at room temperature for 30 – 60 minutes to allow complete clotting. Blood was then centrifuged and serum was separated and pipetted in 0.5-mL aliquots into cryovials. Cryovials were labeled and stored at –80°C.

Estrogens, fractionated into estrone and estradiol, and testosterone were measured in serum by liquid chromatography-tandem mass spectrometry (ThermoFisher Scientific, Franklin, Massachusetts and Applied Biosystems-MDS Sciex, Foster City, CA), as previously described (27). Progesterone was measured by a competitive binding immunoassay on the DxI 800 automated immunoassay system (Beckman Instruments, Chaska, MN 55318). Follicular stimulating hormone (FSH) was measured using a two-site immunoassay performed on the DxI 800 automated immunoassay system. Sex hormone binding globulin (SHBG) was measured by a solid phase, two-site chemiluminescent assay on the Immulite 2000 automated immunoassay system (Siemens Healthcare Diagnostics, Deerfield, IL) to allow calculation of bioavailable (free plus albumin bound) estradiol.

Serum progesterone measurements were used to confirm each subject's menstrual cycle phase at the time MBI was performed. Subjects were considered to be in follicular phase if progesterone level was between 0.2 and 1.50 ng/mL, and in luteal phase for progesterone level between 1.70 – 27.00 ng/mL (28).

MBI Interpretation

MBI exams were interpreted by a breast imaging fellowship-trained radiologist (blinded for review) with 5 years of experience in reading MBI, according to a validated lexicon for gamma imaging of the breast (24, 25). MBI exams were reviewed in two manners: First, the follicular and luteal phase MBI exams were interpreted separately, with the radiologist blinded to subject identity and phase of the menstrual cycle. Background parenchymal uptake (BPU), which refers to the relative uptake within fibroglandular tissue compared to that in subcutaneous fat, was subjectively categorized as follows: photopenic (fibroglandular uptake less intense than uptake in subcutaneous fat), minimal-mild (same or slightly greater intensity than that in fat), moderate (visually more than mild but less than twice the intensity of fat), or marked (at least twice the intensity of that in fat). High interreader agreement

(kappa = 0.84) and intrareader agreement (kappa = 0.87 to 0.94) for BPU has been previously reported (17).

Next, paired follicular and luteal phase MBI exams were viewed together, while the radiologist was blinded to menstrual cycle phase but had access to participants' most recent screening mammogram. The radiologist compared the area and intensity of BPU for each pair of MBI exams and assessed whether they were the same or different. Following completion of the interpretation of all paired MBI exams, the menstrual cycle phase at each exam was revealed in order to determine whether area or intensity of BPU was greater in luteal phase, greater in follicular phase, or unchanged across phases.

Any breast lesions observed during interpretation were noted, and those that persisted on both follicular- and luteal-phase exams and were not explained by comparison with current screening mammogram and review of clinical history led to diagnostic imaging workup and biopsy as warranted, according to an established algorithm (23). All participants were followed for at least 1 year to verify cancer or benign status.

Data Analysis

The set of analyzable participants included those who met eligibility criteria and completed study imaging inclusive of two MBI exams determined to be of adequate diagnostic quality.

For subjects in whom paired MBI exams were obtained, the frequency of BPU categories observed in the follicular phase versus luteal phase was compared in two ways: First, by combining the categories of photopenic and minimal-mild BPU and the categories of moderate and marked BPU, McNemar's exact test for correlated proportions (29) was used to assess differences in BPU between paired follicular and luteal phase MBI exams. Second, the Stuart-Maxwell test was used to test for frequency differences across all four BPU categories. The Stuart-Maxwell test is a generalized McNemar's test for paired, categorical data and allows for outcomes within multiple categories beyond a 2x2 table (30). Bowker's test of symmetry was used to test for a shift in the four categories of BPU between phases (31).

The frequency of observed BPU categories at each phase as a function of mammographic density category was first examined using a graphical summary. Fisher's exact test was then performed to assess association of BPU with mammographic density. For this analysis, the 4 BPU categories were combined into 2: high BPU (moderate or marked) and low BPU (photopenic or minimal-mild); and the 4 density categories were combined into 2: dense (heterogeneously dense or extremely dense) and non-dense (almost entirely fat or scattered fibroglandular densities).

Correlations between BPU, considered as 4 ordinal categories (1-photopenic, 2-minimal-mild, 3-moderate, and 4-marked) and serum levels of estrone, estradiol, progesterone, testosterone, FSH, and SHBG were assessed by Spearman's correlation coefficient. Coefficients were calculated for the correlation between BPU category and each hormone for follicular and luteal phase separately. We also examined correlations between the change

in BPU category between cycle phases (luteal – follicular) and the change in serum hormone levels between cycle phases by Spearman's correlation coefficient.

All statistical analyses were two-sided with a significance level of 0.05. SAS software, version 9.3, was used to perform analysis.

RESULTS

Of 50 women enrolled in the study, 8 were excluded from analysis, including 4 who did not complete study imaging, 2 who had non-diagnostic, low-count-density MBI exams, and 2 who were later determined not to meet entry criteria due to use of hormonal contraceptives in one participant and irregular menstrual cycle in the other. Thus, the analysis set comprised 42 premenopausal women, whose characteristics are shown in Table 1.

In two of the 42 women, serum progesterone measurements obtained at the time luteal phase MBI was performed were lower than expected range to confirm luteal phase (1.7 – 27.0 ng/mL); both subjects had a progesterone level of 1.1 ng/mL. Analyses excluding these two subjects did not affect results, thus results reported herein are for all 42 eligible participants.

The distribution of BPU categories by follicular and luteal phase MBI are shown in Figure 1. The proportions of moderate or marked BPU and photopenic or minimal-mild BPU differed significantly between luteal and follicular phases (McNemar's test, $p=0.016$) with moderate or marked being observed more in the luteal phase. During the follicular-phase MBI, BPU was moderate or marked in 10 of 42 (24%) women and photopenic or minimal-mild in 32 of 42 (76%). During the luteal phase, the proportion of women with moderate or marked BPU increased to 17 of 42 (40%) and photopenic or minimal-mild BPU was observed in 25 of 42 (60%). Differences in BPU frequency between phases were also found when all four BPU categories were considered (Stuart-Maxwell test, $p=0.010$). The Bowker's test for symmetry also showed a shift in uptake across phases ($p=0.002$).

The majority of women (30 of 42; 71%) did not have a change in BPU with cycle phase. BPU category was found to be higher in the luteal phase compared to follicular among the remainder (12 of 42 [29%]). No women were found to have a lower BPU category in the luteal phase compared to follicular. Although the BPU category was higher in luteal phase than follicular on individual MBI exam interpretations for just 12 women, BPU was determined to be greater in area during luteal phase in 18 of 42 (43%) and greater in intensity during luteal phase in 20 of 42 (48%) when the paired luteal and follicular phase MBI exams were viewed together. Thus, for 6 women with greater BPU area during the luteal phase and 8 with greater BPU intensity during the luteal phase, differences were apparent but were not great enough to result in a difference in BPU category. In the remaining pairs of MBI exams, BPU area ($n=24$, 57%) and intensity ($n=22$, 52%) were judged to be the same between luteal and follicular phase MBI exams.

Based on BPU interpretation of individual MBI exams, four general groups were observed among the 42 premenopausal women: 3 (7%) with photopenic BPU in both phases, 22 (52%) with minimal-mild BPU in both phases, 7 (17%) with minimal-mild BPU in follicular phase that increased to moderate or marked BPU in luteal phase, and 10 (24%) with

moderate or marked BPU in both phases. Example comparisons of BPU during the follicular and luteal phases are shown in Figures 2 – 5.

The distribution of observed BPU categories in each phase by mammographic density, obtained from the mammogram up to one year prior, is shown in Figure 1. Moderate or marked BPU was more frequent in dense breasts compared to non-dense breasts at both the luteal phase (58% [15/26] vs. 13% [2/16], $p=0.004$) and follicular phase (35% [9/26] vs. 6% [1/16], $p=0.061$), although the follicular phase comparison did not reach statistical significance. Of 16 women with non-dense breasts, 14 (88%) were categorized as having minimal-mild BPU that was unchanged between cycle phases. No women with non-dense breasts were categorized as having photopenic or marked BPU. Of 26 women with dense breasts, however, all BPU categories were observed: 3 (12%) had photopenic BPU, unchanged by cycle phase; 8 (31%) had minimal-mild BPU, unchanged by cycle phase; and 15 had moderate or marked BPU in at least the luteal phase.

A breast lesion was detected by MBI in 5 participants, all of whom had either photopenic or minimal-mild BPU that was unchanged between phases. Two women had lesions identified during the luteal-phase MBI only. In both cases, the finding was attributed to background uptake within benign fibroglandular tissue in luteal phase, but not follicular-phase MBI (example shown in Figure 5) and therefore no further workup was performed. Three women were found to have lesions persisting across phases: 1 lesion was deemed stable and benign after comparison with past mammograms; 1 was deemed benign after subsequent evaluation with MRI; and 1 was found to represent proliferative fibrocystic changes after biopsy. No breast cancers were diagnosed in any participant within the 1 year follow-up period.

Serum hormone level measurements for each phase as a function of BPU category are shown in Figure 6. Spearman's correlation coefficients did not show a significant correlation between any of the serum hormones measured and BPU category at either follicular or luteal phase (all $p>0.05$). Figure 7 shows the change in serum hormone levels between phases as a function of the change in BPU category. The only correlations observed were a weak negative correlation between change in BPU and change in two hormones between cycle phases: estrone ($r=-0.31$, $p=0.04$) and estradiol ($r=-0.36$, $p=0.02$).

DISCUSSION

In our sample of 42 premenopausal women with regular menstrual cycles and no exogenous hormone use who underwent MBI during follicular and luteal phases of the menstrual cycle, we observed an association of BPU with cycle phase based on within-woman analyses but variability in the response of BPU to menstrual cycle phase between women. Moderate to marked BPU was more frequently observed in the luteal phase compared to follicular. Consistent with BPU representing uptake in normal fibroglandular tissue (i.e. mammographic density) relative to uptake in fat, changes in BPU across phase of the menstrual cycle were correlated with mammographic density: women with non-dense breasts were most likely to have minimal-mild BPU, unaffected by cycle phase, and those with dense breasts had variable BPU (ranging from photopenic to marked) and were more likely to have an increase in BPU during luteal phase of the menstrual cycle.

Mammographic density, a factor known to limit mammographic sensitivity, has been consistently shown to increase during the luteal compared to follicular phase (1-5), suggesting that mammography should be performed during the follicular phase of the menstrual cycle. However, some studies have determined that density increases in the luteal phase are modest, at most, and unlikely to affect the accuracy of mammography to a clinically meaningful extent (3, 4). We found an increased proportion of women with moderate to marked BPU in the luteal compared with follicular phase. But, because moderate or marked BPU is suspected to limit MBI sensitivity, it is recommended that MBI be performed during the follicular phase for best diagnostic quality (25).

Functional imaging techniques that rely on contrast agents to distinguish breast abnormalities from normal tissue appear to be more sensitive to menstrual cycle effects than mammography. Similar to our findings, studies of breast magnetic resonance imaging (MRI) have reported higher levels of gadolinium enhancement of fibroglandular tissue, termed background parenchymal enhancement (BPE), during the luteal phase compared to follicular (6, 7). BPE can be problematic for MRI interpretation, so it is recommended that breast MRI be performed during the follicular phase (days 3-14) to minimize effects of possible increases in BPE during the luteal phase (7).

We witnessed varying effects of menstrual cycle phase on BPU among the premenopausal women studied. Some exhibited low BPU (either photopenic or minimal-mild) that did not change with phase, some had minimal-mild BPU during the follicular phase that noticeably increased to moderate or marked BPU during the luteal phase, and some had moderate or marked BPU during both phases. This variability in cycle effects between women can be partially explained by mammographic density differences, as it was seen that non-dense breasts are likely to be categorized as minimal-mild BPU. However, when only the women with dense breast tissue are considered, it is still unclear why some women with dense breasts on mammography exhibit an increase in BPU in the luteal phase, whereas other women with the same level of density on mammography exhibit no change in BPU across the menstrual cycle.

The etiology of BPU itself is uncertain. Tc-99m sestamibi is known to pass through the cell membrane and is bound to the mitochondria. The amount of sestamibi that accumulates in a cell is dependent upon cell membrane potential and the number of mitochondria in the cell (32). Once sestamibi has crossed the cell membrane it appears to be relatively stable with little washout occurring over periods of 1-2 hours (approximately 6%) (33). Because extracellular sestamibi will be recirculated into the bloodstream, it is rapidly eliminated from the bloodstream as it is extracted on a first pass basis by the hepatobiliary system and < 10% of the injected dose is known to remain in the blood after 5-10 minutes post injection (34, 35). Hence sestamibi uptake in fibroglandular tissue is most likely reflective of intracellular distribution as extracellular activity will be minimal. Uptake of Tc-99m sestamibi in breast lesions has been correlated with angiogenesis, mitochondrial activity, tissue viability, and cellular proliferation (36-39), so it is hypothesized that uptake of sestamibi in benign fibroglandular tissue may reflect these properties as well.

We hypothesized that differences in hormone levels might correlate with differences in BPU across the menstrual cycle, but serum hormone levels obtained during follicular and luteal phases did not correlate with the observed BPU category. The change in serum hormone levels between phases also did not correlate with change in BPU category, with the exception of a weak negative correlation observed for estrone and estradiol. The clinical importance of these two correlations is questionable as our analysis was limited by sparse data – only one subject had a change in BPU category of 2 (from minimal-mild at follicular phase to marked at luteal phase) – and normal serum estrone and estradiol levels in premenopausal women can range widely (from 17-200 pg/ml for estrone and 15-350 pg/ml for estradiol)(28). Previous work has indicated that measurements of endogenous hormones from breast tissue itself, rather than from serum, may be more temporally stable and a better indicator of hormone responsiveness of the end organ (40). Thus, it may be that for similar levels of circulating endogenous hormones, responsiveness to those hormonal effects within the breast differs between women. It is also not known whether the hormone measurements, performed at the time of MBI exams, are indicative of breast tissue response to hormones at that time, or whether there might be some delay in the observation of a response to hormones on MBI.

Could differences in the change in BPU across phases of the menstrual cycle among premenopausal women reflect differences in breast tissue responsiveness to endogenous hormones? If so, changes in the MBI appearance of the breast during menstrual cycle may mirror hormone responsiveness of the breast tissue, which might correlate with subsequent breast cancer risk. Studying the relationships between hormonal responsiveness of breast tissue, BPU, and ultimately breast cancer risk is beyond the scope of the current study, but an important next step in elucidating these associations will be to examine correlation of BPU with an assessment of hormone responsiveness at the breast tissue level. One approach would be to explore performing MBI with radiolabeled estradiol to determine if women who demonstrate the most change in BPU during the menstrual cycle also exhibit higher uptake of radiolabeled estradiol. Radiolabeled estradiol has been previously used in assessment of tumor response to treatment (41). A second area of future work will be to implement a quantitative method for more accurately assessing BPU and monitoring changes in BPU on serial MBI exams. Efforts are currently underway to develop and validate a quantitative tool for this purpose.

In summary, although we observed variability in menstrual cycle effects on BPU among our cohort of premenopausal women, when higher levels of uptake in benign fibroglandular tissue (moderate or marked BPU) was observed, it was most frequently seen during the luteal phase compared to follicular phase, and in women with dense breasts compared to non-dense breasts. Further research is needed to understand the etiology and clinical significance of high BPU and whether changes in BPU across the menstrual cycle might be predictive of breast cancer risk.

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Abbreviations

BI-RADS	breast imaging reporting and data system
BPU	background parenchymal uptake
MBI	molecular breast imaging
MRI	magnetic resonance imaging

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Figure 1.

Distribution of BPU at follicular and luteal phases of menstrual cycle for mammographically dense and non-dense breasts. Note “jitter” in the y-axis has been applied to reduce overplotting and allow visualization of individual data points.

Figure 2.

Mammography and MBI performed in a 41-year-old premenopausal woman demonstrating no change in BPU with menstrual cycle. Panel A – Mammogram obtained within 1 month of MBI demonstrates heterogeneously dense tissue. Both follicular (Panel B) and luteal phase MBI (Panel C) demonstrate photopenic BPU of similar area and intensity.

Figure 3.

Mammography and MBI performed in a 41-year-old premenopausal woman demonstrating an effect of menstrual cycle on BPU. Panel A – Mammogram obtained within 1 month of MBI demonstrates heterogeneously dense tissue. BPU was minimal-mild on follicular phase MBI (Panel B) and changed to marked on luteal phase MBI (Panel C).

Figure 4.

Mammography and MBI performed in a 40-year-old premenopausal woman demonstrating a small effect of menstrual cycle on BPU. Panel A – Mammogram obtained within 1 month of MBI demonstrates heterogeneously dense tissue. BPU was categorized as marked on both follicular phase MBI (Panel B) and luteal phase MBI (Panel C), however, when viewed together, BPU at luteal phase was interpreted as greater in area and intensity compared to BPU at follicular phase.

Figure 5.

Mammography and MBI performed in a 36-year-old premenopausal woman. Panel A – bilateral mediolateral oblique (MLO) views from mammography demonstrate overall non-dense breasts (BI-RADS density category of almost entirely fat) with a ridge of benign dense tissue in upper left breast. Both follicular phase MBI (panel B) and luteal phase MBI (panel C) demonstrated minimal-mild BPU. However, uptake within the small area of dense tissue occurred only at luteal phase MBI, giving the misleading appearance of a lesion. Subsequent negative mammography screening confirmed benignity of the area.

Figure 6.

Distribution of serum hormone levels across BPU levels at follicular and luteal phases of the menstrual cycle. Spearman's correlation coefficients (r), given for all subjects (N = 42) and for the subset with mammographically dense breasts (N = 26), did not show significant correlation between any of the hormones and BPU category at either phase.

Figure 7.

Distribution of the change in serum hormone levels between cycle phases as a function of the change in BPU. BPU was considered as ordinal categories of 1-photopenic, 2-minimal-mild, 3-moderate, and 4-marked, and the change in BPU was the difference of these assigned ordinal numbers between luteal and follicular phase. Spearman's correlation coefficients (r), given for all subjects ($N = 42$) and for the subset with mammographically dense breasts ($N = 26$), showed a weak negative correlation between change in BPU category and change in two hormones: estrone and estradiol.

Table 1

Participant characteristics of 42 eligible participants.

Characteristic	Mean, Median (Range)
Age at enrollment (y)	41.0, 41.0 (35 – 45)
Length of menstrual cycle (days) ¹	28.1, 28.0 (24 – 34)
Follicular phase MBI	
Day of cycle	7.7, 7.5 (4 – 13)
Estrone (pg/mL)	74.3, 69.0 (28 – 181)
Estradiol (pg/mL)	116.6, 105.5 (29 – 307)
Progesterone (ng/mL)	0.5, 0.4 (0.16 – 1.3)
Testosterone (ng/mL)	24.0, 23.5 (12 – 37)
SHBG (nmol/L)	48.5, 45.8 (18.8 – 102)
FSH (mIU/L)	8.0, 7.5 (3.9 – 16.1)
Luteal phase MBI	
Day of cycle	22.4, 22.0 (19 – 31)
Estrone (pg/mL)	94.7, 88.0 (25 – 175)
Estradiol (pg/mL)	119.1, 110.0 (28 – 233)
Progesterone (ng/mL) ²	11.1, 10.9 (1.1 – 24.1)
Testosterone (ng/mL)	23.2, 23.0 (10 – 45)
SHBG (nmol/L)	54.1, 52.1 (22 – 114)
FSH (mIU/L)	4.1, 4.0 (1.7 – 8.2)
Mammographic density ³	No. of women (%)
Almost entirely fat	3 (7.1)
Scattered fibroglandular densities	13 (31)
Heterogeneously dense	22 (52)
Extremely dense	4 (9.5)

¹ Menstrual cycle was monitored for at least 3 months prior to imaging to determine average cycle length and estimate timing of follicular-phase and luteal-phase imaging.

² In two women, serum progesterone measured at time of luteal phase MBI was below the expected range of 1.7 to 27.0 ng/mL to confirm luteal phase. Analyses performed excluding these two subjects did not affect results.

³ Mammographic density was subjectively assessed from the mammogram performed closest to the time of MBI and within 1 year of MBI. Time between mammography and MBI was on average 96 days, with standard deviation of 75 days.