Effect of Menstrual Cycle Phase on Background Parenchymal Uptake at Molecular Breast Imaging

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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

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 examinations during the follicular and luteal phase. A study radiologist, blinded to cycle phase, categorized BPU as 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: In 42 analyzable participants, high BPU (moderate or marked) was observed more often in luteal phase compared to follicular (P = .016). BPU did not change with phase in 30 of 42 participants (71%) and increased in the luteal phase compared to follicular in 12 (29%). High BPU was more frequent in dense breasts compared to nondense breasts at both the luteal (58% [15 of 26] vs. 13% [2 of 16], P = .004) and follicular phases (35% [9 of 26] vs. 6% [1 of 16], P = .061). Spearman 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.

Conclusions: 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 during the luteal phase compared to follicular phase and in women with dense breasts compared to nondense breasts.

Key Words: Molecular breast imaging; menstrual cycle; background parenchymal uptake; hormones.

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 resonance imaging (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 because of radiographically dense tissue (21–23). MBI can also demonstrate

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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 anatomic 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 in 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 was not compared within the same woman; second, the cohort included perimenopausal and premenopausal women, in whom cycle regularity was not confirmed; and finally, 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 examinations, we designed a prospective study to perform serial follicular- and luteal-phase MBI examinations 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 Web page. The study protocol was approved by the Mayo Clinic Institutional Review Board. Informed written consent was obtained from all participants. Participants were required to be aged between 35 and 45 years, premenopausal with uterus and both ovaries intact, and to have regular menstrual cycles defined as cycle length of 21–35 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 3 months before study imaging to determine cycle regularity and allow scheduling of MBI examinations at appropriate times to coincide with anticipated follicular and luteal phases of cycle.

All participants were required to have had a mammogram performed within 1 year before 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 breast imaging reporting and data system (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 nonmelanomatous skin cancer; and pregnancy or lactation.

MBI Procedure

Each participant underwent two MBI examinations: 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 (midfollicular) but allowed to be performed between days 4 and 13 to accommodate scheduling availability while ensuring timing within the follicular phase. Similarly, luteal-phase MBI was targeted for day 21 (midluteal) but allowed to be performed between days 19 and 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 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 minutes 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, was applied to limit motion. One acquisition of each breast was performed in mediolateral oblique (MLO) projection for 10 minutes per view. The same technologist performed all MBI examinations 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- and luteal-phase MBI examinations.

Serum Hormone Measurements

Hormone levels were measured in serum collected from blood drawn at the time of each MBI procedure. All analyses were conducted by the Immunochemical Core Laboratory, Mayo Clinic. 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.