Can uterine endometrium in luteal phase be differentiated from endometrial diseases? Comparison with normal endometrium in periovulatory phase, endometrial polyp, hyperplasia and cancer

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Aims and objectives

Magnetic resonance (MR) images can clearly visualize three layers of the uterus, which are endometrium, junctional zone and outer myometrium, on T2-weighted image (WI). "Endometrial thickening" is one of the important findings that suggest endometrial diseases including endometrial polyp, endometrial hyperplasia and endometrial cancer. Since an endometrial lesion is usually diagnosed pathologically by endometrial biopsy before the MR examination, the role of MR imaging is evaluation of tumor characteristic and extent. However, we sometimes encounter incidental endometrial thickening on T2-WI on MR examinations performed for other than endometrial pathology after medical examinations by gynecologists. These cases sometimes accompany a low signal intensity area within the endometrium, mimicking endometrial cancer showing similar appearance on T2-WI [1-7].

The MR appearance of the uterus changes according to the menstrual cycle phase including thickness and signal intensities of the endometrium and myometrium on T2-WI [8-11]. The endometrial thickness increases especially in luteal phase to reach a mean peak of over 1.0cm [10,11]. Then, incidental MR imaging findings of "endometrial thickening with a low intensity area" may be explained by normal endometrial changes on T2-WI.

The aim of this study is to evaluate normal endometrial appearance of MR imaging in luteal phase (LP) in comparison to that in periovulatory phase (OP), and to identify MR findings useful in differentiating normal endometrium from endometrial diseases, including endometrial cancer, endometrial polyp and endometrial hyperplasia.
Methods and materials

Study population

The protocol of this study was approved by the Ethics Committee of our institute. The study population consisted of two groups, one was healthy volunteers prospectively recruited and the other was patients with confirmed endometrial diseases who were retrospectively selected.

For the healthy volunteer group, a total of 38 female volunteers with regular menstrual cycle (mean age: 30.8 years; age range: 20-44 years) were recruited from May 2012 to January 2014 and written informed consent was obtained from all subjects. One of 38 volunteers had a history of left oophorectomy and two had histories of Caesarean section. Other 35 subjects were no history of abdominal operation. Exclusion criteria were female with endometrial lesion or distortion of uterine cavity on MR imaging, or taking exogenous hormones or poor image quality for evaluations. The reason we excluded distorted endometrium was that the thickness of the endometrium could not be measured exactly or the area of the endometrium was not large enough for evaluation of the appearance and signal intensity. Among 38 subjects, the following five subjects were excluded due to taking an emergency contraceptive pill (n=1), accompanying an endometrial lesion (n=1), endometrial distortion (n=3) (submucosal uterine leiomyoma (n=1), multiple leiomyoma (n=1) and large adenomyosis in the anterior uterine wall (n=1)) on MR imaging and poor image quality due to severe bowel motion artifact (n=1). As a result, 32 subjects were included in the study.

The patients with endometrial diseases were extracted from the computer databases of Departments of Pathology, Gynecology and Radiology between August 2008 and December 2013. Among patients who were pathologically confirmed to have endometrial disease, patients who underwent MR imaging examinations on 3T magnet unit before surgical procedures were selected. Patients with the following three endometrial disease were included in this study: 15 patients (mean age: 53.2 years; age range: 41-66 years) with endometrial cancer which was limited within the endometrium, eight patients (mean age: 39.3 years; age range: 22-51 years) with endometrial hyperplasia and nine patients (mean age: 47 years; age range: 29-70 years) with endometrial polyp.

MR scanning protocols
MR imaging examinations for 38 healthy female volunteers were performed in luteal phase (Cycle Day (CD) 14-34, 1-12 days before the next cycle (late luteal phase in 27/32 women, early luteal phase in 5/32 women)) and periovulatory phase (CD 6-16, 12-30 days before the next cycle) in the next cycle. All females were asked to note the beginning of the subsequent menstrual cycle to allow menstrual cycle phase confirmation. MR imaging examinations were obtained using a 3.0-T MR unit (Toshiba Medical Systems, Otawara, Japan) with a phased-array coil. After acquisition of localization images, sagittal T2-weighted fast spin-echo (FSE) images, axial T2-weighted fast-advanced spin echo (FASE) images and sagittal T1-weighted FSE images were obtained. Detailed parameters were as follows: sagittal T2- weighted FSE sequence (repetition time (TR)/ echo time (TE) = 5756/80 msec, field of view (FOV) = 260 x 260 mm, slice thickness = 4 mm, matrix = 512 x 256, flip angle (FA) = 90 deg, refocusing FA = 170 deg), axial FASE sequence (TR/TE = 15000/80 msec, FOV = 300 x 330 mm, slice thickness = 5 mm, matrix = 256 x 352, FA = 90 deg, refocusing FA = 160 deg) and sagittal T1- weighted FSE sequence (TR/TE = 571/12 msec, FOV = 260 x 260 mm, slice thickness = 4 mm, matrix = 320 x 256, FA = 90 deg, refocusing FA = 180 deg). Sagittal T1 and T2-WI were obtained in mid-plane of the uterus. Pre-medication, including anti-cholinergic drugs were not administered.

MR imaging examinations for 32 patients with endometrial lesions were performed using 3.0T magnet units (MAGNETOM Trio and Skyra, Siemens, Erlangen, Germany) with phased array coils. After acquisition of localization images, sagittal T1-weighted spin-echo (SE) images and sagittal and axial T2-weighted FSE images were obtained. The following is the detailed parameters: sagittal T2-weighted FSE sequence (TR/TE = 4000-4500/81-83msec, FOV = 260 x 209-212mm, slice thickness = 4 mm, matrix = 448 x 288-328, FA = 90 deg, refocusing FA = 150 deg), sagittal SE T1-WI (TR/TE = 600-608/11 msec, FOV = 260 x 204-208 mm, slice thickness = 4 mm, matrix = 384 x 230-240, FA = 80 deg, Refocusing FA = 180 deg), and axial FSE sequence (TR/TE = 4500/81-83 msec, FOV = 320 x 320 mm, slice thickness = 4 mm, matrix =512 x 512, FA = 90 deg, refocusing FA = 150 deg).

Anti-cholinergic drugs (Buscopan; Nippon Boehringer Ingelheim, Tokyo, Japan) were administered in 14 of 15 patients with endometrial cancer, in all 8 patients with endometrial hyperplasia and 7 of 9 patients with endometrial polyp.

Image analysis

The MR images of 32 healthy subjects were independently interpreted for the appearance of the normal endometrium by two radiologists with six years (F.S. reader A) and 17 years (A.K. reader B) of experience in female pelvic MR imaging. The readers visually evaluated
the endometrium on sagittal T2-WI in luteal and periovulatory phases to categorize as the following three types: type 1) the endometrium with homogeneous signal intensity, type 2) the presence of a low signal intensity area at the periphery of the endometrium and type 3) the presence of a low signal intensity central line within the endometrium (Figure 1).

For all the subjects regardless of the presence of endometrial lesions, maximum thickness of the endometrium was measured on sagittal T2-WI by one radiologist. As for the measurement of signal intensities in the endometrium, polygonal regions of interest (ROIs) were drawn to delineate contour of the endometrium at the plane on the middle of the uterus. Reference ROIs were drawn on the paraspinal muscles and subcutaneous fat in the hip, avoiding vessels and ghosting artifacts. Since MR units and acquisition parameters were different between the volunteers and the patients, signal intensity of each ROI was converted to the relative signal intensity (rSI) by the following formula according to the previous report [12]:

\[
\text{rSI} = \frac{\text{mean SI of each uterine region} - \text{mean SI of paraspinal muscle}}{\text{mean SI of fat} - \text{mean SI of paraspinal muscle}} \times 100
\]

**Statistical analysis**

Three type of the appearance of the normal endometrium was compared between luteal and periovulatory phase using extended McNemar’s tests (GNU R Statistical Software, version 3.0.2).

The maximum thickness and rSI of the normal endometrium was compared between luteal and periovulatory phase by a paired Student’s t-test (MedCalc Software, version 12.7.2.0, Ostend, Belgium).

The maximum thickness and the rSI of the normal endometrium in luteal and periovulatory phase were compared with each of three endometrial lesions by unpaired Student’s t-tests.

A P values of less than 0.05 was regarded as statistically significant.

Concordance of the two readers' results of the appearance of the normal endometrium in luteal and periovulatory phase was measured by the kappa coefficient. A kappa value less than 0.00 signified poor agreement; 0.00-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60; moderate agreement; 0.61-0.80, substantial agreement; 0.81-1.00, almost perfect agreement [13].
Images for this section:

**Fig. 1:** The sagittal FSE T2-weighted images in luteal and periovulatory phase were categorized as the following three types: type 1) the endometrium with homogeneous signal intensity, type 2) the presence of a low signal intensity area at the periphery of the endometrium and type 3) the presence of a low signal intensity central line within the endometrium.

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Results

There was a significant difference in the appearance of the normal endometrium between luteal phase and periovulatory phase (P<0.05) (Figure 2). The type 2 was more frequently identified in luteal phase than in periovulatory phase (Figure 2). Interobserver agreement was almost perfect for the image evaluation of the normal endometrium in luteal and periovulatory phase (κ = 0.859 and 0.873, respectively).

Figure 3 shows a box and whisker plot of the maximum thickness of the normal endometrium in luteal and periovulatory phase and those with each endometrial disease. The average maximum thickness of the normal endometrium was 1.04 cm (range: 0.39-2.04 cm) in luteal phase and 0.65 cm (range: 0.21-1.40 cm) in periovulatory phase, and the difference was significant (P<0.05) (Figure 4). There was no significant difference in the maximum thickness between the normal endometrium in luteal phase and those with all endometrial diseases including endometrial cancer, hyperplasia and polyp (P = 0.14, 0.85 and 0.88, respectively). Regarding comparison with the normal endometrium in periovulatory phase, a significant difference was observed with endometrial hyperplasia and with endometrial polyp (p < 0.05), but not with endometrial cancer (p = 0.067).

Figure 5 shows a box and whisker plot of the rSI of the normal endometrium in luteal and periovulatory phase and those with each endometrial disease. The rSI of the normal endometrium was significantly lower in luteal phase than in periovulatory phase (P<0.05). The rSI of the normal endometrium in luteal phase was significantly higher than that of patients with endometrial cancer (P<0.05) and with endometrial polyp (P<0.05), but not with endometrial hyperplasia (p = 0.55). The rSI of the normal endometrium in periovulatory phase was significantly higher than that of patients with endometrial cancer (P<0.05) and with endometrial polyp (P<0.05), but not with endometrial hyperplasia (p = 0.08). Figure 6-10 shows the images of subjects with normal endometrium in periovulatory and luteal phases and endometrial hyperplasia, polyp and cancer as specific examples. The normal endometrium in luteal phase shows a low signal intensity area at the periphery of the endometrium (Fig. 6). The normal endometrium in periovulatory phase shows homogeneous intensity (Fig. 7). The endometrial diseases show low signal intensity area in the endometrium (Fig. 8, 9, 10).
The type of the normal endometrial appearance in luteal and periovulatory phase evaluated by two readers. There was a significant difference in the appearance of the normal endometrium between luteal phase and periovulatory phase (reader A: \( p = 0.007 \), reader B: \( p = 0.003 \)). The type 2 and 3 appearance was more frequently identified in luteal phase than in periovulatory phase.

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**Fig. 2:** The type of the normal endometrial appearance in luteal and periovulatory phase evaluated by two readers. There was a significant difference in the appearance of the normal endometrium between luteal phase and periovulatory phase (reader A: \( p = 0.007 \), reader B: \( p = 0.003 \)). The type 2 and 3 appearance was more frequently identified in luteal phase than in periovulatory phase.

<table>
<thead>
<tr>
<th>Type</th>
<th>Luteal Phase</th>
<th>Periovulatory Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>9 (28%)</td>
<td>21 (66%)</td>
</tr>
<tr>
<td>Type 2</td>
<td>13 (41%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Type 3</td>
<td>10 (31%)</td>
<td>8 (25%)</td>
</tr>
</tbody>
</table>

**Fig. 3:** A box and whisker plot showing the maximum thickness of the normal endometrium in luteal and periovulatory phase and those with each endometrial disease. *\( p < 0.05 \) Abbreviation: OP = in periovulatory phase, LP = in luteal phase.
The maximum thickness of the normal endometrium in luteal phase is significantly thicker than in periovulatory phase. There is no significant difference between the normal endometrium in luteal phase and those with all endometrial diseases including endometrial cancer, hyperplasia and polyp. Regarding comparison with the normal endometrium in periovulatory phase, a significant difference is observed with endometrial hyperplasia and with endometrial polyp, but not with endometrial cancer.

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<table>
<thead>
<tr>
<th></th>
<th>maximum thickness (cm)</th>
<th>rSI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>average (range)</td>
<td>average (range)</td>
</tr>
<tr>
<td>normal endometrium (OP)</td>
<td>0.64 (0.21-1.40)</td>
<td>83.12 (56.10-112.77)</td>
</tr>
<tr>
<td>normal endometrium (LP)</td>
<td>1.04 (0.39-2.04)</td>
<td>75.93 (56.36-109.44)</td>
</tr>
<tr>
<td>endometrial hyperplasia</td>
<td>1.07 (0.35-1.66)</td>
<td>71.74 (43.14-120.22)</td>
</tr>
<tr>
<td>endometrial polyp</td>
<td>1.06 (0.50-1.95)</td>
<td>63.21 (43.62-86.21)</td>
</tr>
<tr>
<td>endometrial cancer</td>
<td>0.86 (0.10-1.70)</td>
<td>57.21 (35.95-81.74)</td>
</tr>
</tbody>
</table>

**Fig. 4:** The maximum thickness and relative signal intensity (rSI) of the normal endometrium and those with each endometrial disease. Abbreviation: OP = in periovulatory phase, LP = in luteal phase.

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Fig. 5: A box and whisker plot showing the relative signal intensity (rSI) of the normal endometrium in luteal and periovulatory phase and those with each endometrial disease. *p<0.05 Abbreviation: LP = in luteal phase, OP = in periovulatory phase. The rSI of the normal endometrium is significantly lower in luteal phase than in periovulatory phase. The rSI of the normal endometrium in luteal phase is significantly higher than that of patients with endometrial cancer and with endometrial polyp, but not with endometrial hyperplasia. The rSI of the normal endometrium in periovulatory phase is significantly higher than that of patients with endometrial cancer and with endometrial polyp, but not with endometrial hyperplasia.

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**Fig. 6:** Sagittal T2-weighted image in 23-year-old woman with normal endometrium in luteal phase. The normal endometrial thickness increases in luteal phase to about 13 mm with a low signal intensity area at the periphery of the endometrium.

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**Fig. 7:** Sagittal T2-weighted image in the same woman with figure 6 in periovulatory phase, obtained 18 days after figure 6. In periovulatory phase, the endometrium becomes homogeneously high signal intensity with a thickness of 7 mm.

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Fig. 8: Sagittal T2-weighted image in 28-year-old woman with endometrial hyperplasia. In endometrial hyperplasia, it may be difficult to differentiate it from normal endometrium.

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**Fig. 9:** Sagittal T2-weighted image in 54-year-old woman with endometrial polyp. In endometrial polyp, the endometrial thickness is thinner than normal endometrium in luteal phase. However, a prominent low signal intensity area called fibrous core can lead to the diagnosis of endometrial polyp.
Fig. 10: Sagittal T2-weighted image in 50-year-old woman with endometrial cancer. In endometrial cancer, the endometrial thickness is thinner than normal endometrium in luteal phase and the endometrium shows low signal intensity.

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Conclusion

Discussion

MR appearance of normal uterine endometrium on T2-WI has been known as "high signal intensity". However, this study showed typical appearance of that homogeneous high signal intense endometrium can be observed in periovulatory phase, but not so often in luteal phase. The signal intensities of the endometrium in luteal phase tended to be rather inhomogeneous in 23/32 (72%) subjects accompanying peripheral or central low signal intensity area. The difference of signal was also quantitatively confirmed using rSI.

The reason of low signal intensity at the periphery or the middle of the endometrium in normal volunteer could not be verified because of no correlation with pathology in this study. Anatomically, it is supposed that the peripheral lesion reflected the thickened endometrium itself and the higher signal intensity of the central endometrium in Type2 and low signal line in Type 3 may be the endometrial cavity pooling liquid in uterine cavity. The pathophysiology of the endometrium changes according to the menstrual cycle[14]. The endometrium is thin and consisted of only basalis layer just after the menstruation and then subsequently gland cell, stromal cells and vascular endothelial cells increase and the endometrium become to be thick most in late follicular phase to mid luteal phase. Functional layer is shed and bleeding occurs in menstrual phase[14]. In our study, the most of the MR images in luteal phase (27/32 subjects (84%)) were obtained in late luteal phase. In this phase, peridecidualization of the stroma is characteristic in pathological examination[14]. It begins by cycle day 22-23 around spiral arterioles and capillaries of the functional layer. It is characterized by the conversion of uncommitted spindle-shaped stromal cells into plump epithelial-like cells with enlarged nuclei and increased cytoplasm [14]. The cause of low signal intensity of the endometrium may be affected by these changes, but pathological correlation with MR imaging will be required in the next step.

Development of MR units may contribute to show detailed contrast within the endometrium. First, we used 3T MR units in this study and they resulted in higher signal to noise ratio (SNR) than 1.5T, 0.35T or 0.15T MR units previously reported for evaluation of the endometrial visualization in MR imaging [1, 2, 8, 10, 15, 16]. According to increased SNR, the slice thickness can make thinner with increased matrix, and thus the more improved spatial resolution can be obtained on 3.0T MR units. Therefore we supposed that the endometrium can be distinguished from the uterine cavity. Second, our T2 weighted images were obtained with FSE while T2 weighted images in the previous study were obtained with spin echo (SE) [1, 2, 8, 10, 15, 16]. Since image acquisition time of a FSE sequence is shorter than that of a SE sequence, the images could be less affected by motion artifacts such as bowel peristalsis and breathing motion.
Our results show that the averaged thickness of the endometrium was 0.60cm in periovulatory phase and 1.04cm in luteal phase and this results accord with previous reports. The range of the endometrial thickness was 0.21-1.40cm in periovulatory phase and 0.39-2.04cm in luteal phase. Although upper limit of the normal endometrium with reproductive age is thought to be 1cm[9, 3], we should know normal endometrium can be more than 1cm according to the menstrual cycle phase. From the results of this study, differentiation of normal endometrium both in luteal and periovulatory phase from endometrial cancer was difficult only by its thickness. In addition, the maximum thickness of the normal endometrium in luteal phase was not significantly different from those of endometrial hyperplasia and endometrial polyp. Although significant difference in the maximum thickness were indicated between normal endometrium in periovulatory phase and endometrial polyp/hyperplasia, more than 70% of the subjects overlapped. We may say the distinction between the normal endometrium and the endometrial diseases may be difficult if based only on endometrial thickness, particularly in luteal phase.

Although there was no significant difference in the endometrial thickness between the normal endometrium in luteal phase and the endometrial diseases, a significant difference could be observed in the signal intensity between the normal endometrium and endometrial polyp and carcinoma, but not hyperplasia. It is well known that the endometrial cancer shows typically medium to low signal intensity relative to the endometrium on T2-WI [1-7]. Regarding endometrial polyps, a central fibrous core and intratumoral cysts are accepted as MR imaging characteristics. [17, 18]. The result of lower rSI in endometrial polyp in our study may reflect low signal central core on T2-WI. Even if the differentiation of normal endometrium from those with endometrial diseases by the endometrial signal intensity may be significant, we should recognize that they overlapped a lot as shown in figure 5. Some subjects in luteal phase can show low signal endometrium than those with endometrial diseases.

There were no significant difference both in thickness and signal intensity between the normal endometrium in luteal phase and that of the endometrial hyperplasia. When thickening of the endometrium is encountered, it may be better to recommend to gynecologists checking cyclic change of the endometrium or endometrial pathology.

There are some limitations in the present study. Firstly, the population with diseases was small. Although the patients were collected retrospectively, it was better to make prospectively. Second, we could not correlate the imaging of the normal endometrium with its pathological state. It may possible to exam pathologically for the patients with normal endometrium who will be operated for other diseases such as ovarian tumors.

Conclusion
Normal endometrium in luteal phase tends to show thick endometrium with low signal intensity at the periphery of the endometrium. Differentiation of normal endometrium in luteal phase from endometrial diseases such as endometrial polyp, hyperplasia and cancer is difficult especially only by its thickness. The extent of "normal" endometrial appearance in MR imaging is difficult, especially in luteal phase due to dynamic cyclic change of the uterus.
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