Chapter 5

MR imaging in the evaluation of (deep infiltrating) endometriosis: the value of diffusion-weighted imaging

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Abstract

Purpose: To assess the value of magnetic resonance (MR) diffusion-weighted imaging (DWI) in the evaluation of deep infiltrating endometriosis (DIE).

Materials and Methods: In a prospective single center study, DWI was added to the standard MR imaging protocol in 56 consecutive patients with known or suspected endometriosis. Endometriotic lesions as well as (functional) ovarian cysts were analysed for location, size, and signal intensity on T1-, T2-, and DWI. Apparent diffusion coefficient (ADC) values were calculated using b-values of 50, 400, 800 and 1200 s/mm². Statistical analysis included the Spearman correlation coefficient, Mann Whitney U and Kruskall-Wallis tests.

Results: A total of 110 lesions (62 endometrial cysts and 48 DIE) were detected, 60 of which were large enough to analyse. Mean ADC values of endometrial cysts and functional ovarian cysts were $1.10 \times 10^{-3}$/mm²/s and $2.14 \times 10^{-3}$/mm²/s respectively. Mean ADC values of DIE retrocervical, infiltrating the colon and bladder were $0.70 \times 10^{-3}$/mm²/s, $0.77 \times 10^{-3}$/mm²/s and $0.79 \times 10^{-3}$/mm²/s respectively. ADC values of DIE did not show a significant difference between varying pelvic locations (p=0.63).

Conclusion: Results of our study suggest that ADC values of DIE are consistently low, without significant difference between pelvic locations.
Introduction

Deep infiltrating pelvic endometriosis (DIE) is defined as an endometriotic lesion penetrating into the retroperitoneal space or the wall of the pelvic organs to a depth of at least 5 mm [1]. Locations of DIE include the retrocervical area (torus uteri and posterior fornix; in literature often described as in the rectovaginal septum), uterosacral ligaments, rectum, vagina and bladder. If so indicated, accurate preoperative assessment of disease extension is essential for planning of complete surgical excision [2-4]. Imaging techniques that are currently used to evaluate and assess DIE include ultrasonography (US) and magnetic resonance imaging (MRI). Although transvaginal US is considered to be the primary imaging modality for diagnosis of endometriosis, the role of MRI in patients with pelvic pain symptoms has been expanding steadily over the past years [5-8]. Currently, the state-of-the-art imaging protocol for the evaluation of endometriosis includes T2- and fat suppressed T1-weighted sequences in various different imaging planes [7-9]. This provides consistent information on the extent, severity as well as the stage of hemorrhagic components of endometriosis, especially in DIE.

Recent technical advances in diffusion-weighted imaging (DWI) greatly enhanced the value of body MRI [10-12]. The inclusion of a number of different b-values allows for an accurate calculation of apparent diffusion coefficient (ADC) values as a representation of the degree of water molecular diffusion as well as perfusion within the assessed area. As the b-value increases, the amount of intravoxel incoherent motion (IVIM) will show a more accurate representation of the true diffusion within the measured voxel, as the amount of contributing perfusion will decrease [13]. The degree of restricted water diffusion in biological tissues has been shown to inversely correlate to the tissue cellularity and the integrity of the cell membranes [14]. Even though several authors have reported decreased ADC values for a variety of malignant lesions [15,16], ADC values have shown considerable overlap in the differentiation of benign from malignant lesions [17,18].

The value of DWI in the evaluation of gynaecological diseases has been evaluated in a number of different studies, including the assessment of cervical carcinoma, malignant ovarian lesions and benign ovarian lesions [15,16,19-22]. The main
purpose of these studies was to evaluate DWI in the differentiation of benign from malignant lesions. A few studies reported on decreased ADC values in endometrial cysts [19,21,22].

To the best of our knowledge, no study has evaluated the value of DWI in state-of-the-art MR imaging for the evaluation of endometriosis, including DIE. The purpose of our study therefore, was to assess and evaluate the addition of DWI to routine MR imaging for the evaluation of patients with deep-infiltrating endometriosis.

**Materials and methods**

**Patient Population**

The institutional review board (IRB) granted permission for this study; the requirement for informed consent was waived. The study was performed in a tertiary referral center for the evaluation of patients with endometriosis. Between July 2008 and March 2009, all patients who were referred to our department for MR imaging to evaluate pelvic endometriosis were included. A total of 56 consecutive patients (age range, 16-50; mean 33 years) were evaluated, more than half of which (31) were diagnosed with endometriosis previously. Patients presented with a broad spectrum of symptoms. No patients were excluded.

**MR Imaging Technique**

MR imaging of the pelvis was performed at 1.5 Tesla (Avanto, Siemens, Erlangen, Germany) using a six-channel pelvic phased-array coil. Scan sequences included high resolution turbospin echo (TSE) T2-weighted imaging in the axial, coronal, and sagittal planes (repetition-time (TR)msec/echo-time (TE) msec 6000-10000/136, echo-train length (ETL) 61, number of acquisitions 3; and fat suppressed spin-echo T1-weighted imaging in the axial and sagittal planes (540/12; number of acquisitions 2) using a multislice technique. Slice thickness varied from 4 to 6 mm with a 0.8 to 1.2 mm interslice gap. Matrix size varied from 512x435 to 256x144 (the latter for T1-weighted images), and the field of view (FOV) ranged from 350 to 400 (depending on the size of the patient). No intravenous contrast medium was used.
DWI was performed in the axial plane, using a single-shot echo-planner imaging (EPI) sequence (4100/82, number of acquisitions: 4), FOV 350 cm, matrix 192x192, slice thickness /interslice gap 4/ 0 mm, and $b$-values of 50, 400, 800, and 1200 s/mm$^2$. The total imaging time per patient was approximately 24 minutes. The added examination time for DWI was approximately 4 minutes.

**Image Analysis**

Exams were analysed on a picture archiving and communication system (Centricity RA 600) viewing station (GE Healthcare, Milwaukee, USA). Both the quantitative as well as the qualitative assessment was done on evaluation of each single lesion with a minimum size of 15 mm to ensure reproducibility of the observations. All MR images were evaluated by two readers in consensus, with experience in the evaluation of endometriosis patients. All evaluations were done using standardized data scoring sheets.

Following criteria were used for diagnosis: 1) endometrial cysts: homogeneous hyperintensity on T1- and hypointensity on T2-weighted images (shading) [23]. 2) endometrial cysts with fluid-fluid levels or the “hematocrit effect” [24]: iso- to hypointensity of the dorsal part, hyperintensity of the ventral part on T2-; and homogeneously hyperintensity on T1-weighted imaging (indicating extra cellular methemoglobin). 3) DIE: joint presence of signal intensity abnormalities as well as morphologic abnormalities as reported previously by Bazot et al [7].

For quantification of the signal intensity (SI) of lesions and controls (urine, functional ovarian cysts and muscle) on T1- and T2-weighted images, operator-defined regions-of-interest (ROIs) of at least 30 mm$^2$ were placed, taking care not to include major vessels or borders of the lesions. The SI was normalized to muscle, using the rectus abdominis, gluteus maximus and obturatorius muscle. For quantification of DWI images, ADC values were calculated using $b$-values of 50, 400, 800 and 1200 s/mm$^2$. ROI measurements of at least 30 mm$^2$ in endometrial cysts and DIE, copied from the T2-weighted images for accurate anatomical placement, were placed on the ADC map for calculation purposes. Furthermore ADC values of functional ovarian cysts and urine were calculated to compare with ADC values of endometrial cysts.
Statistical Evaluation

Statistical parameters (mean and range) were calculated using the Statistical Package for Social Sciences (SPSS 15.0, Chicago Ill) program. Nonparametric tests (Spearman correlation coefficient) were performed to evaluate whether ADC was correlated with T2SI and T1SI ratios in endometrial cysts and DIE. The Kruskall-Wallis test was used to compare ADC values between different endometriosis locations and the Mann Whitney U test to compare ADC values of endometrial cysts with ADC values of functional ovarian cysts and urine, as well as ADC values of DIE with ADC values of muscle. A p-value of less than 0.05 was considered statistically significant.

Fig 1. 23-year old patient presenting with dysmenorrhea, dyspareunia, hematuria and recurrent cystitis. A, B: Sagittal and axial T2-weighted images showing hypointensity of bladder detrusor endometriosis and deep infiltrating retrocervical endometriosis. C, D: DW images (b-50/b-400). E: Corresponding ADC map shows restriction of Brownian movement in both lesions; ADC value of bladder detrusor endometriosis was $0.88 \times 10^{-3}$ mm$^2$/s.
Results

Conventional MR Findings
A total of 110 endometriotic lesions were found in 44 out of 56 patients. DIE was found retrocervical in 29 patients (torus uterinus, posterior fornix or both), in the rectal wall, rectosigmoid wall and sigmoid in 10, 1 and 3 patients respectively. Four DIE lesions were located in the bladder detrusor wall and 1 in the rectovaginal septum. Two endometriotic lesions were located in the plica vesico-uterina. A total of 62 endometrial cysts were found in 25 out of 56 patients. Functional ovarian cysts were found in 46 out of 56 patients.

ADC, T2SI and T1SI Ratio Calculation
In 60 out of 110 endometriotic lesions we were able to place a ROI of 30 mm² in at least one location of endometriosis (DIE or endometrial cysts).
ADC values, T2SI and T1SI ratios were calculated in 11 of 14 lesions with colon infiltration, 19 of 29 retrocervical, 4 of 4 bladder detrusor endometriotic lesions, 1 lesion in the rectovaginal septum. In all patients in whom rectal infiltration was analysed, DIE was also analysed retrocervical. In one patient three DIE lesions were analysed (retrocervical, rectum and bladder).
Twenty five of 62 endometrial cysts and 22 functional ovarian cysts were evaluated. Although in most patients only a single endometrial cyst was analysed, in 5 patients 2 endometrial cysts and one patient 3 endometrial cysts were analysed (two of which with fluid-fluid levels).
**ADC values**

Mean ADC value of retrocervical endometriosis, bladder detrusor endometriosis (Fig. 1) and endometriosis with colon infiltration (Fig. 2) as shown in Table 1, ranged from $0.70 \times 10^{-3}$ mm$^2$/s to $0.79 \times 10^{-3}$ mm$^2$/s. Mean ADC in DIE lesions did not significantly differ between varying pelvic locations ($p= 0.63$). ADC values in DIE were significantly higher than ADC values of the m.obturatorius, m.rectus abdominis and m.gluteus maximus ($p< 0.01$).

**Table 1.** Relationship between mean ADC values ($10^{-3}$ mm$^2$/s), T2SI and T1SI ratios in DIE, endometrial cysts and controls

<table>
<thead>
<tr>
<th>Location of endometriosis and controls</th>
<th>Number</th>
<th>ADC</th>
<th>Range</th>
<th>T2SI ratio</th>
<th>Range</th>
<th>T1SI ratio</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrocervical</td>
<td>19</td>
<td>0.70</td>
<td>0.13-1.01</td>
<td>2.76</td>
<td>1.09-5.48</td>
<td>1.07</td>
<td>0.81-1.28</td>
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<tr>
<td>Rectosigmoid</td>
<td>11</td>
<td>0.77</td>
<td>0.22-1.27</td>
<td>2.52</td>
<td>1.18-4.14</td>
<td>1.13</td>
<td>0.97-1.48</td>
</tr>
<tr>
<td>Bladder</td>
<td>4</td>
<td>0.79</td>
<td>0.69-0.88</td>
<td>2.84</td>
<td>2.48-3.84</td>
<td>1.09</td>
<td>1.03-1.17</td>
</tr>
<tr>
<td>Rectovaginal septum</td>
<td>1</td>
<td>0.80</td>
<td></td>
<td>2.83</td>
<td></td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td>Endometrial cysts</td>
<td>25</td>
<td>1.10</td>
<td>0.10-2.26</td>
<td>7.81</td>
<td>0.68-17.48</td>
<td>3.21</td>
<td>2.70-3.79</td>
</tr>
<tr>
<td>Control measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional ovarian cysts</td>
<td>22</td>
<td>2.14</td>
<td>1.83-2.47</td>
<td>24.49</td>
<td>7.25-37.68</td>
<td>1.10</td>
<td>0.63-1.22</td>
</tr>
<tr>
<td>Urine</td>
<td>46</td>
<td>2.14</td>
<td>1.62-2.66</td>
<td>24.36</td>
<td>13.33-37.63</td>
<td>0.61</td>
<td>0.48-0.87</td>
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<tr>
<td>M.obturatorius</td>
<td>47</td>
<td>0.32</td>
<td>0.13-0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.rectus abdominis</td>
<td>45</td>
<td>0.55</td>
<td>0.31-0.97</td>
<td></td>
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<td></td>
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<tr>
<td>M.gluteus</td>
<td>47</td>
<td>0.58</td>
<td>0.20-0.86</td>
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</table>
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Fig 2. 38-year old patient with progressive dysmenorrhea. T2-weighted images show DIE located retrocervical, extending to and infiltrating the rectum. A, B: Sagittal and axial T2-weighted images show a retrocervical DIE lesion that extends to and infiltrates the rectum. C: DWI image (b50). D: Corresponding ADC map showing restriction of diffusion in the DIE lesion; Calculated ADC value was $0.73 \times 10^{-3}$ mm$^2$/s.

Mean ADC value of endometrial cysts was $1.10 \times 10^{-3}$ mm$^2$/s (Fig. 3). ADC values of endometrial cysts were significantly lower compared to ADC values of functional ovarian cysts ($2.14 \times 10^{-3}$ mm$^2$/s; $p<0.01$). Furthermore mean ADC value of functional ovarian cysts was similar to mean ADC value of urine. ADC values of the dorsal and ventral part of two endometrial cysts showing fluid-fluid levels were 1.32, 1.00 (dorsal), 2.08 and 2.23 $\times 10^{-3}$ mm$^2$/s (ventral).

In two patients a solid nodule, within an endometrial cyst was found. The first showed endometrioid adenocarcinoma at histological examination. This lesion showed low signal intensity compared to muscle on T2, isointensity compared to muscle on T1, and low signal intensity on DWI. ADC was $0.65 \times 10^{-3}$ mm$^2$/s. The second nodule had an identical appearance on T2-, T1- and DWI (Fig. 4). ADC varied considerably, ranging from 0.43 to $0.74 \times 10^{-3}$ mm$^2$/s. Histologic examination showed fibrotic tissue.
Fig 3. T2-, T1-, DWI, and ADC map in two patients diagnosed with endometrial cysts that show difference in shading, that is related to the ADC value. A 29 year old patient known previously with severe DIE infiltrates the rectum (A-D). Follow-up MRI after treatment with hormone treatment (Gonadotrophin-releasing hormone agonist)and another patient, 27 year old, presenting with progressive dysmenorrhea, chronic pelvic pain, dyschezia and dyspareunia (E-H). A,B: T2-weighted images show endometrial cysts with shading; T2SI ratios were 2.70, 5.32 and 12.68. C,D: T1-weighted images show high intensity of the cysts, indicating their hemorrhagic content. E,F: DWI (b-50). G,H: Corresponding ADC maps; ADC values were 0.49, 1.16 and $1.43 \times 10^{-3}$ mm$^2$/s.
Correlations Between ADC Values and T2SI and T1SI Ratios

ADC values versus T2SI and T1SI ratios (related to the signal intensity of the musculus obturatorius) are mentioned in Table 1. Correlations between ADC, T2SI ratios and T1SI ratios are shown in Fig. 5 and 6.

The T2-weighted signal intensity of the obturatorius muscle showed the smallest variation compared to the rectus abdominis and gluteus maximus muscle, and was therefore chosen to calculate T2SI and T1SI ratios in DIE and endometrial cysts.

Fig 4. 44-year old patient known previously with endometriosis who was referred to our clinic to exclude malignancy (A-C); and a 35 year old patient known with endometriosis and subfertility previously who was referred because of progression of dyschezia and dyspareunia (D-F). A: T2-weighted image shows low intensity (shading) of an endometrial cyst in the left ovary with a solid nodule. Histological examination revealed endometrioid adenocarcinoma. B: T1-weighed image shows marked hyperintensity of the cyst, indicating hemorrhage with a hypointense nodule. C: Corresponding ADC map; calculated ADC of the nodule is 0.65 x 10^-3 mm^2/s. D: Axial T2-weighted image shows hypointensity of a large endometrial cyst in the left ovary (shading) with a solid nodule. E: Axial T1-weighted image shows hemorrhagic content of the endometrial cyst. F: Corresponding ADC map; the ADC value within the solid nodule of the endometrial cyst ranged from 0.43 to 0.74 x 10^-3 mm^2/s. At pathology the nodule consisted of fibrosis and hemorrhagic components.
The correlation between ADC values and T2SI ratios in endometrial cysts of 0.77 was significant \((p<0.05)\). Comparing ADC with T1SI ratios and T1SI with T2SI ratios, correlations were not significant.

In DIE lesions correlations between ADC and T2SI \((0.65)\), ADC and T1SI \((0.45)\), as well as T2SI ratios and T1SI ratios \((0.40)\) were significant \((p<0.05)\).

**Fig 5.** Correlation between ADC values \((10^{-3} \text{ mm}^2/\text{s})\) and T2SI ratios in DIE \((0.65; p<0.05)\)

**Fig 6.** Correlation between ADC values \((10^{-3} \text{ mm}^2/\text{s})\) and T2SI ratios (SI/m. obturatorius) in endometrial cysts \((0.77; p<0.05)\)
Discussion

The main results of our study indicate that DIE shows a consistently low ADC value, irregardless of its location within the pelvis, and that endometrial cysts show a significant lower ADC compared to functional ovarian cysts, with a significant correlation between ADC values and T2SI ratios. Significant correlations between ADC values compared to T2SI and T1SI ratios in DIE were found.

Mean ADC values of DIE are consistently decreased and were not significantly different between pelvic locations. This study supports results of a previous study by Anaf et al, in which DIE lesions showed similar smooth muscle components, independent of their location [25]. Moreover in another study histologic patterns in biopsies of DIE did not show significant differences [26]. Restriction of Brownian movement in DIE may be caused by components of fibrosis and muscle, which are known to be present at histology in DIE [27]. Presence of fibrosis may result in decreased T2SI ratios and T1SI ratios as well as in decreased ADC values and might therefore explain the significant correlation we found between ADC values, T2SI ratios and T1SI ratios in DIE.

Mean ADC value of endometrial cysts ($1.10 \times 10^{-3} \, \text{mm}^2/\text{s}$) was decreased and significantly lower compared to functional ovarian cysts ($2.14 \times 10^{-3} \, \text{mm}^2/\text{s}$). These results are comparable to previous reports, although mean ADC was slightly higher in our study [19,22]. This can probably be explained by a slightly higher percentage of T1 hyperintense lesions with a slightly hyperintense aspect (low grade of shading) on T2-weighted imaging in our study.

A few previous studies involved DWI in endometrial cysts. Cystic components of endometrial cysts and malignant ovarian cystic tumors were demonstrated to exhibited lower ADC values than other benign ovarian cysts [20,22]. Nakayama et al showed a significant difference in the ADC values of the cystic content between benign and malignant lesions, but as the authors reported, this was due to a relatively large number of mature cystic teratomas and endometrial cysts included in their series [22]. In our study ADC values in endometrial cysts showed considerable variation. Moreover in two patients with a quite similar appearance of a solid nodule in an endometrial cyst, histology showed endometrioid adenocarcinoma in one and fibrosis in the other. Mean ADC value of endometrioid adenocarcinoma was comparable to a previous study by Fujii et al [15] and overlapped with the ADC values of the fibrotic component.
of the endometrial cyst in the second patient. Therefore DWI does not seem to be suitable to differentiate between benign and malignant tissue in endometrial cysts. The variation between ADC values of endometrial cysts in our study was found to be almost linearly related to the degree of shading found on T2-weighted imaging (Fig. 3). Our results support the findings of a study by Takahashi et al [28] that reported that the iron concentration and density in endometrial cysts correlated significantly, as well as iron concentration and T2 signal intensity. Our findings are in contradiction to a study by Moteki et al [21] who found a low correlation between ADC values and T2SI and T1SI ratios in endometrial cysts. Their explanation is that the ADC value is almost linearly dependent on blood concentration and almost independent of the methemoglobin-related paramagnetic effect and the diminution of magnetic nonhomogeneity by gradual red blood cell lysis, two factors that significantly affect signal intensity. Using the gluteus muscle to calculate T2SI ratios might result in a lower correlation between T2-ratios and ADC values due to different grades of fatty infiltration and atrophy (especially in women). No significant difference in correlations between ADC, T2SI and T1SI ratios using the m.obturatorius, m.rectus abdominis and m.gluteus maximus muscle as reference was found in the current study.

Some limitations of our study should be highlighted. Firstly, a substantial amount of tissue is needed to generate an accurate ADC measurement. Therefore ADC measurements could only be performed in 60 of 110 endometriotic lesions. Secondly pathology was not obtained in all cases, because most patients were primarily treated medically. Nevertheless, MR imaging has been reported to accurately diagnose endometrial cysts and DIE [7,23] and most patients were known with endometriosis previously. Finally, in the present study, no analysis was done to evaluate quantitative DWI in differentiating endometriosis from other pathologies. Further research is needed therefore, to assess the potential value of DWI in differentiating DIE from other pathologies.

In conclusion, in the present study we have demonstrated that the ADC values of DIE are consistently decreased, without any significant difference between pelvic locations. In addition, in the differentiation between endometrial cysts from other pelvic cysts, ADC values show a comparable diagnostic performance as evaluation of the T2- and T1-weighted images.
References


2. Abrao MS, Podgaec S, Dias JA, Jr., Averbach M, Silva LF, Marino de CF. Endometriosis lesions that compromise the rectum deeper than the inner muscularis layer have more than 40% of the circumference of the rectum affected by the disease. J Minim Invasive Gynecol 2008;15:280-285.


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