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FULL PAPER

3-T diffusion tensor imaging (DTI) of normal uterus in young and middle-aged females during the menstrual cycle: evaluation of the cyclic changes of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values

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Objective: To evaluate cyclic changes of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of normal uterus in different age groups during the menstrual cycle, and the correlation with serum female hormone levels.

Methods: 29 normal volunteers accepted diffusion tensor imaging of the uterus on menstrual phase (MP), follicular phase (FP), ovulatory phase (OP) and luteal phase. FA and ADC values of different uterine layers on midsagittal images were measured. Differences between two age groups during the menstrual cycle were evaluated using liner mixed models and one-way analysis of variance. Pearson correlation analysis compared variation of FA and ADC values with serum female hormone levels measured in MP.

Results: During menstrual cycle, endometrial FA values declined, whereas ADC values increased with significant differences ($p < 0.05$). Serum oestradiol (E) levels correlated moderately with variations of FA values between MP-FP ($p = 0.045$; $r = 0.389$) and MP-OP ($p = 0.008$;

$r = 0.511$). FA and ADC values of junctional zones showed no significant difference ($p > 0.05$) as well as FA values of myometrium ($p = 0.0961$), while ADC values of myometrium showed significant increase from menstrual phase to luteal phase ($p < 0.05$). FA and ADC values of uterine three zonal structures showed significant differences ($p < 0.05$) at each phase during the menstrual cycle. No significant difference of FA and ADC values was found between age groups ($p > 0.05$).

Conclusion: Dynamic changes of uterine FA and ADC values were observed during menstrual cycle. Variation of FA values between MP-FP, MP-OP correlated moderately with serum E levels.

Advances in knowledge: No publications on the relationship between FA and ADC values and the female hormone levels were found; our study prospectively investigated the cyclic changes of FA and ADC values of the normal uterus and the correlation with the basic serum female hormone levels in MP.

Diffusion tensor imaging (DTI) is a well-established technique, which has been widely used in variable neurological diseases¹⁻⁴ and other parts of the body, such as the musculoskeletal system,^{5,6} prostate^{7,8} and kidney.^{9,10}

In recent years, limited publications of its application in the female pelvis have been emerging. Current published studies include *ex vivo* and *in vivo* studies.¹¹⁻¹⁶ In 2006, three-dimensional fibre architecture of the normal human

uterus based on DTI has been *ex vivo* evaluated in five samples by Weiss et al.¹¹ Toba et al.¹² *ex vivo* study showed that DTI might be a useful tool for the diagnosis of myometrial invasion of uterine endometrial cancer. However, fractional anisotropy (FA) value of a normal uterus has not been thoroughly investigated yet. What is more there is no known publication, to the best of our knowledge, found on the relationship between FA value and female menstrual cycle. It would be ambiguous to use

this MR parameter to evaluate malignancy situations without knowing the possible differences in various uterine structures, including endometrium, myometrium and junctional zone. In 2012, Fiochi et al¹³ investigated the feasibility of depicting fibre architecture of the human uterus *in vivo* using 3-T MR-DTI based on 30 volunteers in different menstrual phases (MPs). In 2013, Fujimoto et al¹⁴ compared the DTI parameters in the different uterine layers of nine subjects *in vivo*, but limited their study group to the luteal phase (LP) only. A more comprehensive study based on 11 normal young females was reported by Kido et al;¹⁵ however, only apparent diffusion coefficient (ADC) value changes were evaluated during three phases of menstrual cycle. To the best of our knowledge, there are no published data focused on the cyclic changes of FA value in a normal uterus during four phases of menstrual cycle with a larger study cohort. Moreover, as it has been learned from MRI studies, anatomical and physiological characteristics of uterine structures, such as the endometrium and junctional zone, are heavily related to female hormone levels.^{17–22} Nevertheless, no publications on the relationships between FA or ADC values and the hormone level were found.

So, the aim of our study was to prospectively investigate the cyclic changes of FA and ADC values of the normal uterus in a larger population divided into different age groups during the four phases of the menstrual cycle, and the correlation with the basic serum hormone levels in MP.

METHODS AND MATERIALS

Volunteer data

This prospective study was approved by our local institution's ethics committee, and written informed consent was obtained from all participants. The inclusion criteria were healthy females of 20–40 years old, with regular menstrual cycle (28 ± 7 days) and biphasic basal body temperature, without history of gynaecological diseases or operation, without taking oral contraceptives or hormone replacement therapy in past 6 months, without MR scanning contraindication. 43 volunteers, with no history

of pregnancy and delivery, who met the inclusion criteria were enrolled. Females who had congenital uterine anomalies, multiple uterine leiomyomas or leiomyomas >1 cm, or adenomyosis detected by the first MR scanning and abnormal serum hormone levels were excluded. 14 females were excluded with the following reasons: uterine anomalies ($n = 4$), uterine leiomyomas ($n = 2$), adenomyosis ($n = 2$), MR intolerable ($n = 1$), failed to finish four scans ($n = 3$) and abnormal serum hormone levels ($n = 2$). Therefore, 29 volunteers (age range, 22–40 years; mean age, 28.7 years) (20–30 years, $n = 17$; 31–40 years, $n = 12$) completed four MR scans in our study.

Preparation and MRI acquisition

For each volunteer, MR scans were scheduled during four phases of the menstrual cycle, respectively [the second or third days of MP, follicular phase (FP), peri-ovulatory phase (OP) and LP]. The date of ovulation was estimated as either 14 days before the anticipated first day of the next menstrual cycle or on the basis of elevated basal body temperature. MR scans in the follicular and LP were obtained approximately in the middle of the phases.

10 ml of glycerine enema (Beijing Maidihai Medical Business Co., Ltd, Beijing, China) was administrated into the rectum 1 h before MR scanning to reduce the air in the rectum and sigmoid. A moderately full bladder was required. MRI of the female pelvis was performed in a 3.0-T MRI scanner (Magnetom® Skyra; Siemens Healthcare, Erlangen, Germany) with an 18-channel phase array body coil. Prone and feet-first scanning mode was used to reduce the motion artefacts from the small intestines. Sagittal and axial turbo spin echo (TSE) T_2 weighted images and axial TSE T_1 weighted images were obtained to define the anatomy of the pelvic organs and to screen for gynaecological abnormalities. Sagittal DTI was obtained parallel to the long axis of the uterine corpus, the same imaging plane as that of the sagittal T_2 weighted image. The parameters for DTI were as follows: repetition time/echo time, 4500/66 ms; field of view (FOV)

Figure 1. Measurement of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of the uterus in luteal phase; images obtained from a 26-year-old healthy volunteer. Polygonal-shaped regions of interest (ROIs) were drawn on T_2 weighted images of the uterus on midsagittal plane (a) to cover the three zonal structures of the uterus (endometrium, red; junctional zone, green; myometrium, purple). The corresponding ROIs were automatically drawn on FA map (b) and ADC map (c) simultaneously. FA and ADC values were automatically calculated. FoV, field of view; Sag, sagittal; SL, slice thickness. For colour images please see online.

read, 250 mm, FOV phase, 100%; bandwidth, 1488 Hz per pixel; b -values, 0 and 600 s mm^{-2} ; diffusion direction, 20; averages, 3; slices, 26; slice thickness, 3 mm; distance factor, 20%; phase partial Fourier, 6/8; voxel size, $1.6 \times 1.6 \times 3.0 \text{ mm}$. For fat suppression, the spectral attenuated inversion recovery technique was used. The acquisition time for DTI was 5 min 6 s.

Imaging analysis

DTI data sets were transferred to a post-processing workstation (WWMP3960#; Siemens Healthcare) and processed using Neuro 4D software (Siemens Healthcare). FA and ADC map was automatically calculated. FA values were calculated as follows:

$$FA = \sqrt{\frac{1}{2} \frac{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (1)$$

where λ_1 , λ_2 and λ_3 correspond to the three eigenvalues of the diffusion tensor. ADC values were calculated on a voxel-by-voxel basis by the following formula:

$$ADC = \left(\frac{1}{b} \right) \times -\ln \left(\frac{S}{S_0} \right) \quad (2)$$

where S_0 and S are the signal intensities of each voxel obtained with b -values of 0 and 600 s mm^{-2} , respectively.

Images were evaluated by two radiologists with expertise in female pelvic imaging. Data analysis was based on final consensus readings. FA and ADC values of the uterus were

measured on $b = 0 \text{ s mm}^{-2}$ FA and ADC map images, respectively. Polygonal-shaped regions of interest (ROIs) were drawn to cover the corresponding three zonal structures of the uterus (endometrium: mean total size, 54.5 ± 32.2 pixels; mean area, $1.4 \pm 0.8 \text{ cm}^2$; junctional zone: mean total size, 105.0 ± 42.3 pixels; mean area, $2.7 \pm 1.1 \text{ cm}^2$; myometrium mean total size, 223.7 ± 92.4 pixels; mean area, $5.7 \pm 2.4 \text{ cm}^2$) (Figure 1).

Serum hormone examination

Serum concentrations of oestradiol (E), progesterone (P), luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured in MP just before MR scanning to evaluate the basic hormone levels.

Statistical analysis

Statistical analysis was performed using SAS® v. 9.2.3 (SAS Institute Inc., Cary, NC) and SPSS® v. 19.0 (SPSS Inc., Chicago, IL). A p -value of 0.05 was chosen to indicate a statistically significant difference. Mixed liner models (considering interaction effect) were used to evaluate the differences of FA and ADC values of three zonal structures of the uterus between two age groups and among four MPs. One-way analysis of variance was used to evaluate the difference of FA and ADC values among the three zonal structures of the uterus. Correlation between serum levels of E, P, LH, FSH and the variation of FA and ADC values during the menstrual cycle was estimated by Pearson correlation analysis.

RESULTS

FA and ADC values of three zonal structures of the uterus in different age groups during the menstrual cycle are listed in Tables 1 and 2.

Table 1. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of three zonal layers of the uterus in two age groups during the menstrual cycle

Layers	Age groups (years)	Menstrual phase	Follicular phase	Ovulatory phase	Luteal phase
FA					
EM	20–30 ($n = 17$)	0.279 ± 0.108	0.181 ± 0.047	0.163 ± 0.027	0.138 ± 0.057
	30–40 ($n = 12$)	0.278 ± 0.052	0.200 ± 0.040	0.166 ± 0.049	0.147 ± 0.039
JZ	20–30 ($n = 17$)	0.319 ± 0.068	0.300 ± 0.058	0.304 ± 0.079	0.285 ± 0.071
	30–40 ($n = 12$)	0.312 ± 0.078	0.306 ± 0.088	0.338 ± 0.044	0.288 ± 0.080
MY	20–30 ($n = 17$)	0.247 ± 0.055	0.229 ± 0.031	0.232 ± 0.037	0.214 ± 0.039
	30–40 ($n = 12$)	0.233 ± 0.045	0.212 ± 0.041	0.204 ± 0.037	0.206 ± 0.042
ADC ($10^{-3} \text{ mm}^2 \text{ s}^{-1}$)					
EM	20–30 ($n = 17$)	1.018 ± 0.158	1.320 ± 0.169	1.408 ± 0.116	1.476 ± 0.183
	30–40 ($n = 12$)	1.045 ± 0.105	1.319 ± 0.075	1.445 ± 0.173	1.354 ± 0.219
JZ	20–30 ($n = 17$)	1.170 ± 0.156	1.254 ± 0.087	1.252 ± 0.140	1.277 ± 0.145
	30–40 ($n = 12$)	1.154 ± 0.153	1.199 ± 0.160	1.161 ± 0.064	1.233 ± 0.133
MY	20–30 ($n = 17$)	1.789 ± 0.224	1.859 ± 0.127	1.838 ± 0.191	2.003 ± 0.157
	30–40 ($n = 12$)	1.739 ± 0.160	1.819 ± 0.175	1.901 ± 0.155	1.978 ± 0.147

EM, endometrium, JZ, junction zone; MY, myometrium.
Data are mean $\pm$ standard deviation.

Table 2. Cyclic changes of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values during the menstrual cycle

Layers	$n = 29$				p -values					
	MP	FP	OP	LP	MP-FP	MP-OP	MP-LP	FP-OP	FP-LP	OP-LP
FA										
EM	0.279 ± 0.090	0.189 ± 0.046	0.164 ± 0.038	0.141 ± 0.050	0.000	0.000	0.000	0.042	0.000	0.079
JZ	0.316 ± 0.072	0.302 ± 0.071	0.319 ± 0.068	0.286 ± 0.075	0.443	0.861	0.138	0.333	0.377	0.056
MY	0.241 ± 0.051	0.223 ± 0.036	0.220 ± 0.040	0.211 ± 0.041	0.036	0.091	0.014	0.842	0.181	0.399
ADC ($10^{-3} \text{ mm}^2 \text{ s}^{-1}$)										
EM	1.030 ± 0.139	1.320 ± 0.140	1.424 ± 0.144	1.425 ± 0.207	0.000	0.000	0.000	0.019	0.030	0.968
JZ	1.163 ± 0.155	1.232 ± 0.124	1.213 ± 0.122	1.259 ± 0.142	0.119	0.221	0.024	0.527	0.396	0.142
MY	1.768 ± 0.201	1.843 ± 0.149	1.865 ± 0.179	1.993 ± 0.154	0.137	0.079	0.000	0.605	0.000	0.002

EM, endometrium; FP, follicular phase; JZ, junction zone; LP, luteal phase; MP, menstrual phase; MY, myometrium; OP, ovulatory phase. Data are mean ± standard deviation.

Endometrium

When age increased, FA and ADC values of the endometrium were slightly elevated, but with no statistical difference ($p > 0.05$). During the menstrual cycle, FA values of the endometrium declined, whereas ADC values increased with significant difference (Figure 2, Table 2). Serum E levels showed a moderate correlation with the difference of the FA values between MP and FP ($p = 0.045$; $r = 0.389$), and between MP and OP ($p = 0.008$; $r = 0.511$), whereas serum P, LH, FSH levels did not show such correlation with FA values during the menstrual cycle ($p > 0.05$). Serum hormone levels did not show any correlation with ADC values of the endometrium during the menstrual cycle ($p > 0.05$).

Junctional zone

Although without statistical difference ($p > 0.05$), FA values of the junctional zone showed an increase as age increased, while ADC values showed a decrease. FA and ADC values of the junctional zone showed no significant difference during the menstrual cycle ($p > 0.05$) (Figure 3, Table 2). Serum hormone levels did not show any correlation with FA and ADC values of the junctional zone during the menstrual cycle ($p > 0.05$).

Myometrium

FA values of the myometrium in the 30–40 years group were lower than that in the 20–30 years group, with no statistical difference ($p = 0.0917$). FA values of the myometrium showed no significant difference during the menstrual cycle ($p = 0.0961$) (Figure 4a, Table 2). ADC values of the myometrium showed significant difference during the menstrual cycle (MP vs LP, $p < 0.0001$; FP vs LP, $p = 0.0002$; OP vs LP, $p = 0.0016$), but with no statistical difference between age groups ($p = 0.7618$) (Figure 4b, Table 2). Serum hormone levels did not show correlation with FA and ADC values of the myometrium during the menstrual cycle ($p > 0.05$).

Three zonal structures of the uterus

In MP, FA values of junctional zone were significantly higher than that of the myometrium ($p = 0.000$). FA values of the endometrium were lower than that of the junctional zone ($p = 0.070$) and higher than that of the myometrium ($p = 0.067$), without significant difference. During FP, OP and LP, FA values of the three zonal structures of the uterus showed significant difference: FA values of junctional zone were significantly higher than that of the myometrium (FP, $p = 0.000$; OP, $p = 0.000$; LP, $p = 0.000$; respectively) and endometrium (FP, $p = 0.000$; OP, $p = 0.000$; LP, $p = 0.000$; respectively), while FA values of the myometrium were significantly higher than that of the endometrium (FP, $p = 0.020$; OP, $p = 0.000$; LP, $p = 0.000$; respectively) (Figure 5a, Table 3).

In MP, ADC values of the three zonal structures of the uterus showed significant difference: ADC values of the myometrium were significant higher than that of the junctional zone ($p = 0.000$) and endometrium ($p = 0.000$), while ADC values of

Figure 2. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of the endometrium between two age groups during the menstrual cycle. FA values of the endometrium declined (a), whereas ADC values increased with significant difference (b). No significant difference was found between age groups. FP, follicular phase; LP, luteal phase; MP, menstrual phase; OP, ovulatory phase.

the junctional zone were significant higher than that of the endometrium ($p = 0.006$). During FP, OP and LP, ADC values of the three zonal structures of the uterus showed significant difference: ADC values of the myometrium were significant higher than that of the endometrium (FP, $p = 0.000$; OP, $p = 0.037$; LP,

$p = 0.000$; respectively) and junctional zone (FP, $p = 0.000$; OP, $p = 0.000$; LP, $p = 0.000$; respectively), while ADC values of the endometrium were significant higher than that of the junctional zone (FP, $p = 0.022$; OP, $p = 0.000$; LP, $p = 0.000$, respectively) (Figure 5b, Table 3).

Figure 3. Fractional anisotropy (FA) (a) and apparent diffusion coefficient (ADC) (b) values of the junctional zone showed no significant difference during the menstrual cycle between age groups. FP, follicular phase; LP, luteal phase; MP, menstrual phase; OP, ovulatory phase.

DISCUSSION

This study prospectively investigated menstrual-related layer-specific changes in FA and ADC values of the uterus in 29 normal females aged from 22 to 40 years. Our results provided the initial information for the application of DTI in female pelvis during menstrual cycle. Moreover, we found serum E levels

showed a moderate correlation with the changes of FA values of the endometrium, which had not been reported in previous studies.

As age increased, FA values of the endometrium and junctional zone showed an increase, while FA values of the myometrium

Figure 4. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of the myometrium between two age groups during the menstrual cycle. FA values of the myometrium showed no significant difference during the menstrual cycle (a), whereas ADC values of the myometrium showed increasing tendency during the menstrual cycle with significant difference (b). FP, follicular phase; LP, luteal phase; MP, menstrual phase; OP, ovulatory phase.

showed a decrease, indicating the different variation of uterine microstructural organization such as the density and orientation of fibrous tissue as age increased, although there were no statistical differences. The previous study on cyclic changes of the uterine anatomical structures during menstrual cycle showed an

increasing tendency of endometrium thickness, which exhibited moderate correlation of the serum E levels in the MP.²³ The same correlation had been found between serum E levels and the changes of endometrial FA values, which showed declining tendency during the menstrual cycle. It could be inferred that

Figure 5. Fractional anisotropy (FA) (a) and apparent diffusion coefficient (ADC) (b) values of three zonal structures of the uterus showed significant difference in each menstrual phase during the menstrual cycle. FP, follicular phase; LP, luteal phase; MP, menstrual phase; OP, ovulatory phase.

higher serum E levels were accompanied by larger increase of the endometrium with higher isotropy of water diffusion directionality and lower FA values. Hence, FA values are partially influenced by the role of oestradiol on endometrial cell proliferation. In some oestradiol-related gynaecological diseases, such as endometrial cancer, the interpretation of FA values of the

endometrium should be considered with the patients' serum E levels and certain MPs. FA values of the junctional zone and myometrium showed no significant difference during menstrual cycle, indicating the almost undetectable changes of normal uterine myometrium during menstrual cycle, which could be used as a baseline for individual patients in clinical practice. FA

Table 3. Differences of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values among three uterine zonal structures during the menstrual cycle

Layers	Menstrual phase (<i>n</i> = 29)				Follicular phase (<i>n</i> = 29)				Ovulatory phase (<i>n</i> = 29)				Luteal phase (<i>n</i> = 29)			
	<i>p</i> -value	95% CI		<i>p</i> -value	95% CI		<i>p</i> -value	95% CI		<i>p</i> -value	95% CI		<i>p</i> -value	95% CI		
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper	
FA																
JZ-EM	0.070		−0.003	0.078	0.000	0.085	0.142	0.000	0.127	0.000	0.127	0.182	0.000	0.115	0.175	
MY-EM	0.067		−0.078	0.003	0.020	0.005	0.063	0.000	0.028	0.000	0.028	0.083	0.000	0.039	0.100	
JZ-MY	0.000		0.034	0.115	0.000	0.051	0.108	0.000	0.071	0.000	0.071	0.126	0.000	0.045	0.106	
ADC (10 ^{−3} mm ² s ^{−1})																
EM-JZ	0.006		−0.227	−0.039	0.022	0.013	0.162	0.000	0.113	0.000	0.113	0.356	0.000	0.076	0.257	
MY-EM	0.000		0.644	0.823	0.000	0.449	0.598	0.037	0.008	0.000	0.008	0.252	0.000	0.476	0.659	
MY-JZ	0.000		0.510	0.699	0.000	0.536	0.686	0.000	0.243	0.000	0.243	0.487	0.000	0.643	0.825	

CI, confidential interval; EM, endometrium; JZ, junction zone; MY, myometrium.

values of the three zonal structures of the uterus showed significant difference at each phase during menstrual cycle. The relative order of FA values of these three layers in LP was the same as Fujimoto's studies,¹⁴ reflecting the differences in the density of well-aligned fibre bundles. FA values of each layer in our study were smaller than those in previous studies, which might be explained by the different racial subjects as well as different MR scanners, image quality and ROI measurements in DTI.

ADC values of the endometrium and myometrium tended to increase during the menstrual cycle, the same results were found by Kido et al¹⁵ to study changes in ADC of the normal uterus based on diffusion-weighted imaging. As ADC values are affected by cell density, cell organization and microcirculation,²⁴ it is possible that the changes in ADC values seen during the menstrual cycle may reflect phase-specific physiological changes in three different zonal structures of the uterus. For the endometrium, the blood in MP could decrease the ADC values, just the same as the decreased ADC values seen in ovarian endometrial cyst.²⁵ For the myometrium, myometrial contraction and relatively low water content in MP might contribute to lower ADC values, whereas myometrial oedema in the LP might have higher ADC values. ADC values of the junctional zone showed no significant difference during menstrual cycle, which was the same as for FA values. The possible explanation might be the unique architecture of the junctional zone with concentric arrangement of smooth muscle fibres, even though early MRI studies reported that hormonal variation in the female reproductive cycle contributed to changes in thickness of the junctional zone, parallel to endometrial thickness but to a lesser degree.¹⁷

There were several limitations in our study. Firstly, the results are based on data from 29 subjects, although the changes in different age groups during the four different phases of the menstrual cycle showed almost consistent trends. The feasibility of our results may not necessarily be valid for larger populations, raising concern regarding clinical implications. We will carry out future study on a larger sample size. We could evaluate the influence of uterine location and axis in terms of anteversion or retroversion on FA and ADC values. Secondly, relatively large interindividual variation of FA values of the endometrium had been observed in the 20–30 years group in the MP. The possible reason might be the different contents of blood in the cavity. It would, therefore, be preferable to avoid using FA measurements obtained during the MP in order to minimize the effect of menstrual FA variation on baseline FA changes.

In conclusion, dynamic changes of FA and ADC values of the uterus were observed during menstrual cycle, showing significant differences among three zonal structures in each phase. Variation of FA values of the endometrium correlated moderately with serum E levels in MP.

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