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Diffusion-Weighted Images and its Application in the Clinical Diagnostic Testing of Endometrial Focal Lesions

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ABSTRACT
Background: Numerous endometrial disorders can create several difficulties for the radiologist due to the overlapping of imaging characteristics and diverse endometrial pathologies. The most frequently utilized imaging tool for diagnosing and characterizing endometrial focal lesions is magnetic resonance imaging (MRI) with diffusion weighted images (DWI).
Objective: We conducted this study to determine the efficacy of MRI with DWI in improving the diagnostic accuracy of endometrial focal lesions, especially in the differential diagnosis of benign and malignant focal endometrial masses.
Patients and Methods: This study recruited 36 women (21 postmenopausal and 15 premenopausal) who experienced vaginal bleeding and had endometrial thickness and focal endometrial lesions with a distinct echo pattern on ultrasound (US) examination. The age of patients was between 27 to 85 years, with an average of 45.2 years. Ethics Committee approval was obtained in addition to written informed consent from all included patients.
Results: The 36 patients included in this study, were classified according to their lesions histopathological results; Benign group (15 lesions; 41.67%) and malignant group (21 lesions; 58.33%). The most common benign lesion was endometrial polyp (9/15) while the most common malignant lesion was endometrial carcinoma (21/21). In the current study MRI with diffusion could correctly diagnose 33 lesions out of 36 lesions, achieving (91.6%) sensitivity, (100%) specificity, (100%) positive predictive value (PPV), (95.6%) negative predictive value (NPV) and accuracy (97.05 %)**.**
Conclusion: Integrating DWI and ADC mapping at a high b value in pelvic MRI examination improves the sensitivity, specificity, and precision of diagnosing endometrial focal lesions.
Keywords: ADC value, Diffusion-Weighted, Endometrial Focal Lesions, MRI.

INTRODUCTION

Several endometrial conditions may be challenging for radiologists due to the overlap of imaging features and variable endometrial pathologies. MRI with DWI is the most commonly used imaging technique for the diagnosis and characterization of endometrial focal lesions [(1)].

The majority of endometrial states share imaging characteristics with normal menstrual endometrial phases and diverse endometrial diseases, including endometrial hyperplasia, polyps, as well as endometrial cancer [(2)].

Diffusion-weighted magnetic resonance imaging (MRI) is based on the random mobility of water molecules inside various tissues [(3)]. When combined with apparent diffusion coefficient (ADC) mapping, DWI can indeed be employed to examine metastatic lesions, peritoneal deposits, tumor relapse, as well as therapeutic response [(4)].

DWI is a T2-weighted sequence in which two equal and opposite motion-probing gradients are used prior to and following the 180° refocusing pulse. Whenever freely moving water molecules are subjected to the first gradient pulse, they gain phase shift data; however, because they are moving, they are not at the same place and hence are not subjected to the exact identical gradients. Thus, no signal is generated during acquisition (free diffusion), but static water molecules (diffusion restricted) regain signal, as no significant phase shift occurs even by time of the second gradient, and the signal lost during the first gradient is recovered by the second opposite gradient (restricted diffusion) [(5)].

The ADC value is a quantitative representation of the diffusion in each pixel, and it displays as an image that may be used to examine the diffusion value visually. The amount of b values taken varies; generally, the more b values taken, the more precise the ADC value produced [(6)].

Endometrial diseases ranked among the most common gynecological disorders that affect women globally. These diseases cut across all age groups and contribute significantly to increased maternal morbidity and mortality. Most females with endometrial diseases present with abnormal uterine bleeding (AUB). Thus, AUB justify the need for urgent diagnosis. This is because of the wide range of histopathological patterns of endometrium diseases. These lesions range from simple endometrial hyperplasia to more complex disorders including endometrial carcinoma [(7)].

DWI is not only beneficial for differentiating benign and malignant processes; it could also be used to assess metastatic lesions, peritoneal spread, tumor recurrence, and therapeutic response [(8)]. Due to the fact that it does not necessitate the injection of a gadolinium-based contrast agent, it is suitable for individuals with renal impairment or an allergy to contrast material [(9)].

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We conducted this study to determine the efficacy of magnetic resonance imaging (MRI) with diffusion weighted (DW) images in improving the diagnostic accuracy of endometrial focal lesions, especially in the differential diagnosis of benign and malignant focal endometrial masses.

PATIENTS AND METHODS

This was a cross section study, a total of 36 participants with a localized endometrial lesion were included in this study. Ranging from 27 to 85 years old, the patient had a mean age of 45.2 years, during period from August 2020 to September 2021, all patients referred from the Obstetrics and Gynecology Department at Zagazig University Hospital and were transferred to the Radiodiagnosis Department at the same hospital.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: The study included participants who had abnormal vaginal bleeding or abnormally thickened endometrium monitored on ultrasound.

Exclusion criteria: Patients with absolute contraindications to MRI (patients with cardiac pacemakers, prosthetic heart valves, cochlear implants, or any metallic implant) were excluded, as were patients with claustrophobia.

Patient preparation:

Patients were subjected to the following procedures: a thorough medical history, a gynecological investigation, an ultrasound examination: All patients had undergone preliminary pelvic ultrasound, transabdominal and transvaginal ultrasound approaches using 3-4 MHz and 7-8 MHz probes respectively for 1ry localize endometrial lesions from other uterine lesions such as myometrial lesions. Color Doppler was superimposed on masses to detect vascularity. The examination was performed on high resolution ultrasonography machine (Siemens Acuson x300, USA) and MRI examination: MRI was performed on a 1.5-Tesla MR imaging unit (Philips Achieva). All the patients were imaged in the supine position using pelvic phased-array coil. Patients fasted for 3 hours. Intravenous administration of an antispasmodic drug (10 mg of (Visceralgine; Organon, Livron, France)) was given immediately before MR imaging to reduce bowel peristalsis.

MR Imaging protocol:

Localizer images in axial, coronal and sagittal planes. Fast spin echo (FSE) T1-weighted images (TR 497 ms, TE 12 ms, matrix 320 × 512, slice-thickness: 4–5 mm with an inter-slice gap of 1–2 mm, FOV 250 mm and a flip angle of 90) in axial and sagittal plane. Fast spin echo (FSE) T2-weighted images (TR 3.3 s, TE 90 ms, matrix 320 × 512, slice-thickness: 4–5 mm with an inter-slice gap of 1–2 mm, FOV 250 mm a flip angle of 90) in axial, coronal and sagittal plane.

Diffusion weighted magnetic resonance imaging: using a single shot spin echo planar sequence with free breathing; the following parameters were used (TR 2.8 s, TE 72, matrix 512 × 512, slice-thickness 4 mm with an inter-slice gap of 1 mm and FOV 300 mm) were acquired on axial plane. The diffusion sensitizing gradients were applied using a b factor of: 0, 50, 500 and 1000 s/mm^2 in each patient. ADC maps were automatically generated for all DW images and ADC values were measured at b-value: 1000 s/mm^2.

MR Imaging analysis:

Tumor size (greatest diameter), location (endometrium), tumor signal intensity on T1- and T2-weighted and DW images, tumor margin, myometrial invasion,

In this study the following finding were observed: The existence of a mass (any focal or diffuse abnormalities with endometrial thickening), myometrial invasion, fibrous core (low signal intensity stripe or center on T2WI), intratumoral cysts (smooth-walled cystic structure with a high T2 signal intensity within the mass), necrosis on the mass (irregularly high T2 signal intensity within the mass), and parametrium integrity were all observed in endometrial lesions.

Qualitative Assessment of DWI and ADC Map:

All DW MR images were analyzed. DW MR images were analyzed qualitatively by focusing on the signal intensity of the endometrial focal lesions. DW images with a low b-value as of 0, 50 and 100 s/mm^2 were utilized only for calculation of the ADC values, but not evaluated because of less diffusion effect and larger T2 shine-through effect. The abnormal regions on DWI and ADC map were outlined by using the conventional images as a guide.

Patients who had high signal intensity on DWI and low signal intensity on ADC images; we considered them as diffusion positive. While patient had high signal intensity on ADC images with either DWI of high or low signal intensity were considered as diffusion negative. .

Benign tumors show no signal on DWI, while malignant ones show high signal intensity on high b values with corresponding lowering of the signal in the corresponding ADC maps.

Quantitative Assessment of ADC:

For quantitative analysis, The ADC values were automatically calculated by placing the regions of interest (ROI) on ADC maps at a workstation with standard software (1.5 T superconducting magnet MRI machine, Philips Acheiva 1.5 Tesla version). The circular ROI was placed to be as large as possible within the confines of the tumors, without involving artifact from tumor/air interface or blood flow. For heterogeneous lesions, special attention was paid not to involve necrosis or cystic space within the lesion by referring to conventional T1- and T2-weighted images. For each tumor, the ADC values were measured three times in different regions and the measurements were averaged. The ADC values were expressed in 10^{-3} mm^2/sec.

Pathological correlation:

The Diffusion weighted MRI finding was correlated by histopathological assessment as a gold stander.

Statistical analysis:

All statistical calculations were done using SPSS (Statistical Package for the Social Sciences, version 19). According to the histopathological analysis of the endometrial focal lesions, we divided our patients into benign group and malignant group. Benign (endometrial polyp and endometrial hyperplasia). Malignant groups (endometrial carcinoma). Data were statistically described in terms of range, mean, standard deviation, frequencies (number of cases) and percentages when appropriate. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for conventional MRI and diffusion weighted imaging were calculated separately for each parameter. P value < 0.05 was considered significant.

RESULTS

36 patients with endometrial focal lesions were included in our investigation. They ranged in age from 27 to 85 years, with a mean of 45.2 year, 21 postmenopausal individuals and 15 premenopausal patients were included in the study.

The most common clinical symptom was irregular uterine bleeding and pelvic pain which occurred in about 29.41 percent of patients.

The 36 patients involved in this study were categorized into two groups based on the histological findings of their lesions: benign group (15 lesions; 41.67 %) and malignant group (21 lesions; 58.33%). The most prevalent benign lesion was endometrial polyp (9 lesions; 25%) followed by endometrial hyperplasia (6 lesions; 16.67%), while the most common malignant lesion was endometrial cancer (21 lesions; 58.33%) **(Figure 1).**

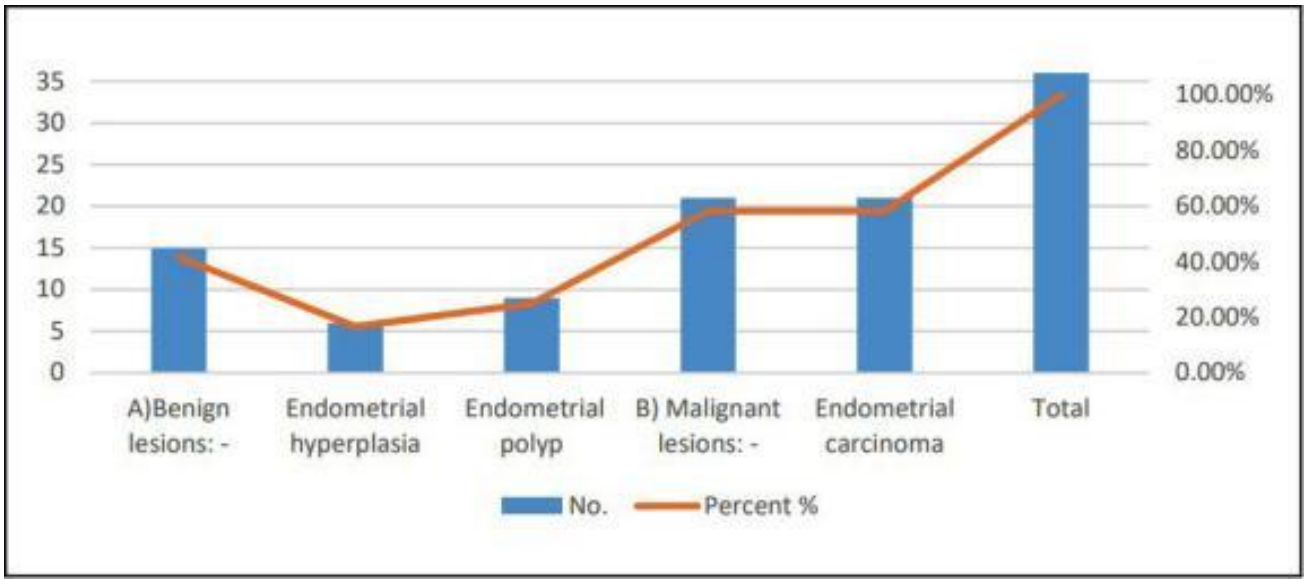


Figure (1): Histopathological results of the all studied lesions (no=36)

Our study revealed fifteen benign endometrial focal lesions by conventional MRI. Endometrial polyps were seen as endometrial lesion with low SI onT1-weighted images and intermediate high SI on T2-weighted images in all lesions. Endometrial hyperplasia was seen as diffuse thickening of the endometrium of low SI on T1- weighted images and homogenous high SI on T2-weighted images with preserved junctional zone (**Table 1).**

Table (1): Conventional MRI findings in the all benign endometrial focal lesions (no=15)

Lesions	Number	Percentage	T1WI	T2WI
Endometrial Polyp	**9**	**25%**	**Low SI**	**Intermediate high SI.**
Endometrial Hyperplasia	**6**	**16.67%**	**Low SI**	**Homogenous high SI**

In our study all benign endometrial focal lesions (15 lesions) were diffusion negative (Facilitated diffusion). The results of DWI, ADC map, ADC value and mean ADC value are shown in table 2.

Table (2): Findings of DWI, ADC map, ADC value and mean ADC value in all benign endometrial lesions

Lesion	No. of lesions	DWI (b1000) Findings	ADC map findings	ADC (range, (10-3 m^2 /sec) a b value=1000	Mean ADC (x-±SD) 10-3 m^2 /sec
Endometrial polyp	**9**	Low SI	High SI	1.816 to 1.924	1.865 ± 0.18
Endometrial hyperplasia	**3**	Low SI	High SI	1.561 to 1.891	1.726 ± 0.25
	3	High SI	High SI		

Our study revealed twenty one malignant endometrial focal lesions by DWI. Endometrial carcinoma (no=21 lesions; 58.33%) was seen as ill define endometrial mass lesion of low SI on T1-weighted images and homogenous (6 lesions) or heterogeneous (15 lesions) intermediate SI on T2-weighted images. The junctional zone was infiltrated in all lesions either partially or totally as interruption of its normal low T2 SI. The staging and description of endometrial carcinoma in our study is shown in table 3. There were no lesions in bladder or bowel mucosa invasion.

Table (3): Staging of endometrial carcinoma in our study (no=21)

Stage	Number	Description
a) Stage IA	**6**	**Less than 50% of the depth of the myometrium was invaded**
b) **Stage IB**	**3**	**More than 50% of the depth of the myometrium was infiltrated**
c) Stage II	**6**	**Cervical stromal invasion**
d) Stage IIIB	**6**	**Parametrical infiltration**

Our study revealed 21 malignant uterine lesions: 18 lesions of the malignant uterine lesions were diffusion positive (restricted diffusion) being with high signal intensity at DWI at high b value (b1000) with low signal intensity at ADC images, only three malignant uterine focal lesions (endometrial carcinoma) were diffusion negative (facilitated diffusion) due to poor cellularity of tumor being with intermediate signal intensity at DWI with high b value (b1000) and with high signal intensity at ADC images. The mean ADC value was about (0.885 ± 0.24) **(Table 4)**.

In current study malignant lesion such as endometrial carcinoma showed marked low ADC values (0.885 ± 0.24 $^{x10-3}mm^2/s$) compared to benign lesions such as 'endometrial polyps (1.865±0.18 x10^-3 mm^2/s) and endometrial hyperplasia (1.726± 0.25 x 10^{-3} mm^2/s) **(Tables 2 and 4)**.

Table (4): Findings of DWI, ADC map, ADC value and Mean ADC value in the studied malignant endometrial lesions (no=21)

Lesion	No. of patient	DWI (b1000) Findings	ADC map findings	ADC (range, $10^{-3}m^2$/sec)b value=1000	Mean ADC (x-±SD) 10^{-3} m2 /sec)
Endometrial carcinoma.	**18**	**High SI**	**Low SI**	0.636 to 1.341	0.885 ± 0.24
	3	**Intermediate SI**	**High SI**		

Using (1.19 x 10^{-3} mm^2/s) as cut-off value for distinguishing malignant from benign lesions achieved (91.6%) sensitivity and (100%) specificity **(Table 5 and Figure 2).**

Table (5): Sensitivity, specificity, accuracy, P value and positive and negative predictive values of ADC values of endometrial focal lesions

DW-MR	Sensitivity	Specificity	PPV	NPV	Accuracy	Cut off point	P value
ADC value	**91.6%**	**100%**	**100%**	**95.6%**	**97.05%**	**1.19**	**0.02**

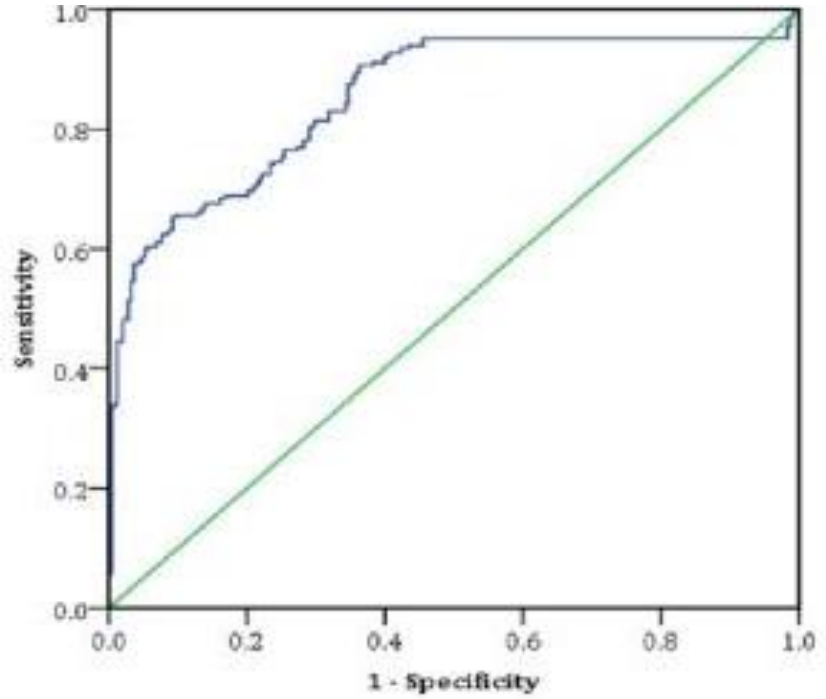
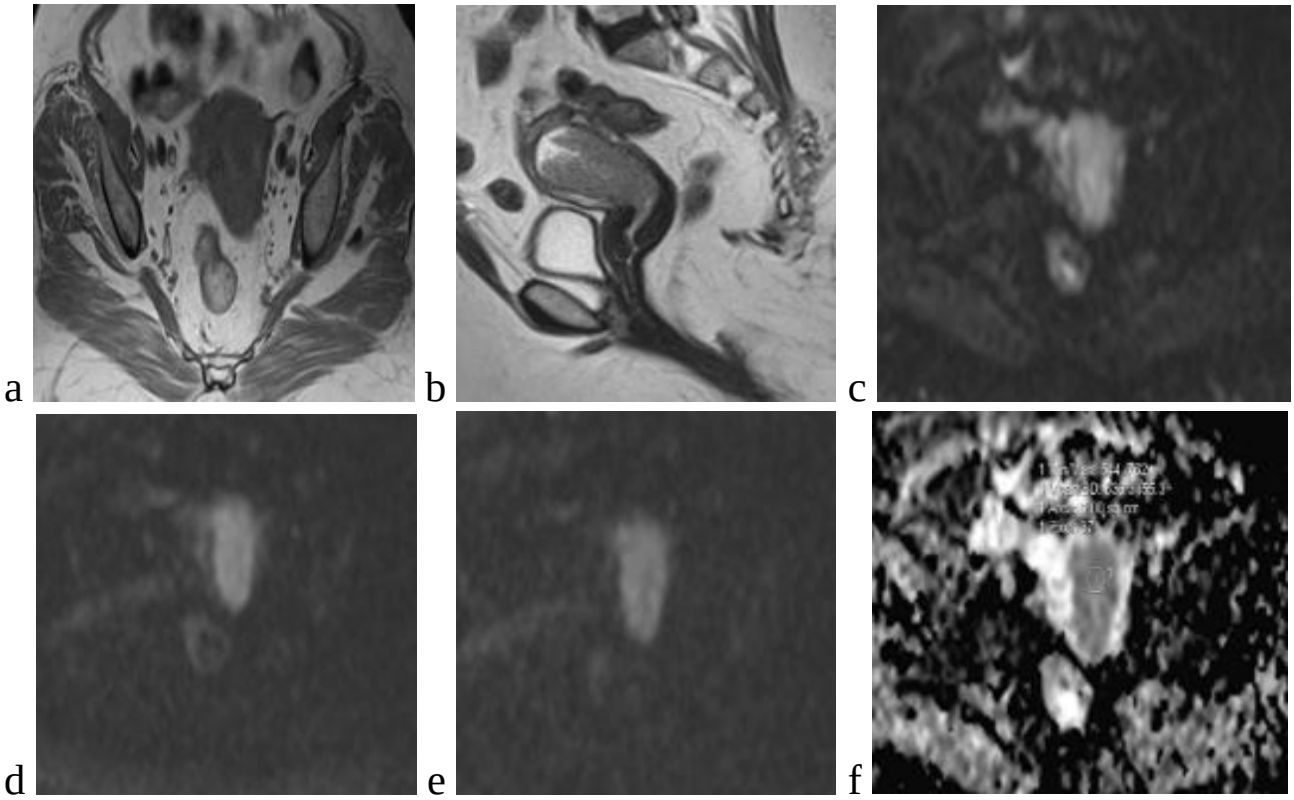
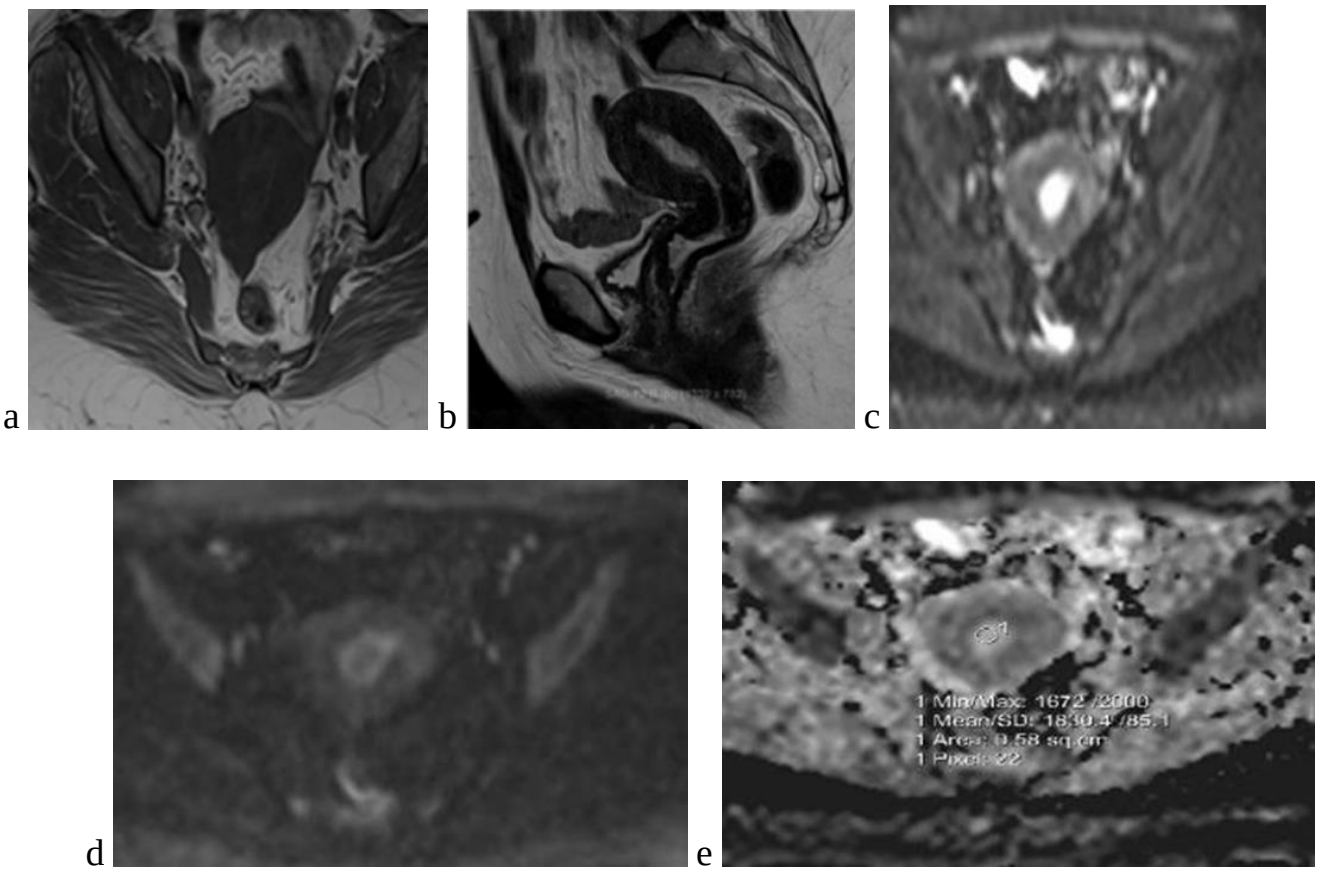


Figure (2): ROC curve for the ADC values of endometrial focal lesions to predict malignant cases



Case (1): 50 years old, female patient. Clinical presentation: irregular uterine bleeding. MRI pelvis axial T1WI (a) reveals bulky uterus with iso to hypointense lesion occupying the endometrium, sagittal T2 WI (b) the lesion appeared as an endometrium mass of homogenous intermediate SI with infiltration of the junction zone and affection of more than 50 % of the myometrium. DWI at 3 b-values (0 (c), 500 (d) and 1000 (e) revealed lesions of high signals even with high b value (malignant feature). At ADC map (f) the lesion exhibit hypointense signal with ADC value averaging 0.636 $x10^{-3}$ mm^2/sec. Radiologic diagnosis: matched with malignant endometrial mass lesion likely high grade endometrial carcinoma with >50% invasion of myometrium. Final histopathology diagnosis: Endometrial carcinoma grade IB.



Case (2): 55 years old female patient, clinical presentation is post-menopausal bleeding. MRI pelvis axial T1WI (a) reveals well define small hypointense focal lesion seen in the uterine endometrium and in sagittal T2 WI (b) the lesion appeared more well define and showed hyperintense signal, no myometrial invasion and preserved low signal junctional zone. DWI at 2 b-values (0) (c) and 1000 (d) revealed reduction of the lesion signal with increasing b-values (benign feature). At ADC map (e) the lesion exhibits hyperintense signal with ADC value averaging $1.83x10^{-3}$ mm^2/sec. Radiologic diagnosis: matched with small benign featuring lesion seen inside the endometrium likely endometrial polyp. Final histopathology diagnosis: Endometrial polyp.

DISCUSSION

In the context of female pelvic masses, uterine masses are subject to a wide range of differential diagnoses, which include benign and malignant neoplasms as well as non-neoplastic pathologies [(1, 2)]. Recently, MRI was considered better than CT for the detection and staging of gynecological and pelvic malignancies [(10)].

This study aims to highlight the role of MRI with diffusion weighted (DW) images in better diagnosis of endometrial focal lesions, especially in differentiation between benign and malignant masses and initial staging of known malignancies. Consequently, this study recruited 36 women (21 postmenopausal and 15 premenopausal) who experienced vaginal bleeding and had endometrial thickness and focal endometrial lesions with a distinct echo pattern on US examination. The age of patients ranged between 27 to 85 years, with an average of 45.2 years.

Patient age was found to be substantially greater in malignant lesions (ranging from 50 to 85 years, with a mean age of 62.3 years) than in benign lesions (ranging from 27 to 63 years, with a mean age of 45.3 years) in our study. This was consistent with the findings of **Kilickesmez *et al.*** [(11)], who discovered that patient age was considerably greater in indeterminate or malignant masses (mean, 57.2 (range = 40.5–81.7)) than in benign masses (40.2 (range = 23.3–69.5)) in comparison to benign masses.

Histopathological examination findings from our investigation revealed that the 36 endometrial lesions involved in the study were comprised of 21 malignant endometrial carcinomas and 15 benign lesions (9 endometrial polyps and 6 endometrial hyperplasias). When using T2 weighted images, endometrial cancer exhibited moderate mixed signals, whereas endometrial hyperplasia produced hyperintense signals. This matched with results of **Kierans *et al.*** [(12)], which demonstrated that on sagittal T2-weighted imaging, endometrial carcinomas have a low or intermediate signal intensity, particularly in comparison with the hyperintense signal of normal endometrial tissue. Endometrial polyps and benign hyperplasia, on the other hand, are frequently seen as either a focal mass filling the uterine cavity or a

nonspecific endometrial thickening with intermediate to high signal intensity on T2WI scans. They are insufficient for making a reliable diagnosis of cancer, hyperplasia, and polyps [12].

Throughout the present research, all benign endometrial lesions (nine polyps and six hyperplasias) were found to be diffusion negative; twelve lesions had low SI on DW images at a high b value (b=1000) and high SI on ADC images, while three endometrial hyperplasia had high SI on both DW images and ADC images in what's called T_2 shine through effect. 18 of the 21 malignant endometrial cancers investigated were diffusion positive, with high SI on DW images at high b values (b=1000) and low SI on ADC images, with the exception of three endometrial cancer that was diffusion negative, with intermediate-high SI on DW images at high b values (b=1000) and high SI on ADC images. Our findings were almost similar to those of a research published by **Wang *et al.*** [13] who employed a b value of 1000 s/mm^2 and revealed that endometrial carcinoma, demonstrated hyperintense signal on DWI, whereas all endometrial polyps revealed intermediate signal or a relatively lower signal particularly in comparison to the spared myometrium. **Valdes-Devesa *et al.*** [14] observed that endometrial polyps had moderate signal on diffusion-weighted images and higher ADC values particularly in comparison with endometrial cancer, which was in accordance with the result of our study. **Thomassin-Naggara *et al.*** [15] **and Kono *et al.*** [16] reported that malignant endometrial neoplasm most frequently manifests as an irregular endo-myometrial interface or a localized lesion with great signal intensity on DWI and low signal intensity on ADC map on imaging studies, which was in accordance with the result of our study.

The mean ADC value of endometrial cancer ($0.885 \pm 0.24 \times 10^{-3}$ m^2/sec) was substantially lower than that of endometrial polyps ($1.865 \pm 0.18 \times 10^{-3}$ m^2/sec) and endometrium hyperplasia ($1.726 \pm 0.25 \times 10^{-3}$ m^2/sec) in the present work. These findings were in definitive agreement with the findings of **Fujii *et al.*** [17] who assessed a wide range of endometrial lesions and come to the conclusion that malignant tumors, including endometrial carcinoma as well as carcinosarcoma, gave lower ADC values than benign tumors, including endometrial hyperplasia and endometrial polyps; and the findings of **Malayeri *et al.*** [18] and **Masroor *et al.*** [19] studies that confirmed that there was a significantly lower ADC value for malignant endometrium when compared to benign endometrium lesions. Furthermore, the findings of the **Yen *et al.*** [20] investigation revealed that the mean ADC of endometrial cancer was $0.88 \pm 0.16 \times 10^{-3}$ m^2/sec, which would have been significantly lower (P 0.01) than the mean ADC of normal endometrium, that was $1.53 \pm 0.10 \times 10^{-3}$ m^2/sec. Whereas in a study by **Bharwani *et al.*** [21] they employed a variety of b-values (0, 50, 100, 250, 500, and 750 s/mm^2) and discovered a statistically significant difference between the mean ADC values of benign lesions tend to range from (1.49 ± 0.14) to (1.16 ± 0.22) 10^{-3} m^2/sec and malignant lesions tend to range from (0.97 ± 0.13) to (0.72 ± 0.23) 10^{-3} m^2/sec.

In current study malignant lesion such as endometrial carcinoma showed significant low ADC values (0.885 ± 0.24 $^{x10\text{-}3}$mm^2/s) compared to benign lesions such as endometrial polyps (1.865±0.18 x10^-3 mm^2/s) and endometrial hyperplasia (1.726± 0.25 x 10^{-3} mm^2/s). Using (1.19 x 10^{-3} mm^2/s) as cut-off value for distinguishing malignant from benign lesions achieved (91.6%) sensitivity, (100%) specificity. **Kececi *et al.*** [22], reported that the mean ADC value of the endometrial cancer (0.94 ±0.18 x10-3 mm^2/s) was statistically significantly lower than the ADC value of benign lesions (1.45 ±0.22 x10–3 mm^2/s) and the ADC threshold value to determine whether the lesions were benign or malignant was (1.10 x10-3mm^2/s) with 85.7% sensitivity and 92.8% specificity. **Elsammak *et al.*** [23], study revealed also that a significant difference was found between the mean ADC values of malignant masses (0.82 x10^{-3} mm^2/s) and benign lesions (1.44 x10^{-3} mm^2/s), they had 88.9% sensitivity, 100% specificity and accuracy 88.9% when used (1.19 x10^{-3} mm^2/s) as a cut off value for differentiation benign from malignant endometrial lesions. The results of the previous studies were slightly similar to our results, According to **Kececi *et al.*** [22] **and Elsammak *et al.*** [23], the differences in ADC values in the studies can be explained by the difference in many technical variables that affect the ADC value such as different MRI units, pulse sequences, or b values.

The diagnostic finding of DWI and ADC map in this study had 91.6 % sensitivity and 100% specificity in identifying endometrial lesions. This was in agreement with **Bharwani *et al.*** [21], who reported that the combination of DWI with conventional MRI raised the sensitivity and specificity in the identification of endometrial lesions in the uterus to 86 % and 100 %, respectively, in the detection of uterine endometrial lesions. According to **Chinen *et al.*** [24], the sensitivity and specificity of DWI in endometrial lesions seemed to be 100 % and 81 %, respectively, when used in this setting.

In our study, we had three false negative lesion (3 endometrial carcinoma with intermediate-high SI on DW images at high b values (b=1000) and high SI on ADC images). That was radiographically identified as benign lesions, but the histopathological findings revealed that it was a well-differentiated adenocarcinoma due to the poor cellularity of the tumor. A similar finding was made by **Whittaker *et al.*** [5], who discovered that certain malignant tumors have little cellularity and, as a result, have much more limited water limitation that cannot be detected using DWI.

CONCLUSION

DW imaging can be used to discriminate between endometrial benign focal lesions and malignant lesions,

in conjunction with conventional MRI characteristics. It is possible to measure tissue diffusivity using DW-MR imaging, both qualitatively and quantitatively. DWI and ADC map can be used to distinguish between benign and malignant endometrial focal lesions. Limited diffusion patterns with elevated SI on high b-value images and low SI on ADC images are found in malignant lesions. On DWI, benign lesions show diffusion with lower SI, indicating that they encourage diffusion. According to our research, DWI and ADC images can accurately (97.05%) distinguish between benign and malignant lesions in the uterus with (91.6%) sensitivity, (100%) specificity, (100%) PPV, and (95.6%) NPV.

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