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Uterine Cavity Assessment and Endometrial Hormonal Receptors in Women with Peri and Post Menopausal Bleeding

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Abstract

Objectives: To compare the accuracy of 2D-Transvagfinal ultrasound (TVUS), saline infused sonohysterography (SIS) and hysteroscopy (DH) in assessment of the uterine cavity in women with peri- and postmenopausal bleeding and to study the expression of endometrial estrogen receptors (ER) and progesterone receptors (PR) in them.

Study design: 100 women with abnormal uterine bleeding (peri and postmenopausal) were subjected to TVUS, SIS and DH and fractional curettage followed by histopathological examination and immunohistochemical analysis for ER and PR.

Results: Measurement of endometrial thickness by TVUS showed a significant difference between normal and atrophic endometrium and between atrophic endometrium and endometrial polyp (P value 0.004 and 0.001 respectively) DH had the best sensitivity, specificity, PPV and NPV as a diagnostic procedure followed by SIS then TVUS (97.7, 100,100,99.4 % vs. 74,91.2,67.3,93.5 and 52.9,89.4,56.3, 88.1 respectively) Both ER and PR scoring among glands and stroma showed a significant difference between normal and abnormal endometrium. ER expression in glands showed a significant difference between endometrial polyp and surrounding endometrium (P value 0.006)

Conclusions: Sonohysterography is superior to ultrasound and very close to hysteroscopy, especially with intra-cavitary lesions. Hysteroscopy remains the gold standard for uterine cavity assessment, but cannot replace the histopathology. The expression of endometrial steroid receptors is important in the pathogenesis of endometrial polyps and endometrial hyperplasia.

Keywords: Perimenopausal bleeding; Postmenopausal bleeding; Transvaginal ultrasound; Sonohysterography; Hysteroscopy; Estrogen receptors; Progesterone receptors; Endometrial polyp

Introduction

Abnormal uterine bleeding (AUB) is the cause of many gynecological visits in pre and postmenopausal and can be due to the presence of either benign conditions or the presence of endometrial cancer [1]. Dilatation and curettage (D&C) is the currently accepted method for diagnosing diffused endometrial conditions as endometrial cancer and hyperplasia. However, when focal endometrial conditions (as endometrial polyps and leiomyomas) or myometrial conditions (such as adenomyosis) are present, D&C is not capable of diagnosing them [2].

Transvaginal ultrasound (TVUS) is a method routinely used for differentiating between the causes of AUB. However, in TVUS images it is difficult to distinguish between a thickened endometrial lining and other diffuse or focal endometrial abnormalities [3]. An improved TVUS method is saline infused sonohysterography (SIS) which allows uterine abnormalities to be seen more clearly by pushing apart the walls of the uterine cavity with saline infused into the cavity [4]. Hysteroscopy (DH) with biopsy has become the gold standard for evaluation of the uterine cavity, as a reliable and safe method in routine outpatient settings [5].

Studying the immunohistochemical reactivity of the postmenopausal endometrium using monoclonal antibodies against ERs (estrogen receptors) and PRs (progesterone receptors) showed thicker endometrium in menopausal women for 1 to 10 years than in those who were menopausal for more than 10 years. Within the glands +ve ER was found in 26/33 and +ve PR was found in 18/33 of cases [6].

Endometrial polyps (EP) are a frequent cause of AUB, but their pathogenesis is poorly understood. EP may result from a decrease in ER and PR expression in stromal cells [7]. The aim of this study is to compare the accuracy of both 2D TVUS and SIS in relation to DH in assessment of uterine cavity and to detect ER and PR in endometrium and their association with endometrial polyps in women with peri and postmenopausal bleeding.

Material and Methods

The present prospective study included 100 patients with AUB who attended the outpatient gynecology clinic at Kasr El-Aini Hospital in Cairo, Egypt, between June 1, 2011, and October 31, 2014. The study was approved by the local Ethics Committee and informed consents about the study and expected value and outcome were obtained from all participants.

The 100 women included in our study were older than 45 years with AUB for more than 3 months duration. Of these women 50 had postmenopausal bleeding, 10 had premenopausal menorrhagia, 4 had premenopausal metrorrhagia and 36 had premenopausal menometrorrhagia Exclusion criteria included history of hormonal treatment or hormonal contraception within the last 6 months. Women

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who had used IUD or those had hystroscopy or fractional curettage done within the last 6 months were also excluded.

All the patients were subjected to Full history, clinical examination including general, abdominal and pelvic examination and Laboratory investigations as complete blood count, coagulation profile, fasting and post-prandial blood sugar, liver and kidney functions and pregnancy test (for the premenopausal women).

Conventional TVUS was done to all participants to measure the uterine size and endometrial thickness and other pathology. TVUS was done with an empty bladder in the lithotomy position using the Sonoace-X6 (Medison Co. Ltd., Korea) ultrasound machine, with an endovaginal curved linear probe (EV 4-9/10 ED) with frequency 4-9 MHz. SIS was performed for all patients at the same setting of TVUS. With the patient in the lithotomy position, a speculum was inserted into the vaginal introitus. The cervical os was localized and cleaned with a povidone-iodine solution. A 6 or 8 French Foley's catheter was inserted through the external cervical os into the cervical canal. Its balloon tip was inflated with 2-3 mL of saline, depending on patient comfort, to help hold it in place. The speculum was then removed.

The vaginal probe was then reinserted and a 5-10 mL syringe filled with sterile saline was attached to the catheter. Fluid was instilled while the transducer was moved from side to side (cornua to cornua) in a long-axis projection then the transducer was rotated 90° into an axial plane. More fluid was instilled while fanning down toward the endocervical canal and up toward the uterine fundus to obtain a detailed survey of the endometrium. Every portion of the uterine cavity should be imaged, to exclude any focal abnormality as polyps, myomas, hyperplasia, and carcinoma. Any detected intrauterine pathology is described; including its shape, size and site.

The hysteroscope used in this study was Karl Storz (Germany). It is a rigid continuous flow panoramic hysteroscope, 25 cm in length, 4 mm in diameter with an outer sheath 5 mm diameter and 30° fibro-optic lens. The light source used in this study was a metal halide automatic light source from Circon ACMI G71A (Germany) with a 150 Watt lamp, connected to the hysteroscope through a fibro-optic cable.

The technique used to provide constant uterine distention was by attaching plastic bags of saline. Infusion pressure was elevated by pneumatic cuff under manometric control at a pressure of 100-120 mmHg. The procedure was monitored using a single chip video and the image is displayed on a monitor visible to the operator. The camera was Karl Storz (Germany) with a focal length varying from f 70 to f 140.

Detailed hysteroscopic examination was performed under general anesthesia with the patient in the lithotomy position, cleaning the area around the vulva, vagina and the cervix with a nonfoaming aseptic solution, Emptying the bladder by a metal catheter, Bimanual examination, Introduction of a vaginal retractor into the vagina to expose the cervix and a multiple toothed volsellum was applied to the anterior lip of the cervix, The endocervical canal was curetted before introduction of the telescope, Dilatation of the cervix was needed –in some cases– up to Hegar no. 6; but it was better to be avoided as the tight cervical os avoids loss of the distending medium, The telescope was introduced through the external cervical os under direct vision, Once the cavity was entered, a panoramic view of the uterine cavity then systematic; first the fundus, then anterior, posterior and lateral walls of the uterus consecutively, ending by visualization of the utero-tubal junctions, The thickness, colour, aspect and vasculature of the mucous membrane lining the uterine cavity was observed and recorded. If there was any intrauterine pathology detected; the shape, size and site were estimated. If an endometrial polyp was found it was removed using a ring forceps. At the end of the procedure, the hysteroscope was slowly withdrawn through the cervical canal to visualize it.

Endometrial curettage was done to all patients, and specimens were fixed in Formalin 10% solution for histopathological examination. Patients in whom endometrial polyps were found by hysteroscopy, had polypectomy performed before curettage. The first sample was taken from the endocervical canal before hysteroscopy or cervical dilatation. Following diagnostic hysteroscopy, cervical dilatation up to Hegar no. 7 or 8 was done. A sharp curette was introduced into the uterine cavity, and curettage was done starting with the fundus then posterior, anterior, right and left lateral walls consecutively.

Histopathological examination, all curettage and polypectomy specimens were embedded in paraffin wax, then slides were prepared to be stained by the conventional Haematoxylin and Eosin (H & E) stain.

Detection of estrogen and progesterone receptors in the specimens (formalin-fixed, paraffin wax-embedded) using immunohistochemical staining which was carried out by using the Dako ER/PR pharmDx™ Kit which specifically detects the ERα protein as well as the PR-A protein located in the cell nuclei of ER and PR expressing cells, respectively. An intensity score is assigned according to the estimated average staining intensity of ER or PR positive cells, as follows: Grade 0 negative, Grade 1 weak, Grade 2 intermediate and Grade 3 strong (Figure 1).

Data was statistically represented in terms of mean, standard deviation and percentages. Comparison was done using Two-tail Student t test for parametric data. For comparing non-parametric data, Chi-Square (x^2) test was performed. A probability value (P value) less than 0.05 was considered significant (Figures 2-8).

All statistical calculations were done using computer programs Microsoft Excel (Microsoft Corporation, NY, USA) and SPSS (Statistical package for the social science) statistical programs (SPSS Inc., Chicago, IL, USA).

Results

The main characteristics of the study group including age, parity and diagnosis of lesion were shown in Table 1. There was no relation between either age or parity to diagnosis (Table 1). TVUS could detect all cases with submucus myoma (SMF), half of cases with endometrial polyps and endometrial atrophy, only 2/16 of women with normal endometrium and over diagnosis of endometrial hyperplasia (Table 2). SIS could detect all cases with SMF, most cases with endometrial polyp and endometrial hyperplasia, 10/16 of cases with endometrial atrophy and normal endometrium (Table 2).

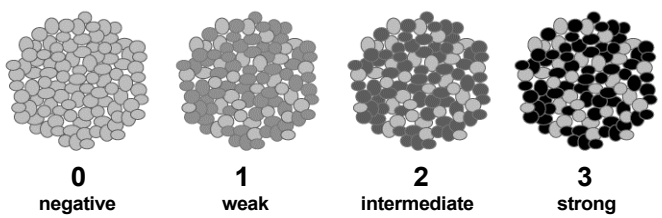


Figure 1: ER and PR intensity scoring.

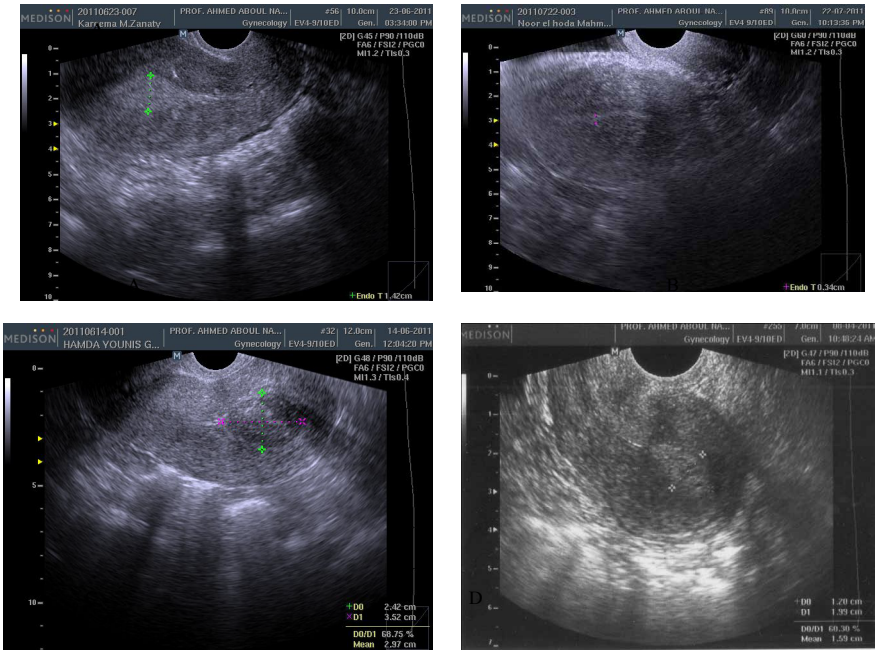


Figure 2: TVUS picture of A) simple endometrial hyperplasia, B) atrophic endometrium, C) submucous fibroid, D) endometrial polyp.

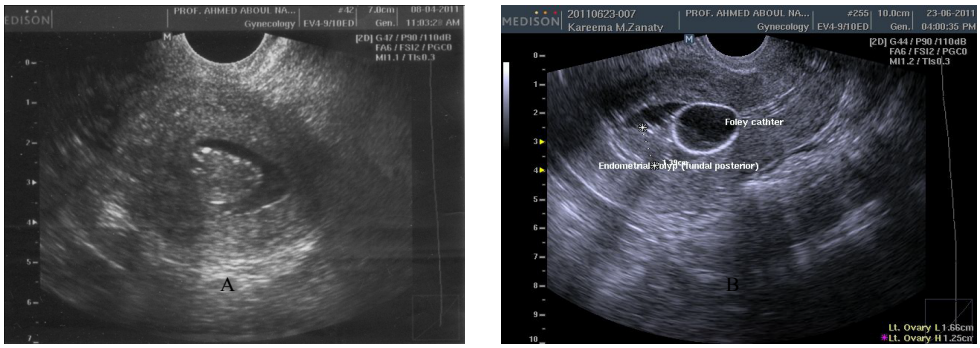
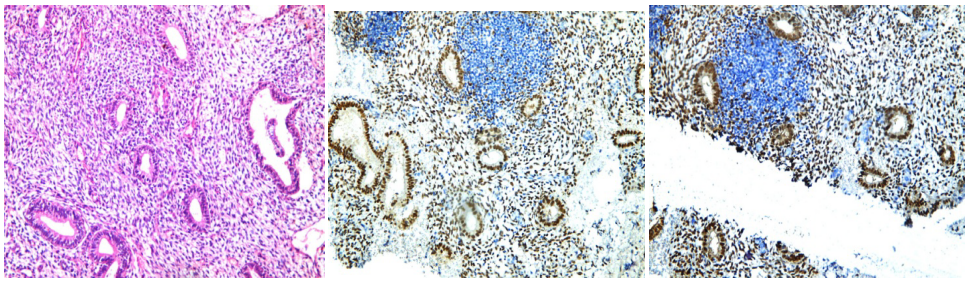


Figure 3: SIS picture of A) endometrial polyp, B) false positive endometrial polyp. Hysteroscopy showed endometrial shreds which may be misinterpreted as a polyp.

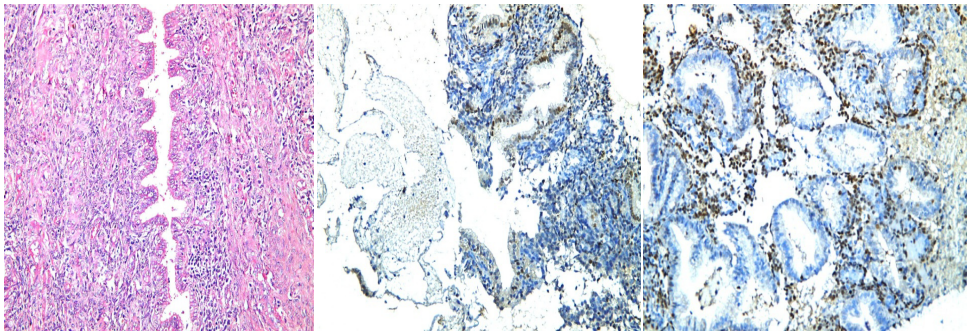


A B C

Figure 4: Proliferative endometrium (200X)A H&E, B) ER expression Glands Grade 2; Stroma: Grade 2, C) PR expression Glands: Grade 2; Stroma: Grade 2.

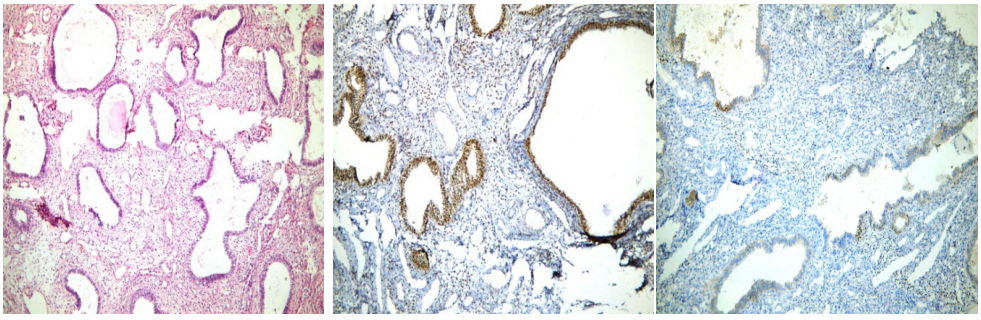
DH could detect all cases with endometrial polyp, endometrial atrophy, normal endometrium and 16/18 of cases with endometrial hyperplasia (Table 2).

Measurement of endometrial thickness by TVUS showed a significant difference between normal and atrophic endometrium and between atrophic endometrium and endometrial polyp and a non significant difference between normal endometrium and endometrial polyp, normal endometrium and endometrial hyperplasia, atrophic



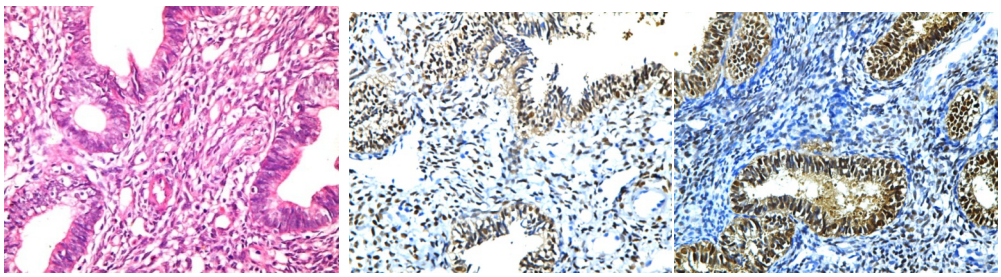
A B C

Figure 5: Secretory endometrium (200X) A) H&E, B) ER expression Glands Grade 1; Stroma: Grade 2, C) PR expression Glands: Grade 1; Stroma: Grade 2.



A B C

Figure 6: Simple endometrial hyperplasia (100X) A) H&E picture, B) ER expression Glands Grade 3; Stroma: Grade 2, C) PR expression Glands: Grade 3; Stroma: Grade 2.



A B C

Figure 7: Complex endometrial hyperplasia (400X) A) H&E picture, B) ER expression Glands Grade 3; Stroma: Grade 3, C) PR expression Glands: Grade 3; Stroma: Grade 3.

endometrium and endometrial hyperplasia, endometrial polyp and endometrial hyperplasia (Table 3).

DH had the best sensitivity, specificity, PPV and NPV as a diagnostic procedure followed by SIS then TVUS (Table 4).

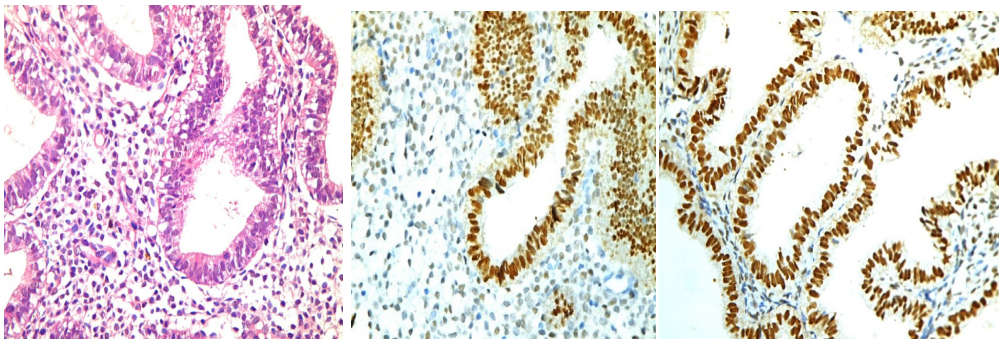
ER scoring among glands showed a significant difference between normal and atrophic endometrium, normal and endometrial polyp, atrophic endometrium and endometrial polyp, atrophic endometrium and endometrial hyperplasia (Table 5).

ER scoring among stroma showed a significant difference between normal and endometrial polyp, normal and endometrial hyperplasia, atrophic endometrium and endometrial polyp, atrophic endometrium and endometrial hyperplasia (Table 5).

PR scoring among glands showed a significant difference between normal and atrophic endometrium, atrophic endometrium and endometrial polyp, atrophic endometrium and endometrial hyperplasia (Table 5).

PR scoring among stroma showed a significant difference between normal and atrophic endometrium, normal and endometrial polyp, atrophic endometrium and endometrial polyp, atrophic endometrium and endometrial hyperplasia (Table 5).

ER expression in glands showed a significant difference while ER expression among stroma and PR expression among both glands and stroma showed a nonsignificant difference between endometrial polyp and surrounding endometrium (Table 6).



A B C

Figure 8: Hyperplastic polyp (400X) A) H&E picture, B) ER expression Glands Grade 3; Stroma: Grade 3, C) PR expression Glands: Grade 3; Stroma: Grade 3.

		Age (50.52 ± 6.31)		Parity (5.20 ± 2.59)	
	Number and percentage	**Mean ± SD**	**P value**	**Mean ± SD**	**P value**
Endometrial polyp	32	51.44 ± 6.84	0.35 NS	5.31 ± 2.11	0.295 NS
Endometrial hyperplasia	22	52.09 ± 8.30		5.73 ± 2.26	
Endometrial atrophy	16	51.88 ± 5.21		4.25 ± 2.59	
Normal endometrium (DUB)	16	48.25 ± 2.39		6.38 ± 3.71	
Submucous fibroid	14	47.00 ± 2.45		3.86 ± 1.25	

Table 1: Relation of age and parity to different diagnoses.

	TVUS	**SIS**	**DH**	**Diagnosis**
Endometrial polyp	16	32(1)	32	32
Endometrial hyperplasia	24	18(2)	16	18
Endometrial atrophy	8	10	16	16
Normal endometrium	2	10	16	16
Submucous fibroid	14	14	14	14

TVUS: Transvaginal ultrasonography, SIS: Saline-infusion sonohysterography, DH: Diagnostic hysteroscopy, HP: Histopathology.
(1) With endometrial polyps, SIS had 2 false negative result by missing one case, and 2 false positive result by diagnosing a case of 2 endometrial hyperplasia as polypi.
(2) With hyperplasia, SIS had 6 false negative results (by missing 6 cases), and 6 false positive results (2 cases was found to have polypi and 4 cases were normal).

Table 2: Comparison of diagnoses using different uterine assessment modalities with the actual diagnosis.

		Mean Endometrial Thickness
Normal endometrium		12.38 ± 5.80 mm
Endometrial atrophy		4.88 ± 2.30 mm
Endometrial polyp		16.56 ± 11.30 mm
Endometrial hyperplasia		**8.89 ± 5.37 mm**
	***P* value**	**Significance**
Normal/Atrophy	0.004	Significant
Normal/Polyp	0.339	Non-significant
Normal/Hyperplasia	0.218	Non-significant
Atrophy/Polyp	0.001	Significant
Atrophy/Hyperplasia	0.066	Non-significant
Polyp/Hyperplasia	0.069	Non-significant

Table 3: Endometrial thickness by 2D-TVUS in different diagnoses.

Discussion

Our study concluded that measurement of endometrial thickness using TVUS has limited value in differentiation of causes of thickened endometrium and SIS is superior in assessment of the uterine cavity. It can be used as the primary method for the detection of the uterine cavity among women with AUB. SIS improves the efficiency of TVUS as a diagnostic tool, especially with intra-cavitary lesions as endometrial polyps and SMF. DH remains the gold standard for assessment of the uterine cavity, but cannot replace the histopathology.

Our study found that the expression of ER and PR plays an important role in the pathogenesis of endometrial polyps and endometrial hyperplasia.

In our study endometrial polyp (32%) was the commonest endometrial lesion followed by endometrial hyperplasia (22%). Bingol et al. stated that 38% of patients with AUB had endometrial polyps and 28% had hyperplasia [8].

The diagnostic accuracy of DH was almost 100% in our study for all lesions, and gave just 2 false negative result by missing two cases of

	Sensitivity	Specificity	PPV	NPV
Overall				
TVUS	52.9%	89.4%	56.3%	88.1%
SIS	74.0%	91.2%	67.3%	93.5%
DH	97.7%	100.0%	100.0%	99.4%
Endometrial polyp				
TVUS	50.0%	94.1%	80.0%	80.0%
SIS	87.5%	94.1%	87.5%	94.1%
DH	100.0%	100.0%	100.0%	100.0%
Endometrial hyperplasia				
TVUS	63.6%	71.8%	38.9%	87.5%
SIS	54.5%	94.9%	75.0%	88.1%
DH	90.9%	100.0%	100.0%	97.5%
Endometrial atrophy				
TVUS	50.0%	95.3%	66.7%	90.9%
SIS	62.5%	95.3%	71.4%	93.0%
DH	100.0%	100.0%	100.0%	100.0%
Submucous fibroid				
TVUS	87.5%	100.0%	100.0%	97.7%
SIS	100.0%	100.0%	100.0%	100.0%
DH	100.0%	100.0%	100.0%	100.0%

TVUS: Transvaginal Ultrasonography, SIS: Saline-Infusion Sonohysterography, DH: Diagnostic Hysteroscopy, PPV: Positive Predictive Value, NPV: Negative Predictive Value.

Table 4: Comparison of sensitivity, specificity, positive and negative predictive values of TVUS, SIS and DH in assessment of uterine lesions.

simple endometrial hyperplasia. The high accuracy of DH (approaching almost 100%) is in line with other studies [8-10].

SIS had high accuracy in diagnosis of intra-cavitary lesions, such as polyps and SMF. Regarding endometrial polyps, SIS had 2 false negative and 2 false positive (diagnosing a case of endometrial hyperplasia as a polyp due to the presence of intra-uterine debris (confirmed by hysteroscopy) [11].

However; SIS was less accurate in endometrial hyperplasia by giving 6 false negative and 6 false positive results (1 case was found to have a polyp and 2 cases were normal). This agrees with other study [12]. Most studies proved the high accuracy of SID with intra-cavitary lesions –mainly polyps and SMF [8,10,12].

TVUS missed half the polyps and had 24 false positive results of endometrial hyperplasia and failed to differentiate whether the thickened endometrium was due to an endometrial polyp, endometrial hyperplasia or even a normally thickened endometrium. That was similar to other studies [8,12].

We found that endometrial thickness was statistically significant only in cases of endometrial atrophy (thinner when compared to normal endometrium). It was not reliable in cases of endometrial polyps and endometrial hyperplasia. This is supported by Bingol et al. [8].

TVUS, SIS and DH all had 100% accuracy in diagnosing SMF. However; SIS and DH showed better description of the exact site and estimation of the percentage circumference projecting into the endometrial cavity, compared to TVUS. That was similar to other studies [11,13,14].

Overall sensitivity rates were 52.9% for TVUS, 74% for SIS and 97.7% for DH; while overall specificity rates were 89.4%, 91.2% and 100%, respectively. Overall PPV were 56.3%, 67.3% and 100% for TVUS, SIS and DH respectively. Meanwhile, overall NPV were 88.1%, 93.5% and 99.4% respectively. Our study found that cases of endometrial atrophy showed significant (P value < 0.05) decreased expression of ER in the glandular cells, and decreased PR expression in both glands and stroma; when compared to the normal endometrium [15].

Cases of endometrial hyperplasia showed significant (P value < 0.05) over-expression of ER in both glands and stroma; when compared to the normal endometrium. That was similar to other studies [16,17].

Cases of endometrial polyps showed significant (P value < 0.05) over-expression of ER in both glands and stroma and over-expression of PR in stromal cells when compared to the normal endometrium. These findings are similar to the results of other studies [18-20].

	Mean ER score		Mean PR score	
	Glands	Stroma	Glands	Stroma
Normal endometrium	2.00 ± 0.53	1.13 ± 0.35	2.13 ± 0.64	1.37 ± 0.74
Endometrial atrophy	1.25 ± 0.46	0.50 ± 0.76	1.25 ± 0.46	0.50 ± 0.53
Endometrial polyp	2.63 ± 0.50	2.31 ± 0.60	2.44 ± 0.63	2.31 ± 0.35
Endometrial hyperplasia	2.63 ± 0.81	1.91 ± 0.54	2.36 ± 0.81	1.91 ± 0.30

	P value		Significance		*P* value		Significance	
	Glands	Stroma	Glands	Stroma	Glands	Stroma	Glands	Stroma
Normal/Atrophy	0.010	0.060	Significant	Non	0.007	0.017	Significant	Significant
Normal/Polyp	0.010	0.000	Significant	Significant	0.266	0.006	Non	Significant
Normal/Hyperplasia	0.070	0.020	Non	Significant	0.500	0.088	Non	Non
Atrophy/Polyp	0.000	0.000	Significant	Significant	0.000	0.000	Significant	Significant
Atrophy/Hyperplasia	0.000	0.000	Significant	Significant	0.002	0.000	Significant	Significant
Polyp/Hyperplasia	0.964	0.087	Non	Non	0.792	0.054	Non	Non

Table 5: ER and PR scoring (of both endometrial glandular cells and stromal cells) in different uterine lesions.

			P value	Significance
Polyp/Surrounding Endometrium	ER	Glands	0.006	Significant
		Stroma	0.610	Non
	PR	Glands	0.131	Non
		Stroma	0.792	Non

Table 6: Difference in expression of ER and PR between endometrial polyps and the surrounding endometrium of the same cases.

Antunes and colleagues studied ER and PR expression in the glandular epithelium and stroma of benign and malignant endometrial polyps of 390 postmenopausal with endometrial polyps who underwent surgical hysteroscopy.

They concluded that polyps in postmenopausal patients have high ER expression in the stroma and glandular epithelium. However, this expression is lower in premalignant /malignant polyps compared with benign polyps. These results indicate that lower ER expression may be one more risk factor for the malignancy potential of polyps in postmenopausal females [21,22].

We recommend that SIS should be used as an initial routine investigation instead of TVUS in cases of AUB.

Authors' Contribution

Ahmed L Aboul Nasr: Protocol/project development, Mostafa A Salem: Protocol/project development, Sherine H Gad Allah: Data collection or management, Data analysis, Ahmed A Wali: Data collection or management, Data analysis, Ahmed M Maged: Manuscript writing/editing.

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