Transvaginal Ultrasonography, Sonohysterography, Hysterosalpingography And Operative Hysteroscopy

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Transvaginal Ultrasonography, Sonohysterography, Hysterosalpingography And Operative Hysteroscopy In Predicting Endometrial Hyperplasia

Abstract

Objective: Assessment of diagnostic accuracy of transvaginal sonohysterography in comparison with transvaginal ultrasound, hysterosalpingography and hysteroscopy in predicting endometrial hyperplasia.

Study design: A prospective study was performed at Al-Azhar University Hospital, Cairo, Egypt and Hadi Hospital, a private hospital in Kuwait. A total of 255 patients (160 Egyptian and 95 Kuwaiti) with abnormal uterine bleeding were enrolled (165 premenopausal, 90 postmenopausal). All participants were evaluated with transvaginal sonography (TVS), transvaginal sonohysterography (TV-SH) and operative hysteroscopy (HSC). Hysterosalpingography (HSG) was performed only for 40 Egyptian and 10 Kuwaiti patients. Endometrial curettage and/or histopathology of hysterectomy specimen were considered the gold standard diagnostic procedures.

Results: The mean age of patients with endometrial hyperplasia (EH) was 44.34 ±3.33 years. The level of pain experienced by patients at HSG procedure was significantly higher than during TV-SH (P <0.0001). EH was found in 70 patients. TV-SH clearly delineated the endometrial cavity and successfully differentiated between endometrial polyp, submucous myoma and hyperplasia. In all EH cases, TV-SH had sensitivity of 95.7%, specificity 96.8%, PPV 91.8%, NPV 98.35% and diagnostic accuracy 96.5% compared to TVS (77%, 94.6%, 84.4%, 91.6% & 89.8%), HSC (75.7%, 97.3%, 91.4%, 91.4% & 91.4%) and HSG (29.4%, 97%, 83.3%, 72.7% & 74%) respectively. In premenopausal patients the corresponding figures were, 67.4%, 94.3%, 80.6%, 89.2% & 87.3% for TVS, 95.5%, 95.9%, 89.1%, 98.3% & 95.8% for TV-SH and 67.4%, 96.7%, 87.9%, 89.4% & 89.1% for HSC and in postmenopausal patients, 89.1%, 95.2%, 89.3%, 95.2% & 93.3%, for TVS, 96.3%, 98.4%, 96.3%, 98.4% & 97.8%, for TV-SH and 88.9%, 98.4%, 96%, 95.4% & 95.6%, for HSC, respectively.

Conclusion: TV-SH is an advanced enhancement of conventional TVS. It is an easy, safe, rapid and tolerable procedure. It has an excellent diagnostic accuracy in EH, but it cannot substitute tissue diagnosis.

Key words: Endometrial hyperplasia, transvaginal sonohysterography, hysterosalpingography, hysteroscopy.

Introduction

Abnormal uterine bleeding (AUB) is a common reason for gynaecologic visits for both premenopausal and postmenopausal women. (1) Up to 33 % of women referred to gynaecological out patient clinics have AUB and this proportion rises to 69 % in a peri or post menopausal group. (2) Endometrial hyperplasia (EH) is considered to be a frequent cause of abnormal uterine bleeding (3) Traditionally, dilatation and curettage (D&C) has been the method of choice for obtaining an endometrial sample, however, in studies comprising both pre – and post menopausal women with AUB, 43–66 % of hyperplasia were missed by D&C. (4) Also D&C is an invasive procedure requiring inpatient and general anesthesia. (5) Approximately 80 percent of all curettage procedures performed for post menopausal bleeding results in benign diagnosis. (6) Therefore, if a non invasive modality can be accurately used to determine endometrial thickness measurements below which pathology is less likely, sampling may be avoided. (7) In this cost conscious era, other less expensive, outpatient, simpler and apparently safer investigations have been advocated (8). These include: measurement of endometrial thickness by
Transvaginal Sonography (TVS)(9), Sonohysterography (TV-SH)(1)(9)(10), Hysterosalpingography (HSG)(6)(11), and hysteroscopy (HSC) (with directed biopsy, if necessary)(1)(6)(12).

The aim of this prospective comparative study was to evaluate the diagnostic accuracy of all these investigations (TVS, TV-SH, HSG & HSC) in the diagnosis of endometrial hyperplasia in women with abnormal uterine bleeding.

**Patients and Methods**

We conducted a prospective study in two centers: Department of Obstetrics and Gynecology, AL-Azhar University Hospital, Cairo, Egypt and Department of Obstetrics and Gynecology, Hadi Hospital, private hospital in Kuwait, during the period from March 1998 to March 2002. The study included 255 patients (160 Egyptians and 95 Kuwaiti). All were admitted for management of abnormal uterine bleeding (165 premenopausal and 90 postmenopausal). Complete evaluation of patients included conventional transvaginal sonography (TVS), transvaginal sonohysterography (TV-SH), and inpatient day case hysteroscopy (HSC). X-ray hysterosalpingography (HSG) was performed only for 40 Egyptian and 10 Kuwaiti patients. Endometrial curettage and/or histopathology of hysterectomy specimens were considered the gold standard diagnostic procedures. In each center every physician performed the same procedure on each patient and recorded his results separately without knowledge of the other findings. The same physician performed each procedure throughout the study. The study and procedures were explained to the patient and consent was obtained. Antibiotics or analgesics were not used prophylactically unless indicated by medical risk factors.

**Transvaginal Sonography (TVS)**

The sonographic examinations were carried out using Creds (Combison) 410 plus, with multifrequency transvaginal probe and a frequency range of 5: 7.5 MHz transducer (for Egyptian patients) and Aloka Co., ltd SSD 1700 Dyna View II Tokyo-Japan (for Kuwaiti patients). Trained ultrasonographer performed the scans. The uterus was scanned in three major planes: longitudinal axis, an oblique plane, and short axis (transverse) view to obtain images in varying directions, planes and depths and using the diagnostic criteria described by previous investigator.(13)

We used endometrium thickness <5 mm as the cut off level for abnormality in postmenopausal patients and <15 mm in premenopausal patients.** After imaging of the uterus, the parametrium and adnexa were imaged systematically in transverse, sagittal and oblique planes.

**Transvaginal Sonohysterography (TV-SH)**

Immediately after the performance of TVS, TV-SH was carried out. The cervix was inspected through a vaginal speculum and cleansed with bovidine iodine solution (Betadine). A polyethylene cannula of the type used for intrauterine inseminations (Unimar KDF-2.3 Intrauterine cannula: Prodimed, Neuilly en Thelle, France) was introduced into the cervix. Traction of the cervix was rarely necessary. The speculum was then removed. Then, the sterile sheathed vaginal ultrasound probe was reintroduced. The sonographer adjusted the image so that all the endometrium and myometrium were visualized on the screen at the time of saline infusion to visualize immediately distension of uterine cavity in the longitudinal plane. Scanning was maintained during infusion and also repeated on transverse plane. Infusion was gradual, with a slow and sustained flow and air bubbles were allowed to disappear before depiction of endometrial cavity. In the case of a patulous cervix, when saline solution reversed its flow and back out of the uterus, more solution was continuously infused. The uterine cavity was re-evaluated in longitudinal oblique and transverse planes and selected pictures were taken.

Endometrial echo, regularity and shape were depicted and endometrial thickness surrounding the fluid was measured. During each study; pre and post instillation scans were recorded on hard copy photos for patients record using Sony Graphic Video printer.

Sixty patients completed questionnaires on a four point scale by the investigator: 0 = no or minimal discomfort, 1 = mild discomfort (tolerable pain), 2 = moderate discomfort (intense pain) and 3 = severe discomfort (unreliable pain) in which they rated the pain they experienced (15).The four point scale assessed pain during application of the instruments and during injection of contrast media. Post procedure complications were also recorded.

Thirty five patients were followed up 3 to 6 months after treatment by TVS and TV-SH.

**X-ray Hysterosalpingography (HSG)**

It was performed one week after ultrasound examinations using a non-ionic, monomeric, triiodinated, water soluble, x-ray contrast medium {IOHEXOL (OMNIPAQUE)} Nycomed Ireland Ltd. Patient pain rating was determined by the same way as that in TV-SH.

**Hysteroscopy**
It was performed one week after X-ray HSG or after TV-SH in patients who did not perform HSG. All hysteroscopic examinations were done under anaesthesia for all cases using rigid panoramic type with a continuous irrigation and suction sheath (26 French gauge) and a 4 mm forward oblique telescope (Karl Storz, Tuttlingen, Germany). The distending medium used was 1.5% glycine solution. The technique was terminated by target hysteroscopic biopsy of suspected endoluminal masses. All patients underwent D&C after hysteroscopy. For cases scheduled for TAH, D&C only was done leaving endoluminal masses in situ till histopathological diagnosis of hysterectomy specimens.

**Statistical Analysis**

The results were statistically analysed using the McNemar test and Chi-square test. Evaluation of predictive power was based on. sensitivity= true positive (TP) X 100/TP +false negatives (FN), specificity=true negatives (TN) X 100/TN+false positives (FP), positive predictive value (PPV)=TPX100/TP+FP, negative predictive value (NPV)=TN X100/TN +FN, diagnostic accuracy (DA) =TP +TN X 100/total, false negative rate = FN/TN+FNX100 and false positive rate = FP/TP+FPX100.Univariate analysis using t-test used for the quantitative variables. The probability level 0.05 (p = 0.05) was used to test the significance of the tests.

**Results**

An endometrial sample was obtained by D&C in all cases. Thirty one patients were dropped during the study because of incomplete investigations due to several reasons. They were not included in the statistical evaluation. Conventional TVS failed in three cases; in one case because of severe vulval and vaginal atrophy, in other case because of third degree uterine prolapse and a third case could not withstand the vaginal probe, all of them were postmenopausal. In six cases the TV-SH was contraindicated; three patients had acute cervicitis, one had cardiac disease and a two cases were suspected to be pregnant. TV-SH procedure failed in seven cases because of cervical stenosis in three cases, and multiple myoma obscuring visualization of the uterine cavity in two cases, severe Asherman's Syndrome in one case and, in one case for unknown reason.

**Table 1** represents the characteristics of the study group. The mean age of patients with EH was 44.34 ±3.33 years. Simple hyperplasia was diagnosed in 54 patients (36 pre- & 18 postmenopausal), and complex hyperplasia without atypia was diagnosed in 16 patients (5 pre- & 11 postmenopausal)

The mean operative time was 5 ±1.7 minutes for TVS, 9 ±2.1 minutes for TV-SH from insertion of the catheter to completion of the procedure. It usually took <15 minutes to complete TVS and TV-SH. The average volume of saline needed for infusion was 10 to 30 cc. In this study only one patients developed mild endometritis after the procedure and did not complete the study. She had performed D&C 2 days prior to TV-SH.

EH were found in 70 patients,(43 premenopausal & 27 postmenopausal). EH was associated with endometrial polyph (EP) in 9 cases (fig. 1) and with submucous myoma in 8 cases (fig. 2).TV-SH clearly delineated the endometrial cavity and successfully differentiated between EP, submucous myoma and EH (Fig 1,2 & 3).The thickened hyperplastic endometrium around the sonolucent infused saline takes different unique shapes while the myometral junction is intact except when there is subendometrial cyst, polypoid like shape, cryptiform shape, a homogenous hyperechoic thick band and a velvety shape which was confused with secretory endometrium. Hyperplastic endometrium may be found in patches or in one wall rather than the other. Myometrial sonolucent small cysts were found associated with polypoid and cryptiform types where histopathology revealed associated adenomyosis in 3 patients.

The level of pain experienced by patients at HSG procedure was significantly higher than during TV-SH (P <0.0001). At the TV-SH procedure, 90% of patients experienced no discomfort, 7% had mild and 3% had moderate discomfort during application of the catheters, while during infusion of saline, 80% had no discomfort 13% had mild, 5% had moderate and 2% had severe discomfort. While at HSG procedure, 40% had no discomfort, 45% had mild and 15% had moderate discomfort during application of instruments, while during infusion of contrast material, 20% had mild, 35% had moderate and 40% had severe discomfort.

In table 2 the agreement between TV-SH and pathologic diagnosis of endometrial hyperplasia was almost perfect (diagnostic accuracy 96.5%),TV-SH was more superior than other procedures with marked difference compared to HSG and HSC, while TV-SH showed superiority to TVS. In all EH cases
the false positive rate (FPR) was 15.7% in TVS, 8.2% in TV-SH, 16.7% in HSG and 8.6% in HSC. The false negative rate (FNR) was 8.3% in TVS, 1.6% in TV-SH, 27.3% in HSG and 8.6% in HSC. In premenopausal patients, the FNR & FPR were 10.9% & 19.4% in TVS, 1.7% & 10.9% in TV-SH, 10.6% & 12.1% in HSC. In postmenopausal patients, 4.8% & 10.7% in TVS, 1.6% & 63.7% in TV-SH, and 4.6% & 4.0% in HSC.

The response to progestin therapy was evaluated in subsequent sonographic examinations. In 35 cases, proved to have simple EH and after 5 months treatment, the sagittal endometrial image at TVS regressed to a line less than 5 mm in thickness prior to infusion. After infusion (TV-SH), the endometrium became thinner with a smooth line that reverted to secretory endometrium at histopathology (Figure 4).

**Discussion**

This study assessed the use of TVS, TV-SH, HSG and hysteroscopy (HSC) in the evaluation of pre- and post menopausal bleeding. Clinicians have long hoped for an accurate & non-invasive screening tool for endometrial pathology. There are several non-invasive methods for the evaluation of the endometrial cavity, TVS, TV-SH, HSG and HSC are such methods.

In the present study high false positive rate (16.7%) was observed with HSG in the diagnosis of EH. This finding is in agreement with many authors.

Accurate positive findings is essential as it directs the patient to a more beneficial procedure and correct management whereas, false positive findings exhaust normal patients and expose them to hazards of unindicated operative intervention. False negative results (27.3% for HSG) have the problem of directing the patient who has an organic lesion to medical treatment with its failure and recurrence to a more progressed state.

Hysterosalpingography delineates the uterine and tubal lumen. Therefore, disease processes that do not cause a filling defect or abnormality in the luminal contour have no hysterosalpingographic expression. Ultrasonography is a safe, readily available modality for non-invasive imaging of the endometrial cavity. It can allow visualization similar to hysteroscopy. especially if one resorts to saline infusion sonohysterography.

In the present study, for TVS, the sensitivity, specificity, PPV, NPV and DA in all EH cases were 77%, 94.6%, 84.4%, 91.6% & 89.8%, in premenopausal patients the corresponding figures were 67.4%, 94.3%, 80.6%, 89.2% & 87.3%, and in postmenopausal patients were, 89.1%, 95.2%, 89.3%, 95.2% & 93.3%, respectively.

TVS had a sensitivity of 88% in premenopausal and 96% in postmenopausal women in diagnosing endometrial abnormalities, and a sensitivity of 88% and specificity of 68% in premenopausal women. Tsuda et al., reported a sensitivity of 97.4%, specificity 75.7%, PPV 23.8% & NPV 99.7% for detection of endometrial pathology in postmenopausal women, while, Sousa et al. 2001, reported, 77.8%, 93.3%, 88.9% & 98.3%, Krampl et al 2001, reported 33.3 %, 88.6 %, 25 % and 92.1 % respectively. Giorda et al., reported 96% & 8% for NPV & PPV for TVS in detecting EH in postmenopausal patients.

This study and previous studies reveal the inability of traditional TVS alone, to identify true endometrial abnormalities. In the present study evaluation of pain rating revealed that the level of pain experienced by patients at TV-SH was significantly lower than HSG. This is in agreement with most investigators.

On the other hand, some investigators reported higher pain ratings with TV-SH. This may be due to the need for more injections and other contrast media which may be more painful.

An interesting finding elicited in the present study was the marked superiority of TV-SH in demonstration of EH and superiority was higher in postmenopausal compared to premenopausal women (Table 2). The superiority of TV-SH in diagnosis of EH compared with TVS was consistent with findings of many authors. The sensitivity and specificity were 97.9% and 33.2%, with an accuracy of 52.3% in postmenopausal women. TV-SH has become the standard test in evaluation of AUB because it allows reliable differentiation between focal and diffuse endometrial and subendometrial lesions. Because TV-SH allows distinction between diffuse or focal abnormalities, it provides physicians with a cost-effective way to plan the next step in case management. For instance, when sonographic characteristics suggest diffuse hyperplasia and not polyp or myoma, an office biopsy to exclude cancer is quite sufficient. It can be simply performed nowadays with small flexible biopsy instruments which are very popular with physicians despite the tendency to sample less than 15% of the endometrial cavity. When there is a focal lesion or asymmetry a hysteroscopically directed biopsy is necessary to ensure removal for diagnosis as well as remission of symptoms. EH usually appears as diffuse thickening of the echogenic endometrial stripe without focal abnormality, but occasionally focal EH, can be seen.
In this series, TV-SH clearly delineated the endometrial cavity, provided accurate measuring of single layer endometrial thickness and excellently differentiated endometrial hyperplasia from submucous myoma (Figure 2) and from endometrial polyp (Figure 1). Thus, it can change the classic concept of further investigations for hyperplasia and a less invasive interference by aspiration biopsy to exclude cancer would likely be sufficient. In the present study, TV-SH was able to demonstrate focal or patchy endometrial thickness and presence of EH on one wall rather than the other (Figure 4). Accordingly, it can assist the gynecologist to direct the curette properly to the desirable site. Consequently, it increased the potential to convert the blind curettage to a directed one contracting the expected high false negative results with the blind procedures.

Regression of endometrial thickness at TV-SH after three to six months progestin therapy is an additional advantage. Follow-up of the endometrium by TV-SH after progestin therapy can help track the response of EH to medical treatment. Unfortunately, TV-SH could not provide specific criteria to different histopathological types of hyperplasia; and thus, it could not substitute tissue diagnosis. The demonstration of subendometrial and myometrial microcysts associated with polypoid and cryptiform endometrium, together with the pathological finding of associated adenomyosis, is an additional advantage of TV-SH. Demonstration of combined EH with submucous myoma or EP is one of the important indices required for endometrial resection, (8) In this study, TV-SH clearly delineated these lesions that were missing at conventional scanning.

A great variation had been reported by many authors regarding diagnostic potential of HSC in diagnosis of EH. The DA was 43% by Widrich et al., 1996 (22), 66.6 % by Embaby and El-Sherlf 1996 (28), and also the sensitivity of HSC was 54% by Motashaw and Dave 1990 (29), 75% by Abou El-kheir et al.1992 (30), 71.8 % in premenopausal and 85.1% in postmenopausal women by Torrejon et al., 1997 (31). HSC showed a sensitivity of 95.8% and 93.9% specificity for detecting endometrial pathology, in postmenopausal women (32). Sensitivity, specificity, and NPV of HSC accounted for 98%, 95% and 99%, PPV was higher in postmenopausal patients compared to women in the fertile age (72 vs.58%) (3). HSC revealed sensitivity of 88.9%, specificity 98.3%, PPV 88.9% and NPV 98.3% in postmenopausal patients with AUB (6). The great variability could be explained by the fact that all hysteroscopic findings are not yet internationally standardized to allow all hysteroscopists to speak the same language. We still find a great similarity between endometrial hyperplasia and late normal secretory endometrium in agreement with the findings of previous investigators (28)(29).

**In conclusion:** TV-SH is an advanced enhancement of conventional TVS. It is an easy, safe, rapid and tolerable procedure. It has an excellent diagnostic accuracy in EH. It can evaluate the endoluminal abnormalities more definitely. Hence, it may then direct biopsy procedures and minimize false negative results, but it cannot substitute tissue diagnosis.

[Click images to open larger view in separate window]

**Table 1**
Table 1: Characteristics of the study group (Mean±SD)*

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<tr>
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<th>Premenopause (N=43)</th>
<th>Postmenopause (N=27)</th>
<th>P-Value</th>
<th>Total (N=70)</th>
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<tr>
<td>Age (years)</td>
<td>42.02±1.50</td>
<td>47.62±2.25</td>
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<td>44.34±3.33</td>
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<td>Duration of marriage (yrs)</td>
<td>22.85±3.15</td>
<td>25.41±5.38</td>
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<td>Parity (No)</td>
<td>5.60±2.72</td>
<td>5.62±2.73</td>
<td>N.S</td>
<td>5.61±2.70</td>
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<td>Duration of bleeding (days)</td>
<td>9.12±1.76</td>
<td>7.20±3.02</td>
<td>&lt;0.005</td>
<td>8.32±2.53</td>
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<td>D&amp;C (No)</td>
<td>1.00±0.70</td>
<td>1.34±0.85</td>
<td>&lt;0.05</td>
<td>1.14±0.78</td>
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<td>Duration of hormonal treatment (months) (n = 36)</td>
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<td>Haemoglobin% (g/dl)</td>
<td>8.79±1.08</td>
<td>9.08±1.14</td>
<td>N.S</td>
<td>8.91±1.10</td>
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<td>Body weight (kg)</td>
<td>71.31±12.21</td>
<td>72.17±12.66</td>
<td>N.S</td>
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<td>Uterine size (cm)</td>
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<td>8.95±1.87</td>
<td>N.S</td>
<td>8.82±1.73</td>
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<td>Pathology EH</td>
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<td>Complex</td>
<td></td>
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<td>16.89±2.84 (N=36)</td>
<td>20.20±1.30 (N=5)</td>
<td>&lt;0.001</td>
<td>14.38±4.41</td>
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<td>Complex</td>
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<td>9.59±1.78 (N=18)</td>
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<tr>
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<td>17.48±2.89</td>
<td>12.07±3.63</td>
<td>&lt;0.001</td>
<td>15.24±4.17</td>
</tr>
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</table>

* t: Test was used to compare between the two mean values. = Endometrial thickness*

Table 2
**Figure 1:** A-TVS of the uterus in long plane. Thickened hyperechoic endometrium measuring 23.1 mm (callipers). Pathology revealed simple hyperplasia without atypia. B-TV-SH in the same plane. Thickened hyperechoic homogeneous endometrium surrounding a sonolucent distended cavity. The single layer endometrial thickness measured 8.4 and 9.6 mm, respectively (callipers). The summation (18 mm) is less than the total thickness at TVS. C- TV-SH at oblique plane. It demonstrates corporofundal small endometrial polyp 5 mm in diameter. This explains the difference in endometrial thickness at both procedures.
**Figure 2:** A- TVS of the uterus in the long plane. Central ovoid endometrial thickening suggesting a submucous myoma (arrows). The endometrial mass is hyperechoic with intact E-M junction. Hyperplasia is also considered. B- TV-SH in the same plane. Markedly thickened endometrium with polypoid appearance and intact E-M interface. Note the associated anterior wall corporeal small submucous myoma. Also, note anechoic polypoid structure which was stable during infusion. It represents the intrauterine insemination cannula. C-TV-SH of the same patient in the same plane. Myometrial microcystic spaces representing reactivation of foci of adenomyosis. C-HSG of the same patient. Wide endometrial cavity with irregular endometrial contour. The small submucous myoma was missed.

**Figure 3:** A- TVS in the long plane. Central echogenic mass with its cranial part thicker than the slippered caudal part and an intact E-M junction. TVS suggested large endometrial polyp. B-TV-SH revealed thickened endometrium with single layer thickness 7.6 and 7.5 mm respectively and intact E-M junction. The endometrial surface irregularity showed cryptiform appearance surrounding a sonolucent cavity. Note small microcystic spaces representing reactivation of foci of adenomyosis. C-HSG of the same patient. Wide endometrial cavity with irregular endometrial contour. D-HSC of the same patient. Irregularly thick heaped up endometrium with increased vascularity. It is difficult to distinguish it from late secretory endometrium.
Figure 4: A-TV-SH in the standard longitudinal view revealed thickened endometrium only at the posterior and fundal walls with velvety appearance like brush border while the anterior endometrium is smooth and thin. Target biopsy revealed hyperplastic endometrium without atypia in the thickened areas while the smooth anterior endometrium was proliferative. B-TV-SH of the same plane after 3 months progestin therapy. The thickened areas contracted to a small thickened fundal patch. Targeted biopsy revealed fundal hyperplasia while the remaining endometrium was proliferative. C-TV-SH after another two months progestin therapy. The residual hyperplastic fundal patch reverted to secretory endometrium at target biopsy. The secretory endometrium shows also a velvety appearance.
References:


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