

Original Research Article


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

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## Abstract

**Background:** Abnormal uterine bleeding (AUB) is any heavy or unusual bleeding from the uterus (through your vagina). It can occur at any time during your monthly cycle, including during your normal menstrual period.

**Aim:** This study aimed to compare the accuracy of TVUS and SIS in relation to hysteroscopy in assessing the uterine cavity and in detecting ER and PR in endometrium and their relation with endometrial polyps in women with peri and postmenopausal bleeding.

**Materials and methods:** The present study was a prospective study which included 120 patients with AUB who were attending the department of gynaecology at Gandhi Medical College, Hyderabad from July 2012 to November 2015.

**Results:** 120 patients were selected in this study. Patients suffering from endometrial polyp were 40 (33.34%), endometrial hyperplasia were 25 (20.83%), endometrial atrophy were 19 (15.83%), normal endometrium were 19 (15.83%) and submucous fibroid were 17 (14.17%). Age was shown in mean±SD and p-value was 0.39 and it was statistically non- significant. Parity was shown in mean±SD and p-value was 0.283 and it was statistically non-significant. SIS had 4 false negative results by missing 2 cases with endometrial polyps, 4 false positive result by diagnosing a case of 4 endometrial hyperplasia as polypi. SIS had 8 false negative results (by missing 6 cases), 8 false

positive results (3 cases was found to have polypi and 5 cases were normal). Mean endometrial thickness in mm in various diagnosis by TVUS as follows; endometrial polyp had  $15.49 \pm 10.98$ , endometrial hyperplasia had  $8.19 \pm 5.55$ , endometrial atrophy had  $4.55 \pm 2.97$  and normal endometrium had  $12.68 \pm 6.80$ .

**Conclusion:** Especially with intra-cavitary lesions, sonohysterography is superior to ultrasound and very close to hysteroscopy. Hysteroscopy remains the reliable standard for uterine cavity assessment, but cannot replace the histopathology. In the pathogenesis of endometrial polyps and endometrial hyperplasia, the expression of endometrial steroid receptors is crucial.

## Key words

Uterine Cavity Assessment, Endometrial Hormonal Receptors, Peri and Post- Menopausal Bleeding.

## Introduction

Abnormal uterine bleeding (AUB) is any heavy or unusual bleeding from the uterus (through your vagina). It can occur at any time during your monthly cycle, including during your normal menstrual period [1]. AUB should be suspected in patients with unpredictable or episodic heavy or light bleeding despite a normal pelvic examination. Typically, the usual minimal symptoms that accompany ovulatory cycles will not precede bleeding episodes. A variety of things can cause abnormal uterine bleeding. Pregnancy is a common cause. Polyps or fibroids (small and large growths) in the uterus can also cause bleeding. Rarely, a thyroid problem, infection of the cervix, or cancer of the uterus can cause abnormal uterine bleeding [2]. In most women, abnormal uterine bleeding is caused by a hormone imbalance. When hormones are the problem, doctors call the problem dysfunctional uterine bleeding, or DUB. Abnormal bleeding caused by hormone imbalance is more common in teenagers or in women who are approaching menopause [3]. These are just a few of the problems that can cause abnormal uterine bleeding. These problems can occur at any age, but the likely cause of abnormal uterine bleeding usually depends on your age. AUB can be due to benign conditions or the presence of endometrial cancer. The currently accepted diagnostic method for endometrial cancer and hyperplasia is dilatation and curettage (D&C). But D&C is not capable of diagnosing endometrial polyps, leiomyomas,

adenomyosis. Transvaginal ultrasound (TVUS) is generally used to differentiate the causes of AUB. From images of TVUS, distinguishing between a thickened endometrial lining and other diffuse or focal endometrial abnormalities [4]. Saline infused sonohysterography (SIS) is an improved TVUS method. It allows uterine abnormalities to be visually seen precisely by pushing apart the walls of the uterine cavity in which saline infuses. Hysteroscopy (DH) with biopsy is a reliable and safe method for evaluation of the uterine cavity. In conventional TVUS, The first structures to be scanned are the uterus and cervix [5]. It is useful to have performed a bimanual examination prior to this point to determine the position of the uterus (e.g. anteverted or retro-verted). Its characteristic landmark is the endometrial stripe, surrounded by the homogeneous muscular layer of myometrium. Position and size of the uterus are noted. Myomas are the most common pathology of the uterus and cervix. Smaller ones can be seen as round structures with high echogenicity on US. Larger ones distort the shape of the uterus or the endometrial stripe. Sometimes calcifications are seen within a myoma. When a leiomyoma is larger than 5 cm, the view obtained with TVUS may be obscured and in such cases it is more effective to carry out abdominal US. The position of the fibroid is important. Submucous myomas extend into the uterine cavity and may distort it, thereby inhibiting implantation of pregnancy. Mullerian abnormalities are estimated to occur in 2-3% of women. On TVUS a uterine

septum can be seen as two endometrial stripes separated by a myometrial layer. The septum can result in inhibition of implantation and may be removed hystero-scopically. A bicomuate uterus is best discovered in transverse view; in the longitudinal view the intermediate myometrial layer is not continuous. Circulating estrogen and progesterone influence the endometrial thickness and texture. US can clearly depict cyclic changes of texture and may indicate whether the appearance of the endometrium is related to the day of the menstrual cycle or to a suspected functional problem. During and shortly after menses the endometrium appears as a thin echo-genic line. During the proliferative phase it thickens and becomes isoechoic [6]. Toward ovulation the endometrium becomes more echogenic and develops a multilayered pattern. There is a thin hyper-echoic line in the middle, surrounded by an inner hypoechoic layer and an outer echogenic layer that is secondary to stromal edema. This pattern seems necessary for normal pregnancy to develop. Several studies have attempted to correlate endometrial thickness at the time of ovulation with pregnancy rates. It is now generally acknowledged that in the natural cycle, a thickness of 5 mm or less results in poor pregnancy rates, whereas 10 mm or more provides a good possibility of conception. During the secretory phase the endometrium continues to thicken, reaching up to 14 mm, and becomes homogenic and hyperechoic on US. Beginning menstruation toward the end of the cycle may be seen as minimal hypoechoic spots in the endometrium. Polyps and other endometrial abnormalities may pose a problem. Endometrial polyps vary in size from less than a millimeter to several centimeters in diameter. Large polyps may interfere with implantation of the embryo and cause infertility. In US, endometrial polyps typically appear as an unusually high degree of thickening of the endometrium and are best diagnosed early in the menstrual cycle when the proliferative endometrium is still thin. This study aims to compare the accuracy of TVUS and SIS in relation to hysteroscopy in assessing the uterine cavity and in detecting ER and PR in endometrium and their relation with endometrial

polyps in women with peri and postmenopausal bleeding.

## **Materials and methods**

The present study was a prospective study which included 120 patients with AUB who were attending the Department of Gynecology at Andhra Medical College, Visakhapatnam from July 2012 to November 2015. This study was approved by Institutional Ethical committee and informed consent was taken from all the participants involved in the study. The women included in the study were older than 65 years, with AUB for more than 4 months. Out of 120 women, 60 had postmenopausal bleeding, 12 had premenopausal menorrhagia, 6 had premenopausal metrorrhagia, 42 had premenopausal menometrorrhagia. Hormonal treatment history, hormonal contraception in last 6 months were excluded from the study, women who had used IUD or those who had hysteroscopy or fractional curettage done in the last 6 months were excluded from the study. Clinical examination like general, abdominal, pelvic examination, full history, laboratory investigations were done for all the patients. As many as 10-30% of women investigated for infertility do not ovulate regularly. TVUS can be used to monitor ovulation. Follicles can be observed on TVUS when they reach a diameter of 2-3 mm. During the natural cycle, a dominant follicle typically appears during days 8-12. Its growth is linear, about 2 mm per day, and it reaches a size of 18-24 mm before ovulation (mean 21.5 mm). It is rare for other follicles to be present during the natural cycle, but in such cases they usually do not exceed 14 mm in diameter, nor do they ovulate. The size of the dominant follicle correlates with the serum estrogen level, and its size is more predictive of ovulation than serum estrogen levels, although a combination of the two gives the best accuracy. E2 levels at ovulation are between 150 and 400 pg/ml. Ultrasonography can be useful to detect ovulation itself; or in cases of tubal damage on one side, it can help determine on which side ovulation will occur if intrauterine insemination is planned.

Moreover, the shape of a follicle helps determine whether it will ovulate. Fukuda et al. showed that a healthy (type A) follicle contains a cloud in the shape of a cone. The base is positioned at the follicle wall; the tip points into the center of the follicle and has a light spot assumed to be the oocyte-cumulus complex. This can be seen when the follicle is in excess of 15 mm. Type B follicles show an echo free space and become atretic. Ovulation occurs 36-38 hours after the peak serum luteinizing hormone (LH) surge and is seen as a rapid reduction of follicle size. In most cases fluid is detected in the cul-de-sac. This may also be present before ovulation because of transudation. A corpus luteum is present from 45 minutes after ovulation, and on US appears as a round cystic structure with an irregular pattern due to blood clots. It changes rapidly over time. 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.

Average staining intensity of ER or PR positive cells was done by an intensity score which was assigned as follows: Grade 0 negative, Grade 1 weak, Grade 2 intermediate and Grade 3 strong. Statistical data was represented in terms of mean, standard deviation and percentages. Chi-squares test was used for comparing non-parametric data. P value less than 0.05, it was considered significant.

## Results

120 patients were selected in this study. **Table - 1** shows that patients suffering from endometrial polyp were 40 (33.34%), endometrial hyperplasia were 25 (20.83%), endometrial atrophy were 19 (15.83%), normal endometrium were 19 (15.83%) and submucous fibroid were 17 (14.17%). **Table - 2** shows age was shown in mean±SD and p-value was 0.39 and it was statistically non- significant. Parity was shown in mean±SD and p-value was 0.283 and it was statistically non-significant.

**Table - 1:** Distribution based on diagnosis.

Diagnosis	No. of patients	%
Endometrial polyp	40	33.34%
Endometrial Hyperplasia	25	20.83%
Endometrial Atrophy	19	15.83%
Normal Endometrium	19	15.83%
Submucous fibroid	17	14.17%
Total	120	100%

**Table - 2:** Distribution based on age and parity in the study.

Diagnosis	Age	Parity
Endometrial polyp	50.68±6.28	5.20±1.87
Endometrial Hyperplasia	51.05±6.47	5.08±2.96
Endometrial Atrophy	49.39±9.64	4.89±3.97
Normal Endometrium	48.51±3.11	6.57±5.28
Submucous fibroid	47.28±3.55	3.49±0.55

**Table - 3:** Comparison of diagnosis using different uterine assessment modalities.

Diagnosis	TVUS	SIS	DH
Endometrial polyp	22	40 <sup>a</sup>	40
Endometrial Hyperplasia	31	25 <sup>b</sup>	23
Endometrial Atrophy	11	13	19
Normal Endometrium	4	13	19
Submucous fibroid	17	17	17

TVUS: Transvaginal ultrasonography, SIS: Saline infusion sonohysterography, DH: Diagnostic hysteroscopy.

**Table - 4:** Endometrial thickness by 2D-TVUS in various diagnoses.

Diagnosis	Mean Endometrial thickness (mm)
Endometrial polyp	15.49±10.98
Endometrial Hyperplasia	8.19±5.55
Endometrial Atrophy	4.55±2.97
Normal Endometrium	12.68±6.80



**Table - 3** shows a: SIS had 4 false negative result by missing 2 cases with endometrial polyps, 4 false positive result by diagnosing a case of 4 endometrial hyperplasia as polypi. b: SIS had 8 false negative results (by missing 6 cases), 8 false positive results (3 cases was found to have polypi and 5 cases were normal).

**Table - 4** shows mean endometrial thickness in mm in various diagnosis by TVUS as follows; endometrial polyp had  $15.49 \pm 10.98$ , endometrial hyperplasia had  $8.19 \pm 5.55$ , endometrial atrophy had  $4.55 \pm 2.97$  and normal endometrium had  $12.68 \pm 6.80$ .

## Discussion

In present study, 120 patients were selected in this study. Patients suffering from endometrial polyp were 40 (33.34%), endometrial hyperplasia were 25 (20.83%), endometrial atrophy were 19 (15.83%), normal endometrium were 19 (15.83%) and submucous fibroid were 17 (14.17%). Age was shown in mean $\pm$ SD and p-value was 0.39 and it was statistically non-significant. Parity was shown in mean $\pm$ SD and p-value was 0.283 and it was statistically non-significant. SIS had 4 false negative result by missing 2 cases with endometrial polyps, 4 false positive result by diagnosing a case of 4 endometrial hyperplasia as polypi. b: SIS had 8 false negative results (by missing 6 cases), 8 false positive results (3 cases was found to have polypi and 5 cases were normal). Mean endometrial thickness in mm in various diagnosis by TVUS as follows; endometrial polyp had  $15.49 \pm 10.98$ , endometrial hyperplasia had  $8.19 \pm 5.55$ , endometrial atrophy had  $4.55 \pm 2.97$  and normal endometrium had  $12.68 \pm 6.80$ . In a study conducted by Ahmed M Maged, et al. [7]; similar results were found. In their study, 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. 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). Lubna Pal, et al. [8]; compared between office hysteroscopy, transvaginal ultrasonography and endometrial biopsy was performed, in terms of detection of intrauterine lesions. A secondary objective was assessment of evaluatory approach in the management of abnormal uterine bleeding in an outpatient setting. It was reported that the incidence of focal intrauterine lesions in patients presenting with abnormal bleeding was 52% for all ages and 31% for the postmenopausal group. Seventy-five percent of the patients with Hb < 11 gm% and 67% with an enlarged uterus harbored a focal pathology. The incidence of lesions in patients with heavy regular bleeding was 74%. The sensitivity and specificity of transvaginal ultrasound when compared with results of hysteroscopy was 0.60 and 0.88 respectively. A normal endometrial biopsy had a negative predictive value of 51%. The sensitivity and specificity of endometrial biopsy were 0.04 and 0.83, respectively. Iêda Maria Silveira Diógenes Feitosa, et al. [9]; conducted a cross sectional study with 30 patients, aged from 29 to 71 years, 21 (70%) of them premenopausal and 9 (30%) postmenopausal. Saline solution (at 9%) was utilized as contrast agent for SHG. The MacNemar test was utilized for comparison of diagnostic studies. Hysteroscopy diagnosed 18 cases (60%) of intracavitary alterations, and 10 polyps (33.3%). TVUS demonstrated 83.3% sensitivity and specificity, and SHG showed 94.4% sensitivity and 91.6% specificity. The MacNemar test showed similar sensitivity ( $p = 0.500$ ) and specificity ( $p = 1.000$ ) between TVUS and SHG in the detection of endometrial

diseases. In the diagnosis of polyp, SHG showed the highest sensitivity (90.9% vs. 27.3%;  $p = 0.016$ ) with similar specificity (89.5% vs. 94.7%;  $p = 1.000$ ). B.K. Goyal, et al. [10]; aimed at assessing the usefulness of TVS in comparison with hysteroscopy in AUB evaluation. 100 female patients with AUB were enrolled in the study. Each patient was subjected to TVS where uterine cavity was studied in detail and hysteroscopy under anaesthesia using saline as distension medium. Sensitivity, specificity and predictive value of TVS as compared to hysteroscopy were calculated. Subgroup analysis within each group was also performed. Menorrhagia was the commonest presenting symptom in the study population ( $n = 58$ ) followed by metrorrhagia, menometrorrhagia and continuous bleeding  $>21$  days. 74 female patients had normal size uterus. In 57 patients, the uterine cavity was normal on TVS. Thickened endometrium, endometrial polyp and submucous fibroids were seen in 19, 16 and 6 patients respectively. Hysteroscopy showed normal cavity in 59 female patients and polypoidal endometrium, polyps or submucous fibroids in 41. TVS was found to have high sensitivity and specificity (95.23 and 94.82 respectively) and high positive and negative predictive value. Strength of agreement between TVS and hysteroscopy was high (kappa value 0.898). Bingol B, et al. [11]; conducted a prospective, investigator-blind trial, the present study was conducted on 137 postmenopausal women, with abnormal uterine bleeding, admitted to the Department of Obstetrics and Gynecology of Istanbul Bilim University, Florence Nightingale Hospital and Fertigyn Woman Health and IVF Center. After TVS, all patients underwent SIS using Cook Soft 500 IVF transfer catheter and HS, consecutively. Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated to compare the diagnostic accuracy of TVS, SIS and HS. Most commonly encountered endometrial lesions were polypoid lesion (38.0%) and hyperplasia (28.4%) among our study population consisting of 137 women (mean age  $61.6 \pm 9.6$  years) in their postmenopausal stage. Overall sensitivity rates

were 70.0% for TVS, 89.6% for SIS and 92.3% for HS, while the overall specificity rates were 50.0, 77.3 and 80.7%, respectively. HS had PPV of 96.2% and NPV of 65.3%, whereas PPV was determined to be 80.9 versus 95.3% and NPV was 35.4 versus 58.3% for TVS and SIS, respectively.

## Conclusion

Especially with intra-cavitary lesions, sonohysterography is superior to ultrasound and very close to hysteroscopy. Hysteroscopy remains the reliable standard for uterine cavity assessment, but cannot replace the histopathology. In the pathogenesis of endometrial polyps and endometrial hyperplasia, the expression of endometrial steroid receptors is crucial.

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