Research Article

Gynecology & Reproductive Health

The Role of Endometrial Volume in the Prediction of Endometrial Hyperplasia

Wael S Nossair*

M.D. of obstetrics and gynecology, faculty of medicine, Zagazig University, Egypt.

***Correspondence:**
Wael S Nossair, M.D. of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt, E-mail: mohammedelsokkary1@yahoo.com.

Received: 26 Apr 2017; **Accepted:** 18 May 2017

Citation: Wael .S. Nossair. The Role of Endometrial Volume in the Prediction of Endometrial Hyperplasia. Gynecol Reprod Health. 2017; 1(1): 1-5.

ABSTRACT

Objective: *To assess the accuracy of 3D Transvaginal sonar (TVS) in the diagnosis of endometrial hyperplasia in women with premenopausal uterine bleeding.*

Methods: *Fifty-five women with premenopausal bleeding were recruited from outpatient gynecology clinic in Zagazig University Hospitals, and Agial Fertility Center. The study was conducted from January 2014 till January 2017 The endometrial volume obtained by 3D TVS and results of the histopathological examination of the endometrial tissue were evaluated to assess the cut off value of endometrial volume for diagnosis of endometrial hyperplasia and carcinoma.*

Results: *55 premenopausal women presented by abnormal uterine bleeding were included in the study. Women with benign endometrial pathology were 32 (58.2%), which included atrophic and disordered proliferative endometrium. Women with endometrial hyperplasia were 21 which included hyperplastic polyp, Simple Endometrial hyperplasia without atypia and others with atypia and complex endometrial hyperplasia while endometrial carcinoma was found in 2 patients.*

Conclusion: *Endometrial hyperplasia is the commonest observed endometrial abnormality in premenopausal patients with abnormal uterine bleeding. Even though histopathological examination of the endometrium is the gold standard for diagnosis or exclusion of endometrial pathology, 3D TVS are reasonably accurate, helpful & non-invasive tool for assessing the endometrium.*

Keywords
Endometrial volume, Endometrial hyperplasia.

Introduction
Premenopause is a transitional period 3-5 years prior to menopause that is usually characterized by a change in the normal menstrual cycle. The cycles may be longer or shorter, and the flow may vary from light to heavy. As ovarian function is declining, ovulation may not occur. The unopposed estrogen without progesterone will cause the uterine lining to thicken [1]. This thickening will cause endometrial hyperplasia & carcinoma, polyps & fibroids may also cause changes in bleeding pattern [2]. Endometrial sampling is the gold standard for diagnosing abnormalities in the endometrial tissues with sensitivity ranging from 85-95% [3]. There is a growing trend to use noninvasive procedures such as TVS, to measure the endometrial thickness, diagnose dysfunctional uterine bleeding, adenomyosis, endometrial polyps & leiomyomas [4].

Another important ability of 3D TVS is volume calculation using the Virtual Organ Computer-aided AnaLysis (VOCAL) even in irregularly shaped structures. This method has been demonstrated to be more accurate than 2D-volume estimation [5]. The differentiation between benign endometrial pathology, endometrial hyperplasia and carcinomas was not possible due to overlap in the endometrial thickness measurements. When 3D volume measurements were performed, the overlap was much smaller which significantly improved the diagnosis of cancer [6]. The purpose of this study was to assess the accuracy of endometrial

volume estimation by 3D TVS in diagnosis of endometrial hyperplasia in women with premenopausal abnormal bleeding.

Patients and Methods

This study was conducted in Zagazig University Hospitals, and Agial Fertility Center from January 2014 till January 2017, 55 women who sustained premenopausal bleeding were enrolled in this study.

Inclusion criteria: Age 40-55 years with symptoms of abnormal bleeding e.g. menorrhagia, metrorrhagia, and polymenorrhea.

Exclusion criteria: general or local causes of bleeding, drug intake or recent hormonal contraception.

All patients were subjected to the following

- Full history taking with special attention to confirmation of the selection criteria
- Comprehensive general and pelvic examination
- 3D-TVS measuring endometrial volume using VOCAL
- Endometrial curettage and histopathological examination.
- Comparison of the endometrial volume obtained by VOCAL and results of the histopathological examination of endometrial tissue.

Ultrasound instrumentation

With an empty bladder, the patient was examined at the Special Care Center of The Fetus by the same sonographer in the lithotomy position using Voluson Pro 720 transducer with frequency range 5-8 MHZ. Sonar is done to study uterine size, shape and exclusion of any uterine or ovarian pathology. The 3D image was obtained by switching on the 3D volume mode and defining the region of interest by a movable sector on the screen. This sector has the shape of a truncated cone which can be manipulated to ensure that the whole of the endometrial cavity was included in the volume sampling while the patient remain still and the probe is held stationary. Volume sampling lasted about 4 seconds, during that time the conventional 2D plane was rotated through 180^{o} with the rotation axis oriented exactly along the longitudinal axis of the vaginal probe. The data was stored digitally on the internal disc drive for subsequent analysis after the ultrasound probe is removed. For the purpose of volume calculation, 3D data was retrieved and presented in multi-planer display mode which simultaneously displays 3 perpendicular planes on the screen. The actual volume was calculated by the built-in computer program using VOCAL. This is a rotational method based on rotation in given steps (6,9,15,30) on a given orthogonal plane (A,B OR C). The endometrial volume was measured in plane A by delineating the endometrial margin at the endometrial-myometrial interface from the fundus to the internal cervical os in a number of parallel slices which are 1-2 mm apart.

Endometrial curettage

Endometrial curettage was performed under general anesthesia by the same surgeon. The first sample was taken from the endocervical canal before cervical dilatation, then cervical dilatation up to 7-8 Hegar. A sharp curette is introduced and curettage starting first with the fundus then posterior wall then anterior wall then right then left lateral walls. The sample was placed in Formalin 10% and sent for histopathological examination for the nature of the endometrial pathology.

Blind comparison

Sonographer who undergoes 3D TVS was unaware of the result of the histopathological examination of the endometrial tissue. And the pathologist who undergoes the histopathological examination was not aware of the result of 3D TVS.

Ethical consideration

Institutional review board (IRB) approval: The protocol was discussed by the ethical scientific committee for approving the study and informed consent was obtained before participation.

Consent procedure

The Investigator made certain that an appropriate informed consent process was in place to ensure that potential research subjects, or their authorized representatives, were fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The Investigator obtained the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The Investigator retained the original signed informed consent form.

Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site would not include unique personal data to maintain subject confidentiality.

Sample size calculation

The required sample size has been estimated using the Power Analysis and Sample Size software version 08.0.9 (PASS; NCSS; LLC; Kaysville, Utah). The test used for calculation is the two sided z-test and type 1 error has been set at a two sided value of 0.05 (confidence level, 95%).

Results

The current study was conducted in Zagazig University Maternity Hospital on women recruited from the outpatient gynecological clinic from January 2014 till January 2017. 55 premenopausal women presented by abnormal uterine bleeding were included in the study. Women with benign endometrial pathology were 32 (58.2%), which included atrophic and disordered proliferative endometrium.

Women with endometrial hyperplasia were 21 (38.2%) which included hyperplastic polyp, Simple Endometrial hyperplasia without atypia and others with atypia and complex endometrial hyperplasia while endometrial carcinoma was found in 2 (3.6%) patients (Table 1).

Histopathological result	Number (%)
Atrophic endometrium	14 (25.5)
Disordered proliferative endometrium	18 (32.7)
Hyperplastic polyp	4 (7.2)
Simple endometrial hyperplasia without atypia	12 (21.8)
Complex endometrial hyperplasia	2 (3.6)
Simple endometrial hyperplasia with atypia	3 (5.5)
Adenocarcinoma	2 (3.6)

Table 1: The distribution of the histopathological results in women under study.

There was a statistically significant difference between benign endometrium compared to endometrial hyperplasia and to endometrial carcinoma as regard age and parity using Independent sample t-test but there was no significant difference among the groups as regards weight and occurrence of previous abortions. Also, there was a highly statistically significant difference between patients with benign endometrium, endometrial hyperplasia and endometrial carcinoma, as regarding endometrial volume using Kruskal-Wallis test (Table 2).

	Benign endometrial pathology (n=32)	Endometrial hyperplasia (n=21)	Endometrial carcinoma (n=2)	p-value
Age, yr Mean ± SD	48.2 ± 3.1	50.9 ± 3.2†	52.6 ± 3.1†	< 0.05
BMI kg/m² Mean±SD	32.3 ± 5.2	34.3 ±4 .8	32.2 ± 6.2	>0.05
Parity Median (IQR)	3	2	2 ‡	<0.05
Previous abortions Median (IQR)	2	1	2	>0.05
Endometrial volume, ml	8.9 (8.2-12.2)	10.9 (8.7-15.1)	1812 (13.8-23.2) †‡	< 0.05

Table 2: Characteristics of patients with benign endometrial pathology, endometrial hyperplasia, or endometrial carcinoma. IQR: Interqurtile range.

†p-value <0.05 vs. Benign endometrium group (Student-Newman-Keuls test).

‡p-value <0.05 vs. Benign endometrium group (Conover test).

It was shown by the results of receiver-operating characteristic (ROC) curve analysis for classification of patients into those with benign endometrial pathology and those with endometrial hyperplasia or carcinoma using endometrial volume that endometrial volume had a good predictive value. The best cut-off value was an endometrial volume >12.2 ml (Table 3).

Also, the results of receiver-operating characteristic (ROC) curve analysis for classification of patients into those with benign endometrial pathology or hyperplasia and those with endometrial carcinoma using endometrial volume had shown that endometrial volume had a very good predictive value. The best cut-off value was an endometrial volume >13.1 ml (Table 4).

Index	Estimate (95% CI)
Area under the ROC curve (AUC)	0.816
P-value (AUC0=0.5)	0.034
Youden index J	0.865
Best cut-off value, ml	>12.2
Sensitivity %	71.5
Specificity %	84.9
Positive predictive value (PPV %)	91.2
Negative predictive value (NPV %)	48.2

Table 3: shows the results of receiver-operating characteristic (ROC) curve analysis for classification of patients into those with benign endometrial pathology and those with endometrial hyperplasia or carcinoma using endometrial volume.

Diagnostic indices are presented as estimates and their 95% CI.

Index	Estimate (95% CI)
Area under the ROC curve (AUC)	0.865
P-value (AUC0=0.5)	<0.05
Youden index J	0.449
Best cut-off value, ml	>13.1
Sensitivity %	94.2
Specificity %	81.2
Positive predictive value (PPV %)	72.1
Negative predictive value (NPV %)	93.2

Table 4: Receiver-operating characteristic (ROC) curve analysis for classification of patients into those with benign endometrial pathology and those with endometrial hyperplasia or carcinoma using endometrial volume at a cut off value of 13.2 ml.

Diagnostic indices are presented as estimates and their 95% CI.

Discussion

Heavy menstrual bleeding is a major public health problem7. Menstrual disorders interfere significantly with the quality of life in otherwise healthy women. Whenever bleeding occurs, judgment is needed to determine whether investigation is required to rule out benign and malignant causes [8]. Abnormal uterine bleeding is probably the most common symptom in gynecologic practice. Up to 33% of women referred to the gynecological outpatient clinics have abnormal uterine bleeding and this proportion rises to 69% in the premenopausal group [9]. Traditionally, dilatation and curettage used to be the main line of investigation for abnormal uterine bleeding but it is not accurate for diagnosing focal intrauterine lesions which are small or located in areas difficult to curette [10]. Also, in studies comprising both pen and postmenopausal women with abnormal uterine bleeding, 43-66% of eases of hyperplasia were missed by D&C [11].

Transvaginal 2D ultrasonography has been used extensively in cases of abnormal uterine bleeding to evaluate uterine pathology to exclude myomata, polyps and focal lesions and to cheek the adnexa [12]. 3D ultrasound offers new viewing window by allowing for arbitrary plane evaluation through a volume data set acquired from the pelvis [12]. In addition, by 3D ultrasound, more precise anatomical sections for exploring the endometrial cavity;

the relations of myomata and their possible encroachment on the cavity, the diagnosis of endometrial polyps and the measurement of endometrial volume rather than thickness in cases of abnormal uterine bleeding are feasible [13]. The incidence of endometrial cancer has increased in the past decade although the incidence and mortality rates of other types of cancer have stabilized or even decreased [14].

In the current study there was a statistically significant difference as regards the mean age between women with benign endometrial pathology compared to that of either endometrial hyperplasia or carcinoma. In disagreement with our results, the study done by Clark et al. [15] and Ahmad et al. [9] who found no statistically significant difference between the study groups.

In agreement to our results, a study showed that normal endometrium was found in 9 cases (18%), myomas in 16 cases (32%), endometrial polyps in 6 cases (12%), endometrial hyperplasia in If cases (22%) and endometrial carcinoma in 2 cases (4%) [10]. The prevalence of endometrial carcinoma in the present study was 3.6%. This is similar to that reported in previous studies [16,17]. It is author`s opinion that the incidence of endometrial carcinoma in Egypt is more than others and this is according to many factors as obesity which has high incidence & low compliance for treatment & seeking medical advice late after the disease is late in stage but this is still under study by the authors.

As regards endometrial volume, the difference between patients with benign endometrium, compared to endometrial hyperplasia and endometrial carcinoma was highly statistically significant. Also, the difference between patients with benign endometrial pathology and endometrial hyperplasia compared to endometrial carcinoma was statistically significant. In another study [18], the endometrial volume in hyperplasia had the mean value of 7.82 ± 7.60 cc and was significantly higher than the volume ha patients with polyps (mean 2.63 ± 2.12 cc). This was not found in the present study. In another study [19] was done on premenopausal patients, the endometrial volume was 6.87 ± 6.3 cc in the normal group and 13.79 ± 13.2 cc in the pathologic group. Endometrial volume was 18.1 cc in patients with endometrial cancer and 11.2 cc in patients with hyperplasia; both were significantly higher than in the normal. In the study by Stachowicz et al. [20], the mean endometrial volume in women with endometrial cancer was 19.9 ± 7.5 cc. The mean volumes measured in women with endometrial hyperplasia and normal endometrium, were 12.2 ± 7.9 cc and 7.4 ± 4.8 cc, respectively.

Ebrashy et al. [21] examined 65 cases by both TVS 2D and 3D ultrasound and the results are by 2D ultrasound: 13 cases are normal, 7 cases showing endometrial polyps, 29 cases having myomas either single or multiple from which 8 had submucus myomas, 12 cases had thickened endometrium while by 3D ultrasound: 9 cases are normal. In the study carried out by Pyrai et al. on 50 patients with abnormal uterine bleeding, by TVS it detected 13 myomas (26%), 4 polyps (8%), 3 adenomyosis (6%), 10 hyperplasia (20%), 2 endometrial carcinoma (4%), 2 atrophic endometrium (4%) [10].

While in another study which dealt with similar parameters to detect the value of sonography in relation to hysteroscopy in diagnosing intracavitary lesions showed sensitivity for 2D U/S of 74% for myomas and 39% for polyps while sensitivity of hysteroscopy is 100% for myomas and 99% for polyps [22]. Also Dery et al. 2007 revealed the sensitivity of hysteroscopy for endometrial polyps is 94%, specificity 92% and sensitivity for submucus myomas 87% and specificity 95% with overall sensitivity for assessment of the uterine cavity 96% and specificity 90% [23]. Bonnamy et al. 2002 showed sensitivity and specificity of 2D U/S in diagnosis of fibroids is 65% and 94% respectively while that of hysteroscopy is 88% and 94% respectively [24].

A prospective study carried on 56 patients by showed sensitivity, specificity, positive predictive value, negative predictive value of 3D U/S in diagnosis of fibroids is 84.8%, 79%, 82.4%, and 82% respectively. TVS has a high sensitivity for detecting myomas in a uterus <10 weeks size. The use of high frequency probes improves the sensitivity for diagnosing small myomas although their precise location with respect to the uterine cavity often remains uncertain. Hysteroscopy is accurate but invasive in evaluating uterine mypmata [25].

In another study evaluated the accuracy of endometrial volume measurement in the diagnosis of endometrial carcinoma and endometrial hyperplasia in 89 women with premenopausal bleeding. All were scheduled for hysteroscopy, dilatation and curettage, endometrial sampling or hysterectomy and the ultrasound was performed within 24 hr before the procedure. Endometrial volume was measured and compared between the groups of women with different histopathology. 17.9% of patients had an endometrial polyp, 12.5% had hyperplasia and 7.6% had endometrial carcinoma. The mean endometrial volume was 6.87 cc, 5.43 and 15.5 cc respectively ($p<0.001$). Concluding that endometrial volume is a good diagnostic tools i predicting endometrial carcinoma and hyperplasia in women with premenopausal bleeding [19].

Another study was done in 2007 by Mansour and co-workers to assess endometrial volume as a predictor of endometrial malignancy in women with postmenopausal bleeding. Endometrial volume was measured by VOCAL in a group of women with postmenopausal bleeding. Another group of women without postmenopausal bleeding was used for control. 50% of cases in the study group had benign disease, 35% had atypia and 15% had cancer. Whereas endometrial thickness was 9.61+1-5.12 mm (range, 5-20 mm) and endometrial volume was 3+1-1.1 mL (range, 1.8-5.4 mL) in women with atypia or cancer, they were 4.87+7-3.43 mm (range, 2-8 mm) and 1.52+!- 0.82 (range, 0.6-2.2 mL), respectively, in women with benign disease. In the control group, endometrial volume was 1.15+/-0.14 mL (range 0.6- 1.3 mL). Volume was more sensitive than thickness for predicting malignancy, and a cutoff value of 1.35 mL was found to provide the best sensitivity [26].

Conclusion

Conclusion of this study stated that endometrial hyperplasia is the commonest observed endometrial abnormality in premenopausal patients with abnormal uterine bleeding. Even though histopathological examination of the endometrium is the gold standard for diagnosis or exclusion of endometrial pathology, 3D ultrasound is a reasonably accurate, helpful and non-invasive tool for assessing the endometrium. An endometrial volume of 13.1 mL or greater may predict malignancy in women with premenopausal bleeding.

References

1. Fallowfield L, Parmar M, Campbell S, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. The lancet oncology. 2011; 12:38-48.
2. Nandi A, Poretsky L. Diabetes and the female reproductive system. Endocrinol Metab Clin North Am. 2013; 42: 915-946.
3. Holalkere NS, Katur AM, Lee SI. Issues in imaging malignant neoplasms of the female reproductive system. Curr Probl Diagn Radiol. 2009; 38: 1-16.
4. Alcazar JL, Galvan R. Three-dimensional power Doppler ultrasound scanning for the prediction of endometrial cancer in women with postmenopausal bleeding and thickened endometrium. Am J Obstet Gynecol. 2009; 200: 44-46.
5. Goldstein. Modern evaluation of the endometrium. Obstet and gynecol. 2010; 116: 168-176.
6. Timmermans A, Opmeer BC, Khan KS, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. 2010; 67:160-7.
7. Gallos ID, Krishan P, Shehmar M. LNG-IUS versus oral progestogen treatment for endometrial hyperplasia: a long-term comparative cohort study. Hum Reprod. 2013; 28: 2966-2671.
8. Munro MG. Investigation of Women with Postmenopausal Uterine Bleeding: Clinical Practice Recommendations. Perm J. 2014; 18: 55-70.
9. Ahmed AH, Marzouk AA, Gaafar HM. The diagnostic role of office hysteroscopy and three-dimensional endometrial volume measurement in evaluation of women with peri menopausal bleeding. 2012; (coded from thesis at al kaser al aini).
10. Pyari JW, Sachan Rekha, Srivastava PK, et al. A comparative evaluation of hysteroscopy, transvaginal ultrasound and histopathological examination in cases of abnormal uterine bleeding.J Obstet and Gynecology of India. 2006; 56: 242-243.
11. Karampl EM, Bourne T, Hurler, Solbakkan H, et al. Transvaginal ultrasonography, sonohysterography and operative hysteroscopy for the evaluation of abnormal uterine bleeding. Acta Obstet Gynecol Scand. 2001; 80: 616-622.
12. Mencaglia L, Hamou JE. Manual of Gynecologic Hysteroscopy: diagnosis and surgery, Endopress Tuttlingen. 2000; 24.
13. Fleischer AC, Shappell HW. Color Doppler sonohysterography of endometrial polyps and submucosal fibroids. Journal of ultrasound in medicine. 2003; 22: 601-604.
14. Bradley L, Falcone T. Hysteroscopy: Office evaluation and management of the uterine cavity, 1sted, Philadelphia. Mosby-Elsevier. 2009; 110-112.
15. Clark T. Justin, Shagaf H, Janesh K, et al. Evaluation of Outpatient Hysteroscopy and Ultrasonography in the Diagnosis of Endometrial Disease. Obstetrics & Gynecology. 2002; 99: 1001-1007.
16. Damle RP, Dravid NV, Suryawanshi KH, et al. Clinicopathological Spectrum of Endometrial Changes in Perimenopausal and Post-menopausal Abnormal Uterine Bleeding: A 2 Years Study. Journal of Clinical and Diagnostic Research. 2013; 7: 2774-2776.
17. Khare A. Morphological spectrum of endometrium in patients presenting with dysfunctional uterine bleeding. Peoples's Journal of scientific research. 2012; 5: 13-16.
18. Kupesic S, Kurjak A. Color Doppler assessment of the uterine cause's of infertility. In: Kupesic S and Kurjak A (eds). Transvaginal color Doppler, second edition. The Parthenon Publishing group. 2000; 161.
19. Odeh M, Vainerovsky I, Grinin V, et al. Three-dimensional endometrial volume and 3-dimensional power Doppler analysis in predicting endometrial carcinoma and hyperplasia. Gynecol Oncol. 2007; 106: 348-53.
20. Stachowicz N, Czekierdowski A, Danilos J, et al. Three-dimensional sonography in the endometrial volume measurement in women with perimenopausal irregular uterine bleeding. Ginecol Pol. 2002; 73: 970-975.
21. Ebrashy A, Momtaz M, Shawky O, et al. Three Dimentional Transvaginal ultrasound in the assessment of uterine lesions: when do we really need it? Middle East Fertility Society Journal. 2009; 9: 83.
22. Pasqualotto EB, Margossian H, Price LL, et al. Accuracy of preoperative diagnostic tools and outcome of hysteroscopic management of menstrual dysfunction.Am J Assoc Gynecol Laparosc. 2009; 7: 201-209.
23. Dery MC, Van Themsche C, Provencher D. Characterization of EN-1078D, a poorly differentiated human endometrial carcinoma cell line: a novel tool to study endometrial invasion in vitro Reprod Biol Endocrinol. 2007; 25: 5-38.
24. Bonnamy L, Marret H, Perrotin F, et al. Sonohysterography. A prospective survey of results and complications in 81 patients. Eur J Obstet Gynecol Reprod Biol. 2002; 102: 42-47.
25. Pasrija S, Trivedi SS, Narula MK. Prospective study of saline infusion sonohysterography in evaluation of perimenopausal and postmenopausal women with abnormal uterine bleeding. The journal of obstetrics and gynecology research. 2004; 30: 27-33.
26. Mansour GM, El-lamie IK, Elkady MA, et al. Endometrial volume as predictor of malignancy in women with postmenopausal bleeding. International journal of Gynecology and Obstetrics. 2007; 99: 206-210.