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RESEARCH ARTICLE (CLINICAL INVESTIGATION)

Evaluation of endometrial volume and thickness in patients with abnormal uterine bleeding

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Abbreviations:: HB level, hemoglobin level; TVS, transvaginal ultrasound; VOCAL, virtual organ computer-aided analysis; SD, standard deviation; χ^2, Chi square; SPSS, Statistical Package for the Social Science; r, correlation coefficient (denoted symbolically r); IUD, intrauterine device; OCP, oral contraceptive pills; 3D U/S, 3D ultrasound

Abstract

Background and objectives

The main intention of investigating women with abnormal uterine bleeding is to exclude serious intrauterine pathology, particularly endometrial cancer. This is particularly done by obtaining tissue for histological analysis (golden standard method) utilizing blind in-patient dilatation of the cervix and curettage of the endometrium. In this study we aimed to assess the potential value of volume measurements compared with that of endometrial thickness in differentiating between benign and malignant endometrial pathology in women with abnormal uterine bleeding.

Patients and methods

Forty patients with peri or postmenopausal bleeding were included. For all of them clinical examination, HB level, Transvaginal 2D sonography, 3D endometrial volume measurement, histopathological examination were achieved.

Results

Endometrial carcinoma patients had the mean endometrial thickness/mm of 15.9±8.3 and the mean endometrial volume/cm^3 was 19.8±7.9 compared to11.6±7.2 and 4.4±1.9 in benign endometrial pathology respectively. The endometrial volume was significantly higher in patients with malignant pathology (p value =0.000)

Conclusions

The measurement of the endometrial volume was superior to that of the endometrial thickness as a diagnostic test for the detection of malignant endometrial pathology in symptomatic perimenopausal and post-menopausal bleeding.

Keywords: Endometrial volume; endometrial thickness;histopathology;perimenopausal; postmenopausal

Introduction

The main aim of investigating women with abnormal uterine bleeding is to exclude serious intrauterine pathology, particularly endometrial cancer. Endometrial assessment has traditionally been achieved by obtaining tissue for histological analysis utilizing blind in-patient dilatation of the cervix and curettage of the endometrium under general anesthesia. Diagnosis and treatment of endometrial pathology can nowadays benefit from well-established techniques, ranging from clinical examination to transvaginal ultrasound (TVS), 3D ultrasonography and histopathological examination. [1]

In this study, we aimed to assess the potential value of volume measurements compared with that of endometrial thickness in differentiating between benign and malignant endometrial pathology in women with abnormal uterine bleeding.

Patients and Methods

This prospective comparative study conducted on 40 patients complaining of perimenopausal and postmenopausal bleeding at the outpatient clinic of Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University, during the period from January to August 2013.

Inclusion criteria:

1. Post-menopausal bleeding, defined as lack of menstruation for 1year in women older than 45 years.
2. Perimenopausal bleeding defined as being 40- 50 years, having any pattern of bleeding e.g. menorrhagia, metrorrhagia, menometrorrhagia for more than 3 months.
3. Bleeding is not caused by a complication of contraception.

Excluson criteria:

1. Patients who were taking hormone replacement therapy or other hormonal preparations with a known effect on the endometrium.
2. Cases were fibroids located in the anterior wall as endometrial volume could not be measured accurately.
3. Current or suspected pregnancy
4. Vulval, vaginal or cervical cause of bleeding.
5. Having any pathological lesion that distorts the endometrium
   e.g. Septum and subseptate uterus.
6. An evidentgeneral cause of bleeding.

The patients were informed of the purpose and steps of the study and gave their informed consent. The institutional review board of Kasr Al-Ainy School of Medicine approved this study. Each patient was subjected to full history taking,full clinical examination, abdominal examination and pelvic examination.

HB level was done for each patient

Transvaginal 2D sonography was carried out using Toshiba femio 5 (Toshiba Medical Solutions Inc., Ultrasound Division, Japan) equipped with a 6.5 MHz transvaginal transducer. 3D endometrial volume measurement was obtained using a GE Voluson 730 Expert ultrasound system (GE Healthcare, Zipf, Austria) with transvaginal 5- to 9-MHz volume transducer, Maximally 2 days before curettage.

The examinations were stored digitally on an internal disk drive for subsequent measurements in virtual organ computer-aided analysis (VOCAL) program.

VOCAL is the combination of 3D ultrasound tissue presented as voxels and geometric information of surfaces in a 3D data set. It is defined by rotating an image plane around a fixed axis and defining the 2D contours of each plane. In the 730 system, there are four rotation angles to choose from, namely, 6°, 9°, 15°, and 30°, and because the entire data set

is rotated about 180°, these result in 30, 20, 12, and 6 planes, respectively, being available for measurements.

The 2D contours of the polygonal area in each plane can be defined automatically or manually. Measurements can be done in three different planes (A, B, and C). In this study, A plane, the longitudinal view, was used.

Within 1 week after the ultrasound, all patients underwent endometrial sampling by hysteroscopy or office biopsy or hysterectomy. The specimens were fixed in Formalin 10% solution and then sent to the pathology lab where adequate gross dissection and sampling of tissue at 3 mm thick was done. Tissue sections were fixed for 24 hours in 10% neutral buffered formalin then dehydrated, cleared, and embedded in paraffin wax according to routine processing procedures. The paraffin wax blocks were cut of 5µ then mounted on glass slides and stained with H&E for histological evaluation by two independent pathologists.

Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (±SD), median, frequencies (number of cases) and percentages when appropriate. Agreement between ultrasound findings and the endometrial sampling diagnosis was done using kappa statistic. For comparing categorical data, Chi square (χ^2) test was performed. The Fischer Exact test was used instead when the expected frequency is less than 5. All statistical calculations were done using computer programs (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22.

ANOVA (analysis of variance):

It evaluates the equality of several group means, was used to test the difference between mean values of some parameters among multiple groups.

Correlation analysis:

It assesses the strength of association between 2 variables. The correlation coefficient denoted symbolically r, defines the strength and direction of the linear relationship between 2 variables.

P value:

It is the probability of obtaining a result at least as extreme as a given data point, under the null hypothesis. It is significant if below the level of significance (common levels of significance are 5%, 1%, and 0.1%).

Results

The study included 40 patients complaining of perimenopausal and postmenopausal bleeding. Their mean age was 50.15 ± 7.634 years; there were 36 (90%) multiparous patients, 3 nulliparous patients (7.5%) and one (2.5%) patient was a virgin. Regarding methods used for contraception, There were 10(25%) patients on IUD, 4(10%) on OCP, 2(5%) on tubal ligation and 24(60%) not on contraceptives methods.

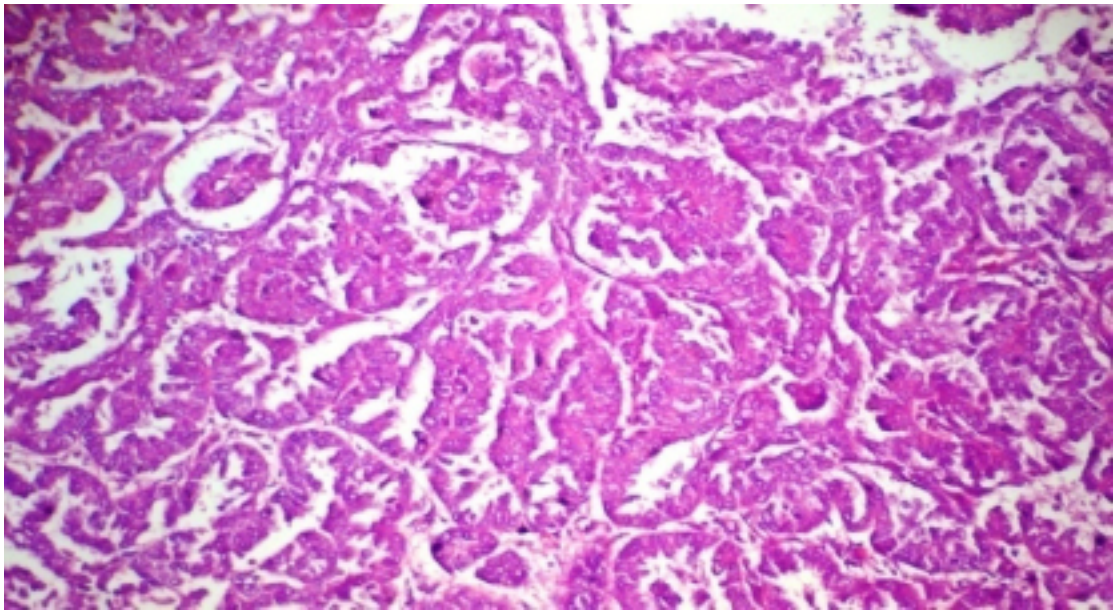
23(57%) patients had perimenopausal bleeding and 17(42%) patients had postmenopausal, 4(10%) of them had mild vaginal bleeding, 28(70%) patients had moderate vaginal bleeding and 8(20%) patients had severe vaginal bleeding.

The mean hemoglobin was 11.98±2.12. When we compared the severity of bleeding and hemoglobin levels we found that there were significant relations with each other (p value=0.001). Hemoglobin levels decrease with increasing severity of bleeding as the mean hemoglobin in mild bleeding was 12.7±2.2 while in moderate bleeding it was 12.5±1.61and in severe bleeding it was9.68±2.3.

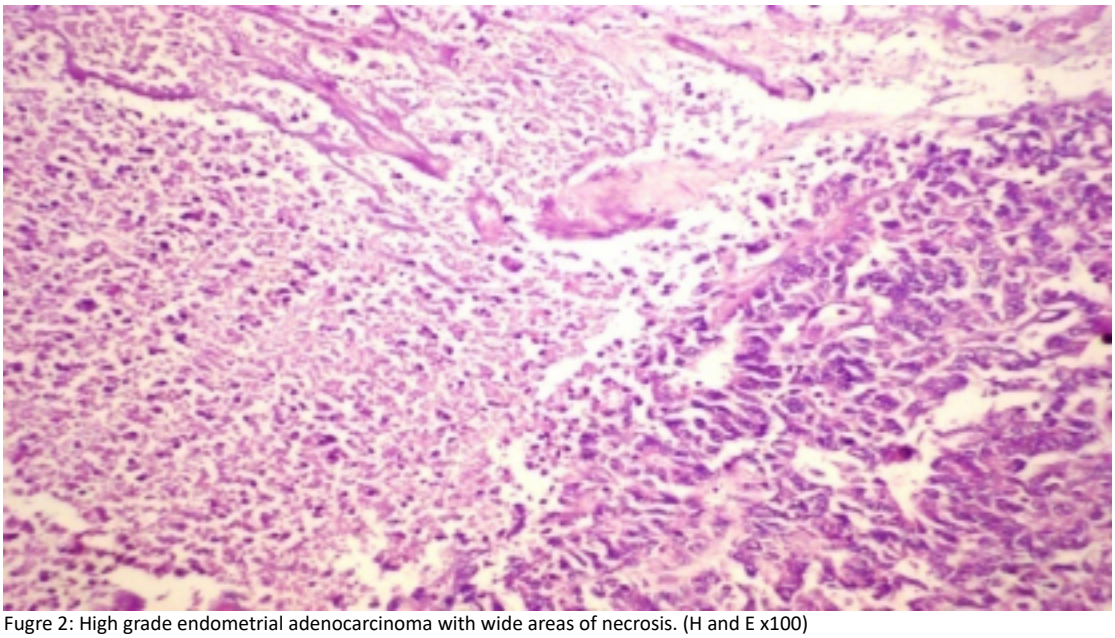
The most common bleeding pattern was postmenopausal bleeding 17(42.5%) followed by menometrorrhagia 13(32.5%), then menorrhagia 6(15%), and finally metrorrhagia 4(10%). 16(40%) patients came by first attack of bleeding and 24(60%) came to our clinic by recurrent attacks.

Seventeen (42.5%) of the pathological samples were taking by FC, 22(55%) by hysterectomy and 1(2.5%) by hysteroscopy.

By histopathologic examination of the endometrium, we found 2(5%) had cystic atrophy, 11(27%) had an endometrial polyp, 6(15%) had disordered proliferative, 15(37%) had simple endometrial hyperplasia and 6(15%) had endometrial adenocarcinoma (fig1, 2). We found that there is an effect of age variation on the endometrial lesion with highly significant correlation (p= 0.007) (Table 1).



Fugre 1: endometrial adenocarcinoma, serous type showing complex, short, and dense papillae. (H and E x100)



Fugre 2: High grade endometrial adenocarcinoma with wide areas of necrosis. (H and E x100)

Table 1: Comparison between age values of studied groups in relation to histopathology.

Endometrial pathology	Cystic atrophy	Endometrial polyp	Disordered proliferative	Simple hyperplasia	adenocarcinoma	P-value
Ages	46±8.4	51.4±9.1	43.8±4.4	48.9±4.4	58.5±7.0	.007(s)

S = Significant.

Moreover, histopathologic examination of myometrium revealed that 5(12.5%) patients had adenomyosis, 7(17.5%) patients had leiomyoma, 1(2.5%) patient presented with a leiomyomatus polyp, 2(5%) had both adenomyosis&leiomyoma and 25(65%) of patients were normal. Also, we found 12(30%) patients had pathological ovarian lesionswhile 28 (60%) showed no ovarian pathology.

All patients were subjected to 2D/3D transvaginalultrasonographic evaluation of the endometrial thickness and volume; the results were compared to the histopathological examination of the endometrium (Table 2, 3).

Table 2: Endometrial volume and endometrial thickness among the study group:

Endometrial pathology	CYSTIC ATROPHY	Endometrial polyp	Simple endometrial hyperplasia	Adenocarcinoma	DISORDERED PROLIFERATIVE	P- value
Mean endometrial volume/cm³	3.1±2.9	9.8±11.5	3.5±1.8	19.8±7.9	4.8±3.8	**0.001(HS)**
Mean endometrial thickness/mm	4.5±3.5	12.9±9.7	10.7±4.9	15.9±8.3	10.7±4.4	0.313(NS)

HS= (Highly significant) . NS = (NOT significant)

Table 3: Endometrial thickness and volume in patients with normal endometrium (atrophic and proliferative), benign pathology (hyperplasia and polyps) and endometrial cancer:

	Normal	Abnormal	significance	Benign pathology	Malignant pathology	Significance
Volume(cm³)	3.15±1.5	5.01±2.3	0.04 (S)	4.4±1.9	19.8±7.9	.000(HS)
Thickness(mm)	9.1±4.8	12.4±7.5	0.253(NS)	11.6±7.2	15.9±8.3	0.25(NS)

S= Significant HS= (Highly significant) . NS = (NOT significant)

In patients with endometrial carcinoma, the mean endometrial thickness/mm 15.9±8.3 and the mean endometrial volume/cm³ was 19.8±7.9compared to11.6±7.2 and 4.4±1.9 in benign endometrial pathology respectively. The endometrial volume was significantly higher in patients with malignant pathology (p value = 0.000). However, the hyperplasia and polyp were similar to each other. The endometrial thickness was not

significantly different in patients with abnormal uterine bleeding.

Myometrial and ovarian findings by sonographic evaluation were exactly the same as by microscopic examination.

Discussion

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. [2]

Transvaginaltwo-dimensional ultrasonography has been used extensively in cases of abnormal uterine bleeding to evaluate uterine pathology to excludemyomata, polyps and focal lesions and to check the adnexa. Three-dimensional ultrasound offers new viewing window by allowing for arbitrary plane evaluation through a volume data set acquired from the pelvis. [3]

We evaluated the endometrial thickness of our patients by 2D ultrasound and endometrial volume by 3D ultrasound in comparison by histopathology and if those diagnostic methods could predict malignant conditions and benign conditions of the endometrium. The entire selected patients had general examination, local pelvic examination, transvaginal 2D pelvic ultrasound assesment, 3D endometrial volume measurement, and then dilatation and curettage (D&C) or hysteroscopic guided biopsy or hysterectomy for focal endometrial lesions and pathological examination of the specimens obtained.

In our study, the mean age was 50.15 ± 7.634 years. The age of our patients was comparable to other studies. In the study by Stachowicz et al. (2002) [4] the mean age was 53 ± 5 years, in the study by Justin et al. (2002) [5] the mean age was 50 years and in the study by Ahmad et al, (2012) [6] the mean age was 49.4 ± 1.22years. Moreover, the mean parity in our patients was 1.13 ± 0.404 which was comparable to what reported by Ahmad et al, (2012) [6] where the mean parity was 3.12 ± 1.6.

The most common bleeding pattern was postmenopausal bleeding presented in 17(42.5%) patients followed by menometrorrhagiain 13(32.5%) patients, 6(15%) patients suffered from menorrhagia finally metrorrhagiain 4(10%) patients. Compared to the study done by Abo Haemila et al, (2005) [7] most common bleeding pattern was menorrhagia (40%) followed by menometrorrhagia (22.8%) then metrorrhagia (34.2%). A similar study was carried out by Pyrai et al, (2006) [2] on 50 patients with abnormal uterine bleeding revealed the most common complaints were: menorrhagia 20 cases (40%), metrorrhagia 9 cases (18%), menometrorrhagia 7 cases (14%). This difference may be attributed to different selection criteria of included patients.

In our study, 3D U/S detected adenomyosis in 9(22%) cases, fibroid in 8 cases (20%), hyperplasia in 15 cases (37%), polyps in 10 cases (25%). These fibroid lesions detected by 3D U/S are located as: submucous in 3 cases (7.5%), intramural in 5 cases (12.5%). Ebrashy et al, (2004) [8] 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 submucousmyomas, 12 cases had

thickened endometrium while by 3D ultrasound: 9 cases are normal. In the study carried out by Pyrai et al, (2006) [2] on 50 patients with abnormal uterine bleeding, by TVS it detected 13 myomas (26%), 4 polyps (8%), 3 adenomyosis (6%), 10 hyperplasias (20%), 2 endometrial carcinomas (4%), 2 atrophic endometrium (4%).

The results of our study showed that by using three-dimensional ultrasound equipment it is possible to measure endometrial volume in the majority of abnormal uterine bleeding.

Our primary objective was to investigate whether the measurement of endometrial volume could be used as ultrasound diagnosis of endometrial carcinoma. Although endometrial thickness is useful in the diagnosis of endometrial atrophy, it has not been possible to differentiate between endometrial cancer and benign uterine pathology by measurements of thickness alone. Therefore, in patients with endometrial thickness of 5mm or more, histological diagnosis is required, to exclude significant pathology and initiate appropriate therapeutic measures. Our results confirm that there is a considerable overlap in endometrial thickness between patients with benign and those with malignant pathology.

When volume measurements were performed, the overlap between different groups of patients was much smaller which significantly improves the diagnosis of cancer. All but one patients with cancer had a large endometrial volume of more than 19ml. with a cut off level of 19 ml, none of the cancers would have been missed. In the study done by Odeh et al, (2007) [9]in 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, (2002) [4], 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.

Endometrial thickness measurements gave less accurate predictions.

Volume measurements also showed significant differences in size between endometrial hyperplasia and polyps which were not detected by the measurement of endometrial thickness. These may be explained by the fact that polyps are usually localized thickenings of the endometrial that do not affect the whole of the uterine cavity. Therefore, it is logical that their volume is much smaller, while the maximum thickness is similar to that of hyperplasia. This was confirmed by the study of Gruboeck, et al (1996) [10].

In patients with a very thin atrophic endometrium, volume measurements contributed little to the diagnostic accuracy. When the endometrium looked atrophic with a thickness of <5mm, measurement of the endometrial volume was more difficult to assess. However, all patients with an endometrium volume <5ml had endometrium atrophy on histological examination.

In patients with endometrial cancer, there was a clear tendency for endometrial volume to increase with grade and stage of the tumor. The depth of myometrium invasion showed a positive correlation with both endometrial thickness and endometrial volume.

However, the differences were not large and it is unlikely that the measurement of tumor size will be more useful for the diagnosis of invasion than B-mode imaging. This was confirmed by the study of Gruboeck, et al (1996) [10].

In our study, histopathological examination we found 5cases with adenomyosis (12.5%), 7 fibroids (17.5%), 15 hyperplasia (37%), 11 polyps (27%), 2 cystic changes (5%), 6 adenocarcinoma (15%) and 6 disordered proliferative (15%).

Pasqualotto et al., (2000) [11] compared nearly similar parameters on 375 patients complaining of abnormal uterine bleeding and the main pathological findings are endometrial polyps 172 (45.9%) and submucousmyomas 105 (28%) Whereas in the study carried out by Ryu et al. (2004) [12] on 105 patients, histopathology revealed the presence of 37 endometrial polyps (35%), 26 submucousmyomas (25%), 12 endometrial hyperplasia (11%), 3 endometrial carcinoma (3%), 2 adenomyomas (2%), 24 cases (23%) showed no organic lesion.

Histopathological examination in the study of Pyrai et al.(2006) [2] showed normal endometrium in 9 cases (18%), myomas in 16 cases (32%), endometrial polyps in 6 cases (12%), endometrial hyperplasia in 11 cases (22%) and endometrial carcinoma in 2 cases (4%). In our preliminary data are confirmed, the volume of the tumor may also be used in the future for the preoperative assessment of patients with endometrial cancer.

Conclusions & Recommendations

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.The measurement of the endometrial volume was superior to that of endometrial thickness as a diagnostic test for the detection of endometrial cancer in symptomatic perimenopausal and post-menopausal bleeding. Further studies are needed to verify these findings.

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Declaration

Authors, states that this research work is original and has not been published in whole or in part elsewhere.

Authorship (contribution or attribution)

All the authorshj have contributed equally.

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