The Relationship between Transvaginal Ultrasound Endometrial Thickness and Body Mass Index and Endometrial Pathology in Women with Postmenopausal Bleeding

AHMED S.A. ASHOUR, M.D.*; TAREK FAWZY, M.D.* and MOHAMMED FAISAL, M.D.**
The Departments of Obstetrics & Gynecology* and Pathology**, Faculty of Medicine, Cairo University

Abstract

Objective: To explore the relationship between obesity (expressed by increased BMI) and ultrasonographic endometrial thickness measurement and their correlation to endometrial pathology in women with postmenopausal bleeding.

Design: Prospective cohort study.

Setting: Kasr El-Aini Hospital.

Patients and Methods: 100 cases, recruited from the Outpatient Gynecology Clinic, Kasr Al-Ainy Hospital, were included in the study. All cases presented with postmenopausal bleeding and all were subjected to measurement of Body Mass Index (BMI) and 2-dimensional transvaginal ultrasonographic evaluation of the endometrium, and the results were correlated to the histopathological picture of the endometrium.

Results: The age ranged between 46-75 years, with the mean 52.7 ± 5.7 years, parity ranged from nullipara to 12, with the mean 4.91 ± 2.2 and BMI ranged between 25-56 with the mean 37.7 ± 6.9 and endometrium thickness ranged between 5mm-50mm. With the mean 13 ± 6.8. The most common endometrial histopathology was endometrial hyperplasia (70 cases, 70%) then disordered proliferative endometrium (22 cases, 22%) then atrophic endometrium (4 cases, 4%) and endometrial carcinoma (4 cases, 4%). It was found that patients with endometrial carcinoma had higher BMI and endometrial thickness than patients with benign endometrial pathology (atrophic disordered proliferative, hyperplasia without atypia).

Conclusion: Screening for endometrial cancer is not recommended for the general population, although in high-risk populations like obese postmenopausal women, it is very important. Transvaginal ultrasonography is an excellent first step diagnostic method of excluding the endometrial abnormalities in women with postmenopausal bleeding.

Key Words: Transvaginal ultrasound endometrial thickness – Body mass index (BMI) – Postmenopausal bleeding (PMB) – Endometrial pathology.

Introduction

MENOPAUSE is derived from the Greek words; men (month) and pauses (cessation) [1].

Cessation of menstruation for a complete one year period is necessary to be considered a menopausal woman, and this is after an average age of 46 years [2].

Postmenopausal Bleeding (PMB) is defined as recurrent attacks of bleeding occurring in women after menopause one year at least after stoppage of cycles [3].

Premalignant lesions and malignant lesions most commonly complex hyperplasia with atypia and carcinoma of the endometrium are present in 1/3 of patients evaluated for postmenopausal bleeding, and so investigations for cases of postmenopausal bleeding are mandatory [4].

Endometrial cancer risk at a 50 years old woman with PMB is approximately 1% and increases to 25% at the age of 80. The presentation of more than 90% of women diagnosed with endometrial carcinoma is irregular perimenopausal bleeding or PMB, but only 20% of them had significant pathology [2].

A low risk of having endometrial malignancy is found in women with an endometrial thickness below 5mm but this risk increases if they develop an endometrial thickness more than 5mm by transvaginal ultrasonography and so by doing ultrason we can distinguish low-risk patients from high-risk ones [8].

Endometrial biopsy is the "gold standard" for diagnosing endometrial tissue abnormalities of
patients with PMB with a sensitivity ranged from 85% to 95% [6].

High body mass index and abdominal obesity (waist circumference >88cm) are the best measures of obesity predicting the risk of endometrial cancer [7].

Screening of obese postmenopausal women is recommended because the risk of endometrial pathological lesions like hyperplasia and endometrial polyp is high [8].

This study is designed to explore the relationship in postmenopausal women between body mass index and ultrasonographic endometrial thickness measurement and their interrelationship to endometrial pathology in cases of postmenopausal bleeding.

**Patients and Methods**

The present study is a prospective cohort study which was conducted at Cairo University, Obstetrics and Gynecology Hospital in the period which started from March 2014 to February 2015. Recruitment of 100 women with postmenopausal bleeding was done. Inclusion criteria involved menopausal women (defined as minimum of 1 year of amenorrhea after the age of 45 years if only the amenorrhea is not related to pregnancy, medication or disease), bleeding after menopause ≥12 months, endometrial thickness by Transvaginal Ultrasound (TVUS) ≥5mm and Body Mass Index (BMI) of the menopausal women is ≥25.

Women with chronic diseases as diabetes mellitus, hypertension or hematological disorders, those received hormone replacement therapy, Tamoxifen or anticoagulant therapy and women with adnexal massed detected by TVUS or apparent causes of bleeding from cervix or vagina e.g. ulcer were excluded.

After taking an informed written consent, all patients were subjected to full history taking with a particular care for age, age at the time of menopause, parity, present history of bleeding (including onset, course, duration, and criteria of bleeding pattern), history of previous fractional curettage and family history of a similar condition. General examination and local examination were done with inspection of external genitalia. Bimanual examination to detect uterine size, mobility, tenderness and adnexal masses and speculum examination for cervical or vaginal lesions.

Laboratory investigations done included complete blood count, coagulation profile, fasting and postprandial blood sugar, liver and kidney functions tests.

Transvaginal ultrasound was done using Medison X4 (Samsung Medison, Seoul, South Korea) machine equipped with 5-7MHz transvaginal transducer.

The bladder was completely emptied, and the procedure was explained to the patient. The patient then placed in a dorsal recumbent position and draped, then the transducer was put in a rubber glove, covered with gel and inserted into the vagina.

*The following was assessed:* Diameters of the uterus, adnexal pathology, any focal lesions as myoma, adenomyosis, endometrial polyp.

*Endometrial thickness was measured as follow:* Endometrium was scanned from cornu to cornu then endometrial thickness was measured at its thickest point between the two basal layers on the anterior and posterior uterine walls in the sagittal plane of the uterus. Calipers were placed perpendicular to the outer edge of the endometrium. We deducted the fluid diameter if included in the double endometrial stripe.

Conventional dilatation and curettage was done with the first sample taken from endocervical canal before dilatation, then cervical dilatation up to 7-8 Hegar.

A sharp-ended curette was introduced and curettage starting first with fundus then posterior wall then anterior wall then right then left lateral walls. Formalin 10% is used to preserve the specimen till examined histopathologically.

Data were statistically represented in the form of the mean ± Standard Deviation (± SD), median and range, or frequencies (number of cases) and percentages. For independent samples, Mann-Whitney U-test was utilized to compare the numerical variables between the study groups. Chi-square ($\chi^2$) test was utilized to compare categorical data. With less than 5 expected frequencies, the exact test was used. Pearson moment correlation equation correlates between various variables. $p$-values are considered statistically significant when they less than 0.05. All statistical calculations were done with computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

**Results**

There was no significant difference between women with benign lesions and those with non-
Ahmed S.A. Ashour, et al. 2019

benign one regarding age at menopause, duration of menopause or history of contraception using hormonal methods (Table 1).

A significant difference was found between the two study groups concerning gravidity and parity and a highly significant difference in regards to age and BMI (Table 1).

The ultrasonographic findings named adenomyosis, fibroid, endometrial thickness, margin and echogenicity among the study women are shown in Table (2) and Fig. (1) whereas the histopathological examination is demonstrated in (Table 3).

There was a highly significant difference between the two groups regarding the presence of atypia but no difference regarding polyp presence (Table 4).

Table (1): Baseline characteristics of the study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Benign</th>
<th>Non-benign</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.30±5.425</td>
<td>62.25±4.272</td>
<td>0.004 (HS)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>5.81±2.381</td>
<td>8.50±2.646</td>
<td>0.047 (S)</td>
</tr>
<tr>
<td>Parity</td>
<td>4.80±2.160</td>
<td>7.50±2.646</td>
<td>0.036 (S)</td>
</tr>
<tr>
<td>Age at menopause (years)</td>
<td>49.40±3.178</td>
<td>52.00±2.160</td>
<td>0.070 (NS)</td>
</tr>
<tr>
<td>Duration of PMB (months)</td>
<td>3.21±2.33</td>
<td>4.17±2.63</td>
<td>0.27 (NS)</td>
</tr>
<tr>
<td>Hormonal contraception*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Users</td>
<td>15.6%</td>
<td>50%</td>
<td>0.133 (NS)</td>
</tr>
<tr>
<td>Non users</td>
<td>84.4%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>37.12±6.242</td>
<td>53.75±3.862</td>
<td>0.001 (HS)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD
* Data are presented as number and percentage.

Table (2): Ultrasonographic findings of uterus of different studied groups in relation to endometrial histopathology.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Benign</th>
<th>Non-benign</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adenomyosis</td>
<td>36.5%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>• Fibroid</td>
<td>9.3%</td>
<td>50%</td>
<td>0.027 (S)</td>
</tr>
<tr>
<td>• Normal</td>
<td>54.2%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>• Endometrial thickness</td>
<td>12.09±4.967</td>
<td>34.75±10.966</td>
<td>0.001 (HS)</td>
</tr>
<tr>
<td>(mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Endometrial margin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>93.7%</td>
<td>25%</td>
<td>0.002 (HS)</td>
</tr>
<tr>
<td>Irregular</td>
<td>6.3%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>• Endometrial echogenicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogeneous</td>
<td>51%</td>
<td>0.0%</td>
<td>0.11 8 (NS)</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>49%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number and percentage.

Table (3): Histopathology of studied groups.

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia</td>
<td>70</td>
<td>70%</td>
</tr>
<tr>
<td>Proliferative</td>
<td>22</td>
<td>22%</td>
</tr>
<tr>
<td>Atrophic</td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4</td>
<td>4%</td>
</tr>
</tbody>
</table>

Data are presented as number and percentage.

Table (4): Comparison between endometrial atypia and polyp in the histopathology of different studied groups in relation to endometrial malignancy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Benign</th>
<th>Non-benign</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial atypia:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.1%</td>
<td>100%</td>
<td>0.0001 (HS)</td>
</tr>
<tr>
<td>No</td>
<td>96.9%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Endometrial polyp:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17.7%</td>
<td>0.0%</td>
<td>0.469 (NS)</td>
</tr>
<tr>
<td>No</td>
<td>82.3%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number and percentage.

Fig. (1): ROC curve of endometrial thickness and malignancy.

Area under the curve: 0.991.

**Discussion**

In women with Postmenopausal Bleeding (PMB), malignancy should be considered; however, atrophic vaginitis or endometritis is the most common cause of postmenopausal bleeding. All patients with postmenopausal bleeding should be evaluated carefully to exclude endometrial malignancy which is present in only 10% of cases [9].

Transvaginal Ultrasound (TVUS) is generally used as an accepted first-line investigation to screen patients with higher endometrial cancer risk. It is a relatively non-invasive procedure with good negative predictive value if properly performed [10]. Evaluation of women with postmenopausal bleeding also includes biopsying the endometrium better hysteroscopically guided or may be done as a blind procedure [11].
In our study, women in the non-benign group had higher age, BMI, compared to those in the benign group with statistically significant difference between both groups, while the benign group had more parity and gravidity than the non-benign group.

In the present study, BMI had a strong correlation with endometrial thickness among both groups as the correlation coefficient between both variables was 0.621.

The observation of this study agrees with the report by Andolf et al., in 1993 who demonstrated that endometrial thickness was correlated with BMI. However, their analysis had excluded the age of those patients and the time period since menopause [12].

Also, there is significant agreement persists as regard the relationship between BMI and sono-graphic endometrial thickness in postmenopausal Japanese women [13].

This disagrees with the report by Van den Bosch et al., in 1996 which indicated that no association between endometrial thickness and weight or BMI. After adjusting for age, they concluded that age is a significant confounder on regression analysis [14].

This study agrees with a meta-analysis done by Zhang et al., who showed that endometrial carcinoma risk is 32% more in overweight (BMI: 25-30) women and 2.5 times greater in obese (BMI: 30+ women), both compared with healthy-weight (BMI less than 25) women [15].

This study also agrees with Friedenreich et al., who studied 223000 women with postmenopausal bleeding and they proved a strong association between the risk of endometrial cancer, obesity, and body fat distribution [16].

They found that the RR for obese women (BMI 30 to <40) when compared to women of normal weight was 1.78 (95% CI: 1.41-2.26), and in morbidly obese patients (BMI ≥40) RR was 3.02 (95% CI: 1.66-5.52).

And these results were in agreement with that of Lukanova et al., who showed that obese women (BMI ≥30) had a 36% more risk of malignancy than women with a normal BMI (18.5-25). Individual cancer site most strongly related to obesity was the endometrium (95% confidence interval: 1.86-7.43) [17].

In a study of Fourberg and Thune, they studied 1 30 cases of endometrial cancer with an RR of 2.57 (95%CI: 1.61-4.10) for obese women (BMI ≥30) when they compared those cases with women of normal weight (BMI <25). They concluded that low energy consumption (<4266kJ/day) is less risky for cancer in women younger than 50 years than consuming high-energy sources (5044-6401kJ/day) (RR: 3.40, 95% CI: 1.52-7.60) and that protection can be offered by recreational activities. It was found that in non-sedentary obese women, the RR falls to 0.18 (95%CI: 0.05-0.62), suggesting that the main risk factors for cancer endometrium are inactivity and high-energy consumption regardless of BMI [18].

This study also agrees with the International Agency for Research in Cancer which classified the evidence concerning the association between obesity and endometrial cancer as ‘strong or convincing.’ and the RR (relative risk) of obese women (BMI 30) compared to non-obese women was established as around two to threefold. However, they omit the premalignant cases from their study [19].

On the contrary to this study; Folsom et al., have found no association between abdominal body fat and the risk of endometrial carcinoma when adjusted for Body Mass Index (BMI) [20]. Also, Austin et al., in 1991 stated that no association between abdominal body fat and the risk of endometrial carcinoma when adjusted for Body Mass Index (BMI) [21].

On the other side, Zaki et al., have shown in their study that abdominal obesity (waist circumference >88cm), compared with general obesity (high BMI), was the best measure of obesity to be utilized in predicting the risk of endometrial cancer in Egyptian females with PMB [7].

With regard to the ultrasonographic results in the present study, the inclusion criteria of the examined women included that Endometrial Thickness (ET) ≥5mm; as most studies agree with that value to exclude endometrial pathology below it. The prevalence of endometrial thickness was 4%. 92%, and 4% for ET 5-6, ET 7-23, ET ≥24 respectively, and the majority of the studied cases were in the range from 7-23mm, with an average thickness of 13mm.

Compared to the benign group, the non-benign group had an endometrial thickness at or above 24mm. This was verified statistically by finding a significant difference between both groups.
In the present study, the cut-off value of endometrial thickness malignant pathology was measured to be equal to or above 24mm. This cut-off value carried sensitivity of 100% and specificity of 69%.

This study shows similar results as found by Karlsson et al., whose study revealed that the mean thickness with endometrial carcinoma was 21.1mm [22].

This study agrees with Gupta et al., which concluded that using ultrasound to measure endometrial thickness if more than or equal to 5mm as an indicator of endometrial pathology compared to uterine curettage has a positive predictive value of 54%, the sensitivity was found to be 83% and the specificity was found to be 77% [23].

Also Granberg et al., have found in their study by measuring the endometrial thickness in 205 women complaining of postmenopausal bleeding that no false negative observation was obtained if a more than 5mm endometrial thickness was used with a sensitivity of 100% for identifying endometrial abnormalities and histological examination might not be done in patients having endometrial thickness 5mm or less [24].

This study disagrees with a study performed by Moodly et al., as they chose endometrial thickness to be at least 4mm in postmenopausal women as a limit value to exclude malignancy unless there are other risk factors [25].

Also in a study performed by Chandavarkar et al., in 2013, no need for a more diagnostic procedure to be done in a woman with postmenopausal bleeding having an Endometrial Echo Complex (EEC) ≤4mm. However, an EEC <4mm does not completely rule out endometrial cancer and cannot prevent histological evaluation [26].

On the contrary; Phillip et al., suggested that the correlation between imaging and pathology was not reliable. Half of their cases with endometrial cancer had an endometrial thickness between 3mm and 4mm. A benign pathology is found in nearly 70% of patients having an endometrial thickness more than 5mm [27].

This study displayed that there was a statistically significant difference between benign and non-benign groups as regard ultrasound endometrial margin and endometrial echogenicity as 75% of non-benign group and 6.3% of benign group had irregular margin while 100% non-benign group and 49% of benign group had heterogeneous endometrium in TVUS.

This study agrees with Epstein an Valentin in 2006 and Opolskiene et al., in 2010 in that irregular surface of the endometrium has been found to be a sign of endometrial malignancy [28,29].

With regard to the endometrial pathology in the present study, 50 cases had endometrial hyperplasia without atypia (50%), 17 cases had hyperplastic endometrial polyp (17%), 22 cases had disordered proliferative endometrium (22%), 4 cases had atrophic endometrium (4%); all these were considered as benign group, while 4 cases had endometrial carcinoma (4%) and 3 cases had endometrial hyperplasia with atypia (3%); these were considered as non-benign group. Non-benign endometrial lesions were found in 7 cases (7%), and benign lesions were found to in 93 cases (93%).

With regard to the presence of endometrial polyp in the endometrial pathology; this study found that there is NO statistically significant difference between benign and non-benign groups.

This disagree with a systematic review and meta-analysis done by Lee et al., that revealed that endometrial polyps have higher endometrial malignancy risk in postmenopausal patients with significant vaginal bleeding [30].

Regarding the effect of the use of hormonal contraception on the endometrial pathology: This study found that there is NO statistically significant difference between benign and nonbenign groups as regard the use of hormonal contraception.

This agrees with Horwitz et al., in 1979 whose case-control study did not find any link between COC(combined oral contraceptive pills) use and endometrial carcinoma (Odds Ratio [OR]; 0.95) [31].

In conclusion, obesity bears a high social price and represents elevated costs for the health care system and any overweight postmenopausal women with increased endometrial thickness whether symptomatic or not must be referred to a gynecologist for an evaluation of endometrial lesions.

It is recommended that all possible ways to decrease the weight of overweight and obese women through exercising and adjustments of dietary habits must be encouraged.

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References


