CONTROVERSIES ON TRANSVAGINAL ULTRASOUND SCREENING FOR ENDOMETRIAL CANCER IN ASYMPTOMATIC POSTMENOPAUSAL WOMEN

P. Tsikouras¹, M. Bacha¹, S. Zervoudis²,³, Zacharoula Koukouli¹, G. Iatrakis²,³, G. Galazios¹, G. Maroulis¹, Ioana Virtej⁴, P. Vartej⁵, M. Onofriescu⁶

Democritus University of Thrace, Greece
1. Department of Obstetrics and Gynecology
2. Rea Hospital Athens Greece
3. TEI Technol University of Athens Greece
“Carol Davila” University of Medicine and Pharmacy Bucharest, Romania
4. Department of Endocrinology and Endocrinology Center, Trikala, Greece
5. Department of Obstetrics and Gynecology “Grigore T. Popa” University of Medicine and Pharmacy Iasi, Romania
Faculty of Medicine
6. Department of Mother and Child Medicine
*Corresponding author. E-mail: ivarge@ yahoo.com

CONTROVERSIES ON TRANSVAGINAL ULTRASOUND SCREENING FOR ENDOMETRIAL CANCER IN ASYMPTOMATIC POSTMENOPAUSAL WOMEN (Abstract): Endometrial cancer (EC) in postmenopausal women is usually associated with abnormal vaginal bleeding. However, asymptomatic cases of EC have been reported. The incidence of EC has been estimated to 1.3-3.05 per 1,000 screened postmenopausal asymptomatic women, the most significant ultrasonographic feature being the thickened endometrium. We reviewed the literature on the accuracy of endometrial thickness measurement by transvaginal sonography (TVS) in predicting EC in asymptomatic postmenopausal women. The use of endometrial thickness as a sole screening test was found not to be of high predictive value and it should be combined with the evaluation of EC risk factors and followed by hysteroscopy and biopsy in suspicious cases. The lack of a universal cut-off value for endometrial thickness that could be correlated to EC is pointed out. Keywords: ENDOMETRIAL CANCER, ENDOMETRIAL THICKNESS, TRANSVAGINAL ULTRASOUND.

Endometrial carcinoma (EC) is the most common malignancy of the female genital tract in developed countries with over 60,000 new cases and over 10,000 deaths from the disease in each year (1). Endometrial cancer affects mainly postmenopausal women. The mean age of women diagnosed with endometrial cancer is 60. It is uncommon in women under the age of 45 (2). Adenocarcinoma of the endometrium is the most common histologic type of uterine cancer.

Postmenopausal vaginal bleeding is the presenting sign in more than 90% of postmenopausal women with EC and is associated with an up to 10% risk of EC (3), the most common cause of postmenopausal bleeding being endometrial atrophy (4).
Risk factors for EC are nulliparity, early menarche age, obesity, diabetes, hypermenorrhea, tamoxifen therapy and hirsutism-polycystic ovary syndrome. Measurement of endometrial thickness by transvaginal sonography (TVS) is a valuable test for estimating the risk of EC in women with postmenopausal vaginal bleeding (5). TVS is a non-invasive and painless procedure, has no complications, requires no special preparation, may be more sensitive in detecting carcinoma than blind biopsy, has a high cancer detection rate, is widely available and the cost is like biopsy (6, 7). Color and spectral Doppler ultrasound examination of uterine and the subendometrial arteries can aid in the differential diagnosis of benign and malignant endometrium (8, 9). Seven to seventeen percent of postmenopausal women diagnosed with EC have no symptoms at the time of diagnosis. The incidence of asymptomatic EC has been reported to range from 1.3 to 1.7 per 1000 screened postmenopausal women (10, 11). The value of endometrial thickness measurement in healthy, asymptomatic postmenopausal women has not been documented yet. The general need for EC screening in these women is questionable and there is lack of consensus regarding the clinical significance of endometrial thickness measured by TVS (12-14).

The aim of this review is to determine the utility of endometrial thickness cut-off value for endometrial sampling in asymptomatic postmenopausal women who do not use Hormone Replacement Therapy (HRT).

**TRANSVAGINAL SONOGRAPHIC EVALUATION OF THE ENDOMETRIUM IN ASYMPTOMATIC POSTMENOPAUSAL WOMEN**

Endometrial thickness is measured as double-layer thickness at its thickest part in the longitudinal plane; homogeneity and echogenicity should also be mentioned. Values of 2-3 mm are considered normal atrophy, whereas a thickened endometrium may represent malignancy, hyperplasia or polyps. Also, to be considered 'normal', the endometrial lining must be regular and clearly visible over the totality of the uterine cavity (15). In symptomatic postmenopausal women, a cut-off value for endometrial thickness of 4-5 mm has been established. Although advanced EC has been identified in cases without noticeable endometrial thickness on TVS, the probability of endometrial cancer below this value is 1% (16, 17).

Little is known about endometrial thickness in healthy asymptomatic postmenopausal women. Universal screening for endometrial malignancy is not considered necessary. The mean endometrial thickness in postmenopausal women without vaginal bleeding ranges between 3-5 mm (18-20). The risk of EC in women with endometrial thickness less than 5 mm is approximately 1% compared to nearly 20% if the measurement is above this threshold (21, 22). A recent meta-analysis suggested that endometrial thickness > 11 mm carries a risk of 6.7% for EC in asymptomatic postmenopausal women (23). The risk of malignancy was found to be small (1%) when a low cut-off value of 4 mm was used (24). In a retrospective study among asymptomatic postmenopausal women with endometrial thickness ≥ 5 mm, 0.9% was diagnosed with EC after endometrial sampling and 12.2% were diagnosed with atypical hyperplasia. For a cut-off value of 5 mm, 106 endometrial samplings needed to be performed for the diagnosis of one case of EC (25). For the detection of all intruterine pathologies the best cut-off value was found to be >8 mm with a positive predictive value of 10.05. The sensitivity for EC was 100% at a cut-off value >10.
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mm (26). In patients referred to hysteroscopy due to thickened endometrial lining, TVS had a total false positive rate of 93.2% and a positive predictive value of 0.7% for EC (27). Retrospective studies of postmenopausal asymptomatic women with TVS endometrium thickness > 5 mm who underwent diagnostic hysteroscopy and biopsy found less than 1% atypical hyperplasia, with most findings (>80%) being atrophy, simple hyperplasia and polyps (28, 29). Endometrial cancer can be diagnosed early by TVS in a prognostically better stage in asymptomatic patients.

Another meta-analysis concluded that the use of TVS endometrial thickness as a screening method in asymptomatic postmenopausal women not on HRT is not justified because of the low incidence of endometrial cancer in the observed population and the insufficient data from the published studies to calculate an optimal threshold for endometrial thickness based on the sensitivity and specificity (30, 31).

The cut-off values for endometrial thickness in asymptomatic postmenopausal women determined by various research groups are presented in Table I (32-35).

**TABLE I**
Endometrial thickness and cancer findings in postmenopausal asymptomatic women

<table>
<thead>
<tr>
<th>Author</th>
<th>Endometrial thickness (mm)</th>
<th>Number of women</th>
<th>Number of cancer cases</th>
<th>Negative of predictive value%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmers et al. 1990</td>
<td>≥ 4</td>
<td>283</td>
<td>10</td>
<td>96.50</td>
</tr>
<tr>
<td>Osmers et al. (1994)</td>
<td>≥ 8</td>
<td>88</td>
<td>18</td>
<td>79.55</td>
</tr>
<tr>
<td>Abu Hmeiden et al. 1992</td>
<td>≥ 10</td>
<td>24</td>
<td>3</td>
<td>87.50</td>
</tr>
<tr>
<td>Varner SE et al. 1991</td>
<td>≥ 4</td>
<td>20</td>
<td>1</td>
<td>95.84</td>
</tr>
<tr>
<td>Brooks SE et al. 1993</td>
<td>≥ 5</td>
<td>66</td>
<td>0</td>
<td>100.00</td>
</tr>
<tr>
<td>Vuento MH et al.</td>
<td>≥ 4</td>
<td>78</td>
<td>4</td>
<td>94.88</td>
</tr>
<tr>
<td>Bourne TH et al. 1991</td>
<td>7</td>
<td>104</td>
<td>1</td>
<td>99.10</td>
</tr>
<tr>
<td>Sheth S et al. 1993</td>
<td>≥ 5</td>
<td>35</td>
<td>5</td>
<td>85.80</td>
</tr>
<tr>
<td>Tsuda et al. 1997</td>
<td>≥3</td>
<td>16</td>
<td>1</td>
<td>93.70</td>
</tr>
<tr>
<td>Tsuda et al. 1993</td>
<td>≥ 2</td>
<td>147</td>
<td>2</td>
<td>98.59</td>
</tr>
<tr>
<td>Gambacciani et al. 2004</td>
<td>≥ 4.5</td>
<td>148</td>
<td>1</td>
<td>99.30</td>
</tr>
<tr>
<td>Fleischer et al. 2001</td>
<td>&gt;6</td>
<td>1750</td>
<td>1</td>
<td>99.95</td>
</tr>
<tr>
<td>Bakos et al. 1995</td>
<td>&gt;6</td>
<td>106</td>
<td>1</td>
<td>99.00</td>
</tr>
</tbody>
</table>

Controversies also exist regarding the significance of intrauterine fluid collection in postmenopausal women. It can be considered as an ominous sign associated with malignancy even in the presence of thin endometrium, or it may represent fluid transuded from an atrophic endometrium which accumulates in the uterine cavity due to cervical stenosis. Small series of such patients reported endometrial mommas,
polyps, hyperplasia and rarely endometrial carcinoma, especially if endometrial thickness was greater than 4 mm (36).

**DISCUSSION**

TVS is being used in the last years as an accurate tool to identify endometrial pathology, including endometrial carcinoma in both symptomatic and asymptomatic postmenopausal women. In asymptomatic women diagnosed incidentally with a thick endometrium, a clinical dilemma concerning the case management arises. While the main presenting symptom is abnormal uterine bleeding, 7% to 17% of endometrial cancers are found in asymptomatic postmenopausal women. Despite the established association between a thick endometrium and endometrial carcinoma in postmenopausal women with vaginal bleeding, there is a lack of consensus regarding the asymptomatic postmenopausal women. Most of the researchers agree that in postmenopausal asymptomatic women endometrium thickness < 3 mm strongly reduces the probability of endometrial pathology, while endometrium thickness > 10 mm is correlated with pathologic histology. But there is a 'gray area' between 4 and 10 mm that needs further investigation, as sometimes EC is found. Most cases of EC in postmenopausal asymptomatic women have endometrial thickness measured with TVS over 5 mm.

The recommendations of the Society of Obstetricians and Gynecologists of Canada (37) state that TVS should not be used as a screening method for endometrial cancer in asymptomatic postmenopausal women not using HRT. In women with incidentally observed thickened endometrium and other positive ultrasound findings (increased vascularity, inhomogeneous endometrium, intrauterine fluid, thickening>11mm) together with endometrial cancer risk factors, case-by-case decisions and further investigation such as endometrial sampling is recommended.

In conclusion, transvaginal sonography (TVS) is a reliable, non-invasive method for the evaluation of the endometrial thickness and morphology in asymptomatic postmenopausal women. Universal endometrial screening is controversial because of the lack of evidence of increased 5-year survival rate for EC patients. The diagnostic success of this method also depends on examiner’s training and experience. The difficult issue of how to manage an asymptomatic postmenopausal woman with an incidentally discovered thick endometrium has yet to be resolved. We believe that TVS should be combined with clinical signs and risk factors for endometrial cancer to achieve the optimal management and avoid unnecessary invasive interventions, procedural complications and psychological stress.

**REFERENCES**

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