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**Increased endometrial thickness
in asymptomatic Postmenopausal women:
Cutt-off values and their clinical significance**

Dr.Oguzhan KURU

Background

- The incidence of sonographic endometrial thickening (>4mm) in postmenopausal (PM) women ranges from %3 to 17 while the incidence of endometrial cancer (EC) in PM is 1.3-1.7/1.000.
- %80 of EC occur in PM women,
%90 present with uterine bleeding,
most women (%72) have stage I disease.

- For any women presented with PM bleeding, the risk of EC is %10.
- Baseline incidence of EC is %0.2-0.6 from necropsy findings and from hormone studies.
- TVUSG is a reasonable alternative to endometrial sampling as a first approach in evaluating PM women with an initial bleeding
(a thin <5mm ET has %99 NPV for end cancer!!)

Hypothesis for EC screening

- There is likely a preclinical phase during which some cancers might be detectable prior to development of symptoms.
- Some EC do not present with bleeding until they progress beyond stage I.

How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding

R. SMITH-BINDMAN*†, E. WEISS‡ and V. FELDSTEIN*

- A “**theoretical cohort**” of 100.000 PM women aged >50y, not receiving HRT, was defined.
- In a PM woman with bleeding,
 - the risk of EC if $ET < 5\text{mm}$ is $< 0.07\%$ (LOW RISK)
 - if $ET > 5\text{mm}$ is 7.3% (HIGH RISK)
- Similarly, **11mm** was found as a cut-off for the separation for low/high risk for EC in asymptomatic PM women
 - the risk of EC if $ET \leq 11\text{mm}$ is **$< 0.002\%$** (LOW RISK)
 - if $ET > 11\text{mm}$ is **6.7%** (HIGH RISK)

Table 2 The risk of endometrial cancer at various endometrial thickness measurements in women who are symptomatic or asymptomatic with vaginal bleeding

<i>Threshold to define a normal endometrium (mm)</i>	<i>Women with vaginal bleeding: cancer risk (%) if the endometrium</i>		<i>Women without vaginal bleeding: cancer risk (%) if the endometrium</i>	
	<i>≤ Threshold</i>	<i>> Threshold</i>	<i>≤ Threshold</i>	<i>> Threshold</i>
≤4	0.07	4.6 ←	0.00	0.2
≤5	0.07	7.3	0.00	0.4
≤6	0.08	7.7	0.00	1.5
≤7	0.09	10.8	0.00	2.1
≤8	0.12	12.7	0.00	2.9
≤9	0.14	15.1	0.00	3.6
≤10	0.18	16.6	0.00	5.8 ←
≤11	0.21	40.3	0.00	6.7
≤12	0.25	42.1	0.00	10.3
≤13	0.30	48.2	0.00	10.9
≤14	0.36	52.2	0.00	12.0
≤15	0.42	53.5	0.01	13.1
≤16			0.01	14.9
≤17			0.01	16.8
≤18			0.01	19.6
≤19			0.01	30.9

- In this analysis, individual risk factors (DM, BMI, Tamoxifen use, age) were not taken into account. So, actual risk could be higher when managing these patients in the case of an incidental endometrial thickening.
- A cut-off of **10 or 11mm** provide an acceptable trade-off between “cancer detection” and “unnecessary biopsies” by an incidental ET.

Biopsies in **%0.25** of the patients cover **%87** of occult cancers



ORIGINAL ARTICLE

Thickened endometrium in asymptomatic postmenopausal women – determining an optimum threshold for prediction of atypical hyperplasia and cancer

Ahmed Ghoubara^{a,b,c} , Emmanuel Emovon^c, Sudha Sundar^{a,c} and Ayman Ewies^{a,c}

^aInstitute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK; ^bObstetrics and Gynaecology Department, Aswan University, Aswan, Egypt; ^cGynaecology Department, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

- **Prospective study**; 1995 consecutive PM women referred, 81 (%4.1) with the incidental finding of ET>4mm in the absence of bleeding
- All of them had Pipelle end biopsy with H/S decision was individualized.
- The prevalance of EC/Atypia: **%4.9** (4/81)

- ROC curve identified the ET threshold for diagnosing EC/EIN as $\geq 10\text{mm}$:
 - Prevalance of EC/EIN: %11.4 (4/35)
 - End polyp: %45.7 (16/35) ($p=0.03$)
 - Sensitivity: %100,
 - Specificity: %60 (AUC=0.8, $P=0.04$)
- As the NICE sets %3 PPV to refer for suspected cancer, end biopsy when $\text{ET} \geq 10\text{mm}$ may be acceptable.

An assessment of the value of ultrasonographic endometrial disease in postmenopausal women without symptoms

Arthur C. Fleischer, MD,^{a, b} James E. Wheeler, MD,^c Iain Lindsay, MD,^d Susan L. Hendrix, DO,^e Scott Grabill, BSc,^f Barbara Kravitz, MS,^f and Brian MacDonald, MD, PhD^f

Nashville, Tennessee, Philadelphia and Collegeville, Pennsylvania, Detroit, Michigan, and London, United Kingdom

- 68 centers in US and Europe, Idoxifene (SERM) for the prevention of osteoporosis, PM women screened for 2 years with placebo controlled study.
- Inclusion: PM, <65y, BMD T score -1 to -2.5
Exclusion: Undergone hysterectomy, HRT use, history of breast cancer/vaginal bleeding

- A total of 2820 women were screened. 894 of them excluded. 1926 women proceeded to undergo TVUSG, of them 1792 also had aspiration biopsy. ET>6mm did not undergo randomization.
- 6 end cancer/atypia detected among 1792 biopsies: %0.3
(5 of them ≤ 6 mm)

- Threshold of **ET 6mm**:

- Sensitivity:%17

- Specificity:%98

- NPV:>%99

- PPV: %2

- **Largest study comparing TVUSG and endometrial biopsy**

- Despite a high NPV, TVUSG may **not be an effective screening** for detection of end cancer in untreated, asymptomatic PM women.

The Oncogenic Potential of Endometrial Polyps

(Obstet Gynecol 2010;116:1197-1205)

A Systematic Review and Meta-Analysis

*Stephanie Cruz Lee, MD, Andrew M. Kaunitz, MD, Luis Sanchez-Ramos, MD,
and Ronald M. Rhatigan, MD*

- 17 studies, 10,572 patients reviewed
- Totally 377 malignant polyps (%3.57)
- The rate of (pre)malignancy in PM women: %5.42 (214/3946)
in Premenopausal: %1.7 (68/3997) (RR:3.86)

- (In subgroup of PM) the rate of malignant polyp in patients
with bleeding: %4.47 (88/1968)
without symptoms: %1.51 (25/1654) (RR:3.36)
- Polyp size do not independently predict risk of malignancy
(although 4 studies suggested an association)

Table 4. Frequency of premalignant and malignant polyps and authors' recommendations

Author	Patients n	Asymp- tomatic	%	Sympto- matic	%	Resection suggested for
Orvieto ^e et al. [19]	146	1/95	1	3/51	5.9	Every patient
Savelli et al. [5]	509	9/235	3.8	11/274	4	Symptomatic patients or risk factors ^a
Shushan ^d et al. [6]	300	0/73	0	4/227	1.8	Symptomatic patients
Lev-Sagi et al. [20]	68	0/68	0	0	0	All patients except high operative risk
Machtinger et al. [11]	438	1/113	0.9	10/325	3	Symptomatic patients or risk factors ^b
Ben-Arie et al. [9]	430	15/236	6.4	12/194	6	Postmenopausal patients
Papadia et al. [21]	90	4/40	10	4/50	8	Every patient
Lieng et al. [12]	411	5/129	3.9	9/282	3.2	Every patient
Ferrazzi et al. [22]	1,922	18/1,152	1.6	46/770	5.9	Symptomatic patients ^c
Golan et al. ^f	1,124	7/527	1.3	16/597	2.6	Every patient

^a Age, hypertension and menopausal status. ^b Age, menopausal status and abnormal uterine bleeding. ^c Only postmenopausal women were considered. ^d Only malignant lesions were considered. ^e Polypectomy was performed with D&C. ^f Present study.

- There is **NO CONSENSUS** regarding removal of asymptomatic polyps.
- But in general, “**symptomatic bleeding**” and “**menopausal status**” increases the risk of malignancy.

Is there a survival advantage in diagnosing endometrial cancer in asymptomatic postmenopausal patients? An Israeli Gynecology Oncology Group study.

Gemer O¹, Segev Y², Helpman L³, Hag-Yahia N³, Eitan R⁴, Raban O⁴, Vaknin Z⁵, Leytes S⁶, Ben Arie A⁷, Amit A⁸, Levy T⁶, Namazov A¹, Volodarsky M¹, Ben Shachar I⁹, Atlas I¹⁰, Bruchim I¹¹, Lavie O¹².

- Retrospective analysis of **1607 PM patients with EC**: 1374 presented with bleeding (Group A), 233 incidentally found (Group B).
- Median follow-up was 52 months.
- No significant difference in proportions of patients with Stages II-IV (%23.5 vs %23.8) and the histological subtypes ($p > 0.05$).

- Within Stage I, more patients were diagnosed at Stage IA in asymptomatic group (%82 vs %23.8, $p < 0.001$).
- No differences were found between 2 groups in terms of 5-year DFS (%79.4 vs %79.1, $p = 0.85$) and OS (%76.8 vs %79.7, $p = 0.37$)
- Interestingly, the lack of survival advantage of preclinical diagnosed cancer is also seen in breast cancer!!

- Asymptomatic PM patients with incidentally diagnosed thick endometrium/polyp should not undergo diagnostic procedures.
- These patients should be re-examined in 3 months.
- If bleeding or change in the size of ET/polyp appears, invasive procedures should be pursued.
- In other cases, yearly follow-up is sufficient.

Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis

M. C. BREIJER*†, J. A. H. PEETERS‡, B. C. OPMEER§, T. J. CLARK¶, R. H. M. VERHEIJEN**
B. W. I. MOL* and A. TIMMERMANS*

- 32 studies reporting **11.100 asymptomatic PM women** were included.
- Aim of the study: a) "Normal" ET
 - b) Prevalance of EC and atypia
 - c) Sensitivity/specificity of ET by USG for diagnosing (pre)malignancy

a)ET: 9 Studies found (median sample size 259)

Estimated mean ET:**2.9mm**

b)Prevalance: 15 studies, Total of 3595 women

Estimated prevalance of EC:**%0.62**

.. of atypia:**%0.59**

.. of EC+Aypia:**%1.21**

c) Diagnostic accuracy of ET: 20 studies, 6974 women

- For different cut-offs: Sensitivity %0-83, Specificity:%72-94

-The utility of a negative test is limited in this population BECAUSE the risk is already low.

REMEMBER: The risk of EC in PM bleeding women is %10 (%5-20)



With the thin endometrium ($\leq 4\text{mm}$) on USG, risk is reduced to <%1

This systematic review do not justify the use of **any endometrial thickness** as a screening test for endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic postmenopausal women not using HRT.

Asymptomatic Endometrial Thickening

Recommendations:

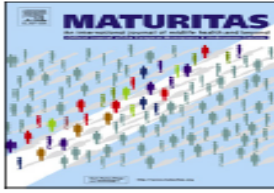
- 1- TVUSG should not be used as screening for EC.
- 2- Indications for PM bleeding women with ET > 4-5 mm should not be extrapolated to asymptomatic women.
- 3- A woman who has endometrial thickening and other positive findings on ultrasound (increased vascularity, inhomogeneity, fluid, or ET > 11 mm) should be referred to a gynaecologist for further investigations.

4-Investigations should be made on a case-by-case in asymptomatic women with increased ET and risk factors for EC (such as obesity, hypertension, and late menopause).

5- In asymptomatic women on tamoxifen, a routine ultrasound for ET should not be performed.

6- Not all PM women who have asymptomatic endometrial polyps require surgery

-Triaged for intervention according to size of the polyp, age, and other risk factors.



EMAS clinical guide: Assessment of the endometrium in peri and postmenopausal women

Eva Dreisler^a, Lars Grønlund Poulsen^a, Sofie Leisby Antonsen^a, Iuliana Ceausu^{b,c}, Herman Depypere^d, C. Tamer Erel^e, Irene Lambrinoudaki^f, Faustino R. Pérez-López^g, Tommaso Simoncini^h, Florence Tremollieresⁱ, Margaret Rees^j, Lian G. Ulrich^{a,*}

Recommendations:

- 1-** In tamoxifen users, ET is increased, and hysteroscopy is recommended in cases of postmenopausal bleeding.
- 2-** Assessment of the endometrium in the absence of bleeding should be limited to women at high risk of endometrial cancer such as those from HNPCC families, with PCOS or grossly overweight.

American Cancer Society Guidelines for the Early Detection of Cancer: Update of Early Detection Guidelines for Prostate, Colorectal, and Endometrial Cancers

ALSO: Update 2001—Testing for Early Lung Cancer Detection

- **No agreed-upon criteria for ET** that has high statistical power enough;
USG not an effective tool for EC screening.
- Recommendations are based on risk factors:
 - Increased risk factors for EC: Late menopause
 - Tamoxifen therapy
 - Nulliparity
 - Infertility
 - PCOS
 - Obesity
 - DM
 - HNPCC

a) For women with average and increased risk factors:

- No benefit of screening.

- Patients should be informed about early symptoms of EC.

(especially bleeding)

b) For women with high risk: HNPCC (with or at risk)

- annual screening for EC with endometrial biopsy by 35years



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 734 • May 2018

(Replaces Committee Opinion Number 440, August 2009)

Committee on Gynecologic Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice in collaboration with committee member Catherine Cansino, MD, MPH.

The Role of Transvaginal Ultrasonography in Evaluating the Endometrium of Women With Postmenopausal Bleeding

1- TVUSG is not an appropriate screening tool for EC in PM women without bleeding.

2- **ET>4mm** that is incidentally found in an asymptomatic PM woman need not routinely trigger evaluation, individual assesment based on “**patient characteristics**” and “**risk factors**” is appropriate.

CONCLUSION-1

1-TVUSG should not be used as a screening tool for EC.

2-Although menopausal status is a well-accepted risk factor for malignancy, there is NO CONSENSUS to remove all incidentally detected asymptomatic endometrial polyps.

CONCLUSION-2

3-There is no survival advantage of preclinical diagnosing of endometrial cancer.

4-ET>4mm that is INCIDENTALLY found in a PM patient without symptom need not routinely necessitate further evaluation INSTEAD, an individualized assessment based on:

- Patient characteristics/risk factors OR

- Patient preference OR

- Re-exam in 3 months

seems reasonable.