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Association between endometrial heterogeneity and endometrial cancer risk stratification in postmenopausal women

Повезаност хетерогености ендометријума и ризика од карцинома ендометријума код жена у постменопаузи

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SUMMARY

Introduction/Objective The normal postmenopausal endometrium typically appears thin, homogeneous, and echogenic on transvaginal ultrasonography. In contrast, endometrial carcinoma is often associated with increased thickness, heterogeneous echogenicity, irregular endometrial–myometrial interface, and enhanced Doppler vascularization. The objective of this study was to evaluate the association between heterogeneous endometrial echogenicity and the risk of endometrial malignancy in postmenopausal women.

Methods This prospective clinical study included 120 postmenopausal women treated at the University Clinic for Gynecology and Obstetrics in Skopje. Participants were divided into a control group (n = 40) and an examined group (n = 80). The examined group was further stratified according to uterine bleeding status and endometrial thickness (5–8 mm, > 8–11 mm, and > 11 mm). Endometrial echogenicity was assessed by transvaginal ultrasonography and classified as homogeneous or heterogeneous. Binary logistic regression analysis was performed to determine independent predictors of malignancy.

Results Heterogeneous endometrial echogenicity was significantly more frequent in the examined group compared with controls (p < 0.001). It was identified as an independent predictor of endometrial malignancy (OR = 4.938; 95% CI 1.24–19.62; p = 0.023). No statistically significant association was observed between echogenicity and endometrial thickness subgroups (p = 0.49) or uterine bleeding status (p = 0.82).

Conclusion Heterogeneous endometrial echogenicity represents a significant independent sonographic predictor of endometrial malignancy in postmenopausal women and should be incorporated into routine ultrasound risk assessment.

Keywords: postmenopause; endometrial echogenicity; endometrial cancer; transvaginal ultrasonography; malignancy risk

САЖЕТАК

Увод/Циљ Нормалан ендометријум у постменопаузи ултрасонографски се приказује као танак, хомоген и ехоген. Карцином ендометријума често је повезан са повећаном дебљином, хетерогеном ехогеношћу и неправилном границом између ендометријума и миометријума. Циљ рада био је да се испита повезаност хетерогене ехогености ендометријума и ризика од малигнитета код жена у постменопаузи.

Методе Проспективна клиничка студија обухватила је 120 жена у постменопаузи лечених на Универзитетској клиници за гинекологију и акушерство у Скопљу. Испитанице су подељене на контролну групу (*n* = 40) и испитивану групу (*n* = 80). Испитивана група је даље стратификована према присуству крварења и дебљини ендометријума (5–8 *mm*, > 8–11 *mm* и > 11 *mm*). Ехогеност ендометријума процењена је трансвагиналном ултрасонографијом и класификована као хомогена или хетерогена. Примењена је бинарна логистичка регресија.

Резултати Хетерогена ехогеност ендометријума била је значајно чешћа у испитиваној групи (*p* < 0,001). Представљала је независни предиктор малигнитета (*OR* = 4,938; 95% *CI* 1,24–19,62; *p* = 0,023). Није утврђена статистички значајна повезаност између ехогености и дебљине ендометријума (*p* = 0,49) нити присуства крварења (*p* = 0,82).

Закључак Хетерогена ехогеност ендометријума представља значајан независни ултрасонографски предиктор малигнитета код жена у постменопаузи и треба да буде укључена у рутинску процену ризика.

Кључне речи: постменопауза; ехогеност ендометријума; карцином ендометријума; трансвагинална ултрасонографија; ризик од малигнитета

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INTRODUCTION

Endometrial carcinoma is the most common gynecologic malignancy in developed countries, with a continuously increasing incidence worldwide [1, 2]. According to recent global cancer statistics, endometrial cancer represents a significant public health burden, particularly in postmenopausal women [1]. The rising prevalence has been associated with metabolic syndrome, obesity, and increased life expectancy [3].

Current international guidelines, including ESGO/ESTRO/ESP and ESMO recommendations, provide standardized approaches for diagnosis, staging, and management of endometrial carcinoma [4, 5]. The 2023 FIGO staging revision introduced important refinements in disease stratification, further emphasizing the prognostic heterogeneity of this malignancy [6, 7].

Transvaginal ultrasonography remains the first-line diagnostic modality in the evaluation of postmenopausal bleeding. Traditionally, endometrial thickness has been considered the primary screening parameter [4]. However, recent evidence suggests that reliance solely on thickness measurement may not provide optimal diagnostic accuracy [8, 9].

Contemporary ultrasound practice incorporates structured reporting systems such as the ISUOG consensus recommendations and IETA terminology, which emphasize qualitative morphological assessment including echogenicity, endometrial–myometrial interface, and vascular patterns [10, 11]. Advanced imaging techniques, including microvascular flow imaging and ultrasound-based predictive scoring systems, have demonstrated improved diagnostic performance in identifying high-risk endometrial lesions [12–15].

Moreover, modern molecular classification has revealed substantial biological heterogeneity in endometrial carcinoma, including mismatch repair deficiency and microsatellite instability [16, 17]. Emerging translational approaches such as cfDNA fragmentomics and radiomics further support the integration of imaging and molecular biomarkers in risk stratification [18, 19].

The objective of this study was to evaluate the association between heterogeneous endometrial echogenicity and the risk of endometrial malignancy in postmenopausal women.

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METHODS

This prospective clinical study included 120 postmenopausal women treated at the University Clinic for Gynecology and Obstetrics – Skopje. Participants were divided into two groups: a control group (n = 40) and an examined group (n = 80). The control group consisted of postmenopausal patients hospitalized and surgically treated for benign urogenital pathology.

The examined group was further stratified according to the presence or absence of uterine bleeding. Based on ultrasound-verified endometrial thickness, patients were categorized into three subgroups: 5–8 mm, >8–11 mm, and >11 mm.

Transvaginal ultrasonography was performed in all participants. Endometrial echogenicity was classified as homogeneous or heterogeneous. Histopathological verification was obtained following fractional exploratory curettage.

Exclusion criteria included: women of reproductive age, inability to undergo fractional curettage, prior or current malignant disease, ovarian tumors, breast cancer treated with tamoxifen, and previous pelvic surgery for other gynecological conditions.

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Statistical analysis

Statistical analysis was performed using SPSS version 20.0. Categorical variables were analyzed using the Pearson chi-square test or Fisher's exact test, as appropriate. Continuous variables were assessed for normality using the Shapiro–Wilk test. Student's t-test, Mann–Whitney U test, and Kruskal–Wallis ANOVA were applied as indicated.

Binary logistic regression analysis was performed to determine independent predictors of endometrial malignancy. Statistical significance was defined as $p < 0.05$.

Ethics: Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje (Approval No. 03-1997/6). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

RESULTS

According to endometrial echogenicity, the study population was divided into two categories: homogeneous and heterogeneous (Table 1). In the examined group, 43 patients (53.7%) had homogeneous endometrial echogenicity, whereas 37 patients (46.3%) had heterogeneous echogenicity. In the control group, all 40 patients (100%) had homogeneous endometrial echogenicity.

A statistically significant difference was observed between the examined and control groups regarding endometrial echogenicity (Fisher's exact two-tailed test, $p < 0.001$).

Analysis of the examined group according to endometrial thickness and endometrial echogenicity

In the subgroup with endometrial thickness of 5–8 mm, 21 patients (58.3%) had homogeneous echogenicity and 15 (41.7%) had heterogeneous echogenicity.

In the subgroup with endometrial thickness >8–11 mm, 10 patients (58.8%) had homogeneous echogenicity and 7 (41.2%) had heterogeneous echogenicity (Table 2).

In the subgroup with endometrial thickness >11 mm, 12 patients (44.4%) had homogeneous echogenicity, while 15 (55.6%) had heterogeneous echogenicity (Table 2).

No statistically significant association was observed between endometrial thickness categories and echogenicity (Pearson $\chi^2 = 1.42$; df = 2; $p = 0.491$).

Analysis of the examined group according to uterine bleeding and endometrial echogenicity

Among patients without uterine bleeding, 21 (52.5%) had homogeneous echogenicity and 19 (47.5%) had heterogeneous echogenicity. Among patients with uterine bleeding, 22 (55.0%) had homogeneous echogenicity and 18 (45.0%) had heterogeneous echogenicity.

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There was no statistically significant difference between bleeding status and echogenicity (Pearson χ^2 = 0.05; df = 1; p = 0.823) (Table 3).

Combined analysis: bleeding status, thickness, and echogenicity

Analysis of the group without uterine bleeding was performed of the endometrium and echogenicity of the endometrium (Table 4). The analysis indicated that the homogeneous echogenicity of the endometrium is most present with 11(52.4%) in patients with an endometrial thickness of 5 mm to 8 mm, followed by 6 (28.6%) patients with endometrial thickness >8 mm -11 mm. In relation to heterogeneous echogenicity of the endometrium, most patients, 8 (42.1%) have an endometrial thickness of 5–8 mm followed by six (31.6%) patients with endometrial thickness >11mm. In patients without uterine bleeding, for p > 0.05, there is no statistically significant difference between the groups with homogeneous /heterogeneous echogenicity of the endometrium relative to the thickness of endometrium (Pearson $\chi 2$= 0.867, df = 2, p = 0.6483).

In patients with Uterine Bleeding, an analysis was performed according to endometrial thickness and endometrial echogenicity (Table 5). Homogeneous echogenicity of the endometrium is most common with 10 (45.5%) in patients with an endometrial thickness of 5 mm to 8 mm, followed by 8 (36.4%) patients with endometrial thickness >11mm. With the heterogeneous echogenicity of endometrium, most patients, and that 9 (50%) are with endometrium >11 mm followed by 7 (38.9%) patients with a thickness of endometrium 5–8 mm.

In the group of uterine bleeding, for p> 0.05, there is no statistically significant difference between subgroups with homogeneous / heterogeneous echogenicity of endometrium relative to endometrial thickness (Pearson $\chi 2$ =0.863; df = 2, p = 0.6493 (table 5).

Echogenicity of the endometrium - is a significant predictor of endometrial malignancy (p <0.05). Women with heterogeneous endometrial echogenicity have 4.938 times [p = 0.023, 95% CI = 1,243-19,619] likelihood of endometrial cancer compared to women with homogeneity endometrial echogenicity (Table 6).

Logistic regression analysis

Binary logistic regression analysis demonstrated that heterogeneous endometrial echogenicity was a significant independent predictor of endometrial malignancy.

Women with heterogeneous echogenicity had 4.938-fold higher odds of endometrial cancer compared with women with homogeneous echogenicity (OR 4.938; 95% CI 1.24–19.62; p = 0.023) (Table 6).

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DISCUSSION

Our results showed that heterogeneous endometrial echogenicity is a significant independent predictor of endometrial malignancy, with nearly a fivefold increase in odds (OR 4.94; 95% CI 1.24–19.62; $p = 0.023$). This finding emphasizes the importance of qualitative ultrasonographic assessment, beyond conventional measurement of endometrial thickness.

These findings are in agreement with the study by Yan et al. [20], who reported that endometrial echogenic heterogeneity is strongly associated with malignancy and significantly improves diagnostic accuracy when incorporated into predictive nomograms. Their model demonstrated that combining echogenicity with other ultrasound parameters enhances risk stratification compared to single-parameter approaches. Notably, while their study integrated multiple variables, our results confirm that echogenicity alone already has substantial predictive value.

Similarly, Ai et al. [21] developed a nomogram for predicting endometrial cancer in postmenopausal women and demonstrated that incorporating ultrasonographic features significantly improves diagnostic performance. In comparison to their multifactorial model, our study provides additional evidence that even a single qualitative parameter—echogenicity—can independently discriminate between benign and malignant conditions.

In contrast to these findings, our study did not demonstrate a statistically significant association between endometrial thickness and echogenicity ($p = 0.491$), nor between thickness and malignancy risk within echogenicity subgroups. This observation is consistent with the meta-analysis by Chee et al. [8], which concluded that endometrial thickness alone has limited specificity, particularly in symptomatic postmenopausal women. Their analysis highlighted that fixed cut-off values may not adequately capture the complexity of endometrial pathology, leading to diagnostic uncertainty.

Our findings also showed no statistically significant association between uterine bleeding status and endometrial echogenicity ($p = 0.823$). This result is in line with the guideline by Wolfman al. [9], which emphasizes that although postmenopausal bleeding is a key clinical symptom, it should not be interpreted in isolation. Imaging findings, particularly qualitative ultrasound features, provide important complementary information and may improve diagnostic accuracy.

Importantly, the significant difference in echogenicity between the examined and control groups ($p < 0.001$) in our study reinforces the discriminatory value of this parameter. This is comparable to findings from multicenter analyses such as the study by Colombi et al. [22], which demonstrated correlations between ultrasonographic features and histopathological as well as molecular characteristics of endometrial cancer. While their work focused on broader imaging-pathology correlations, our study narrows this relationship specifically to echogenicity as a practical and easily applicable marker.

Our findings regarding the predictive value of heterogeneous endometrial echogenicity are supported by earlier sonographic studies reporting that morphologic characteristics enhance malignancy discrimination. In a seminal work by Opolskiene et al. [23], heterogeneous endometrial echogenicity

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demonstrated strong diagnostic performance with an AUC of 0.83 and, when combined with other grey-scale and Doppler parameters, yielded an even higher discriminative ability in predicting endometrial malignancy. This aligns with our observation that qualitative ultrasonographic features – particularly echogenicity – provide valuable diagnostic information beyond endometrial thickness alone.

A key strength of our study is the detailed subgroup analysis according to endometrial thickness and bleeding status. Unlike some previous studies, we demonstrated that echogenicity retains its predictive role even when stratified by these variables, further supporting its independence as a diagnostic factor. However, the lack of statistical significance in subgroup analyses suggests that echogenicity may operate as a global marker rather than being strongly influenced by individual clinical parameters.

From a clinical perspective, our findings support a shift from a purely quantitative to a more integrative ultrasonographic approach. While endometrial thickness remains a useful screening tool, it should be complemented by qualitative assessment, particularly echogenicity patterns. This aligns with contemporary trends in gynecologic imaging, where multiparametric evaluation is increasingly recognized as essential for accurate diagnosis.

Nevertheless, several limitations must be acknowledged. The relatively small sample size and single-center design may limit external validity. In addition, the absence of molecular classification restricts comparison with modern endometrial cancer subtypes, as highlighted in recent literature. Future studies should aim to integrate imaging findings with histopathological and molecular data in large, multicenter cohorts.

CONCLUSION

The observed odds ratio of 4.938 in our study further supports the clinical relevance of echogenicity as a risk stratification parameter. Heterogeneous endometrial echogenicity represents a clinically relevant independent sonographic predictor of malignancy in postmenopausal women. Incorporating qualitative ultrasound assessment into routine diagnostic algorithms may enhance early detection and improve individualized risk stratification.

Conflict of interest: None declared.

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Table 1. Descriptive analysis of the sample according to groups and endometrial echogenicity; data are presented as counts (n) and percentages (%)

Endometrial echogenicity	Examined group n (%)	Control group n (%)	Total n (%)
Homogeneous	43 (53.75)	40 (100)	83 (69.17)
Heterogeneous	37 (46.25)	0 (0)	37 (30.83)
Total	80 (66.67)	40 (33.33)	120 (100)

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Table 2. Analysis of the examined group according to endometrial thickness and echogenicity; data are presented as counts (n) and percentages (%)

Endometrial echogenicity	**5–8 mm n (%)**	**> 8–11 mm n (%)**	**> 11 mm n (%)**	**Total n (%)**
Homogeneous	21 (58.33)	10 (58.82)	12 (44.44)	43 (53.75)
Heterogeneous	15 (41.67)	7 (41.18)	15 (55.56)	37 (46.25)
Total	36 (45)	17 (21.25)	27 (33.75)	80 (100)

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Table 3. Analysis of the examined group according to uterine bleeding and endometrial echogenicity; data are presented as counts (n) and percentages (%)

Endometrial echogenicity	No bleeding n (%)	Uterine bleeding n (%)	Total n (%)
Homogeneous	21 (52.5)	22 (55)	43 (53.75)
Heterogeneous	19 (47.5)	18 (45)	37 (46.25)
Total	40 (50)	40 (50)	80 (100)

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Table 4. Analysis of the non-bleeding group according to endometrial thickness and echogenicity; data are presented as counts (n) and percentages (%)

Endometrial thickness	Homogeneous n (%)	Heterogeneous n (%)	Total n (%)
5–8 mm	11 (52.38)	8 (42.11)	19 (47.5)
> 8–11 mm	6 (28.57)	5 (26.32)	11 (27.5)
> 11 mm	4 (19.05)	6 (31.58)	10 (25)
Total	21 (52.50)	19 (47.50)	40 (100)

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Table 5. analysis of the bleeding group according to endometrial thickness and echogenicity; data are presented as counts (n) and percentages (%)

Endometrial thickness	**Homogeneous n (%)**	**Heterogeneous n (%)**	**Total n (%)**
5–8 mm	10 (45.45)	7 (38.89)	17 (42.5)
> 8–11 mm	4 (18.18)	2 (11.11)	6 (15)
> 11 mm	8 (36.37)	9 (50)	17 (42.5)
Total	22 (55)	18 (45)	40 (100)

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Table 6. Binary logistic regression analysis of the predictive role of certain parameters in relation to endometrial malignancy – examined group

Variable	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)
Echogenicity – homogeneous *vs.* heterogeneous	1.597	0.704	5.149	1	0.023*	4.938	1.243–19.62

B – regression coefficient; S.E. – standard error; df – degrees of freedom; Sig. – significance; Exp (B) – odds ratio;

*statistically significant, $p < 0.05$

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