Aegean Journal of Obstetrics and Gynecology

Original Article

# False Endometrial Thickening in Postmenopausal Patients Using Anticoagulants or Antiplatelets Agents

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ABSTRACT

Objective: There is no report that anticoagulant or antiplatelet use may lead to abnormal endometrial sonographic findings. This retrospective study reports our first results associated with endometrial sampling in asymptomatic postmenopausal women using anticoagulants or antiplatelet.

Material and methods: A total of 268 postmenopausal patients who applied to our gynecology outpatient clinic for any reasons except postmenopausal bleeding were included in the study. Patients were divided into three groups according to using drug status: first healty control group [HCG], second anticoagulants agents group [ACG], and third antiplatelet agents group [APG]. The effects of anticoagulant and antiplatelet agents on endometrial thickness were compared with histopathological findings.

Results: The mean endometrial thickness was significantly greater in group ACG [5.2 mm] and APG [4.1 m] than in group HCG [3.3 mm]. No significant differences were found in the mean endometrial thickness between groups HCG and APG. However, it is noteworthy that the average endomeric thickness in the ACG group is more than the other two groups and this is statistically significant [$p < 0.05$].

Conclusion: If the thickness of the endometrium was > 4 mm. endometrial sampling may be recommended in in asymptomatic postmenopausal women using anticoagulants or antiplatelet agents.

Keywords: anticoagulants; antiplatelets; biopsy; endometrial thickness; menopause; ultrasonography

ARTICLE INFO
Doi: 10.46328/aejog.v3i2.89

*Article history:*
Received: 30 April 2021
Revision received 01 June 2021
Accepted 30 June 2021



## Introduction

Endometrial cancer and atypical endometrial hyperplasia are relatively rare but important pathologies in postmenopausal women. It is very important and vital to diagnose endometrial cancer before cardinal symptoms [especially postmenopausal bleeding] begin. Transvaginal ultrasonography [TVUS], which is used as part of a gynecological examination to view endometrial pathologies helps detect endometrial cancer and provides important information in the differential diagnosis of other endometrial pathologies in symptomatic postmenopausal patients [1, 2]. Although the availability of TVUS as a screening method for endometrial or ovarian cancer is limited, TVUS is performed during routine gynecological examinations in asymptomatic postmenopausal women [3, 4]. It has been clearly demonstrated that variables such as late menopause, diabetes, obesity, nulliparity / infertility, hypertension, early menarche are associated with endometrial cancer. However, there is currently no definitive information as to whether these factors also affect endometrial thickness. Generally, endometrial thickness > 4-5 mm in symptomatic postmenopausal women is accepted as pathological [5]. On the other hand, there is no consensus on the endometrial thickness which should be considered pathological in asymptomatic postmenopausal women [6, 7]. The criteria for symptomatic patients are often used for these patients too [8].

Thickness monitoring of the endometrium in asymptomatic patients may cause the physician to be troubled about the management of the disease and often force him to take a mostly unnecessary biopsy.

Due to the deterioration in living conditions, the risk of cardiovascular disease and peripheral artery disease has increased in postmenopausal women. Therefore, the need for antithrombotic or antiplatelet therapy has increased in recent years [9-11]. These women have sometimes vaginal bleeding or endometrial thickness more than 4-5 mm. We could not find any report that anticoagulant or antiplatelet use may lead to abnormal endometrial sonographic findings in asymptomatic postmenopausal patients. Therefore, we conducted this retrospective study to analyze whether there are any changes in the endometrium sonographically in asymptomatic postmenopausal women using antithrombotic or antiplatelet agents. We hypothesised that coaguloma caused by microscopic hemorrhage in endometrium due to anticoagulant or antiplatelet using may cause false thickness increasing in endometrium. The aim of this study was to compare the effects of anticoagulant and antiplatelet agents on endometrial thickness with histopathological findings and to determine the endometrial thickness cut off limit for endometrial biopsy in asymptomatic postmenopausal patients using anticoagulants and antiplatelet agents.

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## Material and methods

A total of 268 patients who were admitted to gynecology outpatient clinic between 2018 and 2019 were included in the study. The inclusion criteria were that the uterus was preserved, the last menstrual period was> 1 year ago, there was no vaginal bleeding in the postmenopausal period and the patient was not receiving hormone replacement therapy. The study was approved by the ethics committee of Our University.

Table 1. The Basic Characteristics of the Patients

| | HCG | | | APG | | | ACG | | |
|---|---|---|---|---|---|---|---|---|---|
| | <5 mm, n=24 | ≥5 mm, n=104 | p | <5 mm, n=28 | ≥5 mm, n=72 | p | <5 mm, n=12 | ≥5mm, n=28 | p |
| Age | 57,8±5,4 | 54,65±7,46 | 0.381 | 60,13±5,99 | 60,67±12,25 | 0.911 | 64,33±13,61 | 58,57±12,5 | 0.531 |
| Gravida | 4±1,87 | 4,42±2,48 | 0.723 | 5,13±1,55 | 5,22±3,54 | 0.943 | 5±3,61 | 6±2,24 | 0.625 |
| Parity | 3,6±1,82 | 3,62±2,26 | 0.991 | 4,25±1,49 | 3,72±2,35 | 0.571 | 4±2,65 | 5,29±2,56 | 0.492 |
| BMI | 27,59±2,06 | 29,91±4,56 | 0.286 | 29,46±5,87 | 31,53±5,72 | 0.412 | 28,87±1,67 | 32,54±2,69 | 0.069 |
| Smoking | 0 | 12 (%9.37) | 0.424 | 16 (%16) | 26 (%26) | 0.425 | 4 (%10) | 8 (%20) | 0.881 |
| Diabetes | 8 (%6,2) | 20 (%15.6) | 0.309 | 12 (%12) | 28 (%28) | 0.946 | 0 | 8 %20) | 0.301 |
| Hypertension | 3 (%2.34) | 12 (%9.37) | 0.570 | 5 (%5) | 13 (%13) | 0.620 | 0 | 3 (%7.5) | 0.175 |

*BMI: Body mass index, HCG: Healty control group, APC: Antiplatelet agents group, ACG: Anticoagulants agents group*

Patients were divided into three groups according to using drug status, the first group consisted of the healty control group [HCG], the second group consisted of using anticoagulants agents group [ACG], and the third group consisted of using antiplatelet agents [APG]. The effects of anticoagulant and antiplatelet agents on endometrial thickness were compared with histopathological findings

The age of the patients, the age of menopause, the age of menarche, weight, height, medical history [diabetes mellitus and hypertension], smoking, parity, systemic drugs uses, information about the presence of other accompanying gynecological pathology, histopathological diagnosis and measured endometrium thickness data were evaluated. Endometrial thickness measurements were performed in lithotomy position with 5 MHz vaginal transducer. [Mindray Color Doppler DC N2]. The ultrasound section of the uterus in the midsagittal plane was enlarged to cover the entire uterine screen. The calipers were positioned to measure the area between the anterior and posterior hypoechogen basal layer of the uterus. In this way, both leaves of the endometrium were measured together. Thickness of endometrium> 5 mm was accepted as hyperplasic. While the measurement was performed at the fundus level in the patients with regular endometrium, the largest area was measured in cases in which the endometrium was irregular. In patients with free fluid in the uterine cavity, the middle hypoechogenous part was removed from the measurement. Endometrial sampling for histopathological diagnosis done. Endometrial sampling was performed by fractional curettage. Written informed consent was obtained from the patients.

Histopathological results were classified as follows: atrophy / insufficient material, proliferative / secretory endometrium, endometrial polyp, endometrial hyperplasia without atypia, atypia hyperplasia and endometrial cancer. Atrophy / insufficient material, proliferative / secretory endometrium was considered as a benign finding, while others were considered pathological.

SPPS 25 [IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.] was used to evaluate the data. Variables were expressed using mean ± standard deviation, percentage and frequency values. Variables were evaluated after normality, pre-conditions of homogeneity of variances [Shapiro Wilk and Levene Test].

In the analysis of data, Independent 2 group t test [Student tests t test] and Mann Whitney-U test were used for the comparison of two groups. Categorical data were analyzed by Fisher iles Exact Test and Chi-Square Test. In cases where the expected frequencies are less than 20%, the larda Monte Carlo Simulation Method ın is used for the inclusion of these frequencies in the analysis. P <0.05 was considered statistically significant.

## Results

We examined 268 patients who have been in menapouse since at least one year and did not use any hormonoteraphy. TVUS was used for measuring endometrial thickness.

128 patients were control group and 140 patients were using anticoagulant or antiplatellet agents.

Anticoagulant like dabigatran, apixaban, rivaroxaban, edoxaban, warfarin sodium etc. were used by 40 patients and that 100 patients used antiplatellet agents like clopidogrel, dipiridamol, acetylsalicilic acid, ticlopidine etc.

We classified all the patients according to using anticoagulant and antiplatelet agents, endometrial thickness, endometrial biopsy results, laboratory test results, age, parity, gravida etc. The basic characteristics of the patients are shown in Table 1.

The mean age ± standard deviation [SD] in patients with endometrium less than 5 mm; 57,8±5,4 years for group HCG, 64,33±13,61 years for group ACG and 60,13±5,99 years for group APG. The same parameters were 54,65±7,46, 58,57±12,55 and 60,67±12,25, respectively, for patients whose endometrium was higher than 5 mm. Average time since menopause for all patients was 9.1 years [range, 1-14 years]. The average time since menopause ± SD was 9.5 ± 6.1 years for group HCG, 12.4 ± 9.8 years for group ACG and 10.6 ± 4.6 years for group APG. There was no difference between the 3 groups in terms of age and time of menopause. The mean endometrial thickness was significantly greater in group ACG [5.2 mm] and APG [4.1 m] than in group HCG [3.3 mm] [Table 2].

Table 2. The Mean Endometrial Thicknesses of the Groups

| Group | Mean Endometrial Thickness | 95 % CI |
|---|---|---|
| HCG ( n= 128) | 3.3 | 3.4-3.8 mm |
| ACG ( n= 40) | 5.2 | 5.1-7.4 mm |
| APG ( n= 100) | 4.1 | 3.1-5.3 mm |

*HCG versus ACG: p < 0.05; HCG versus APG: p > 0.05; ACG versus APG: p > 0.05*
*HCG: Healty control group, APC: Antiplatelet agents group, ACG: Anticoagulants agents group, CI: Confidence interval*

No significant differences were found in the mean endometrial thickness between groups HCG and APG. However, it is noteworthy that the average endomeric thickness in the ACG group is more than the other two groups and this is statistically significant [p < 0.05] [Table 2].

The distribution of histopathological findings of patients with endometrial thickness ≥ 5 mm is summarized in Table 3.

Table 3. Distribution of histopathological findings of patients with endometrial thickness ≥ 5 mm before endometrial sampling*

| | HCG n:104 | APG n:72 | ACG n:28 | Total n:204 |
|---|---|---|---|---|
| Atrophy | 24 (%37.5) | 20 (%31.3) | 20 (%31.3) | 64 (%51) |
| Endometrial hyperplasia | - | 8 (%100) | - | 8 (%3.9) |
| Endometrial cancer | 4 (%33.3) | 8 (%66.7) | - | 12 (%5.9) |
| Polyp | 36 (%64.3) | 16 (%28.6) | 4 (%7.1) | 56 (%27.4) |
| Insufficient material | 4 (%50) | 4 (%50) | - | 8 (%3.9) |
| Endometritis | 36 (%64.3) | 16 (%28.6) | 4 (%7.1) | 56 (%27.4) |

* P value; 0.272

*HCG: Healty control group, APC: Antiplatelet agents group, ACG: Anticoagulants agents group*

## Discussion

Although there is no evidence of TVUS as a screening method in endometrium and ovarian cancer, in practice, many postmenopausal women are evaluated by pelvic ultrasonography in addition to routine gynecological examination, even if there is no complaint. In these patients, monitoring the endometrium as "thick" may put the physician in trouble about the patient's management and frequently force a biopsy. There is no consensus on the thickness of the endometrium, which should be considered pathological in asymptomatic postmenopausal women. Mostly applies to symptomatic patients in these patients criteria are used. However, the observation of us and others is in the form that the endometrium can be observed as "thick" in some of the postmenopausal patients without vaginal bleeding [12]. Numerous researches are conducted to evaluate the effectiveness of TVUS and diagnostic curettage in the diagnosis of endometrial malignancy in postmenopausal women, and the role of TVUS in reducing the number of diagnostic curettage is examined. Curettage today has a high cost and only 10% of cases where curettage is applied, endometrial cancer is detected [13-16]. In postmenopausal patients, the effect of most drugs on the endometrium, with the exception of hormone replacement drugs or tamoxifen, was not considered [17]. However, to our knowledge, there are no previous reports on the relationship between anticoagulant and antiplatelet use and endometrial thickness. Our study is the first study to examine this issue. In this study, endometrial thickness was increased in women using anticoagulants compared to women who used antiplatelet and never used drugs.

Cardiovascular disease and peripheral arterial diseases are common in postmenopausal women. Most of these patients are treated with medications such as antiplatelets or antiplatelets [18]. These drugs can lead to changes that the frequency, regularity or flow volume of the normal menstrual cycle, which affects the quality of life. Anticoagulation therapy can often cause heavy menstrual bleeding, inter-menstrual bleeding, prolonged menstrual bleeding, or postmenopausal bleeding [19]. This can impair a woman's physical, social, and emotional state. The conditions listed above increase the risk of recurrence, leading to early discontinuation of anticoagulants and incomplete treatment in women with acute venous thromboembolism [VTE] [20]. In cases where bleeding is minimal, the patient may not notice this and this may manifest as thickening in the endometrium. Consequently, understanding the effects of anticoagulant and antiplatelet agents on menstrual bleeding is important for clinicians managing women with acute VTE, but a more important point is that the drugs used can create a false thickness in the endometrium secondary to microscopic hemorrhage before causing visible bleeding.

Hemostasis in the endometrium is a well-regulated multifactorial process, including the coagulation cascade. Endometrial cancer screening was firstly performed by Osmers et al. in the asymptomatic postmenopausal patient population, they argued that endometrial thickness should be < 8 mm in asymptomatic postmenopausal women without endometrial pathology [21]. In many similar studies, the accepted limit value for pathological endometrium thickness varies between> 5 mm and> 8 mm [15, 22, 23]. Some studies have revealed that endometrial thickness is thicker in patients using antihypertensive drugs than those who do not [24-27]. However, although it is not certain whether this effect is due to drugs or as a result of direct hypertension, the studies of Okman-Kılıc and Kucuk [25] and Alcazar [24] have shown that the antihypertensive drugs used can increase the endometrial thickness. In this study, it was shown that endometrial thickness increased in asymptomatic postmenopausal patients using anticoagulants compared to non-using patients. In a study involving a hypothetical cohort of asymptomatic postmenopausal women, it was reported that endometrial thickness > 11 mm in patients without hormone replacement therapy carries 6.7% risk of endometrial cancer. In asymptomatic patients with a thin endometrium [<11 mm] cancer risk was calculated as ‰ 0.02 [28]. For this reason, if symptomatic postmenopausal women with endometrial thickness of 5 mm are performed for endometrial cancer of 7.3%, it is argued that the endometrial thickness that will require biopsy in asymptomatic cases should be> 11 mm. We predict that there may be false endometrial thickness increase in asymptomatic postmenopausal patients due to anticoagulant and antiplatelet use. Therefore, we concluded that the indication for biopsy should be 5 mm and above because the endometrial thickness was measured as 5 mm and above in all patients with endometrial cancer and endomeric hyperplasia in this study.

Our study contains some limitations. Firstly, although the endometrial thickness-cancer relationship has been proven, there is no data on the ultrasound image of the endometrium in asymptomatic women with endometrial cancer [28]. Most of the studies performed to date are based only on the endometrial thickness-cancer relationship. In our study, we only considered the thickness of the endometrium. Three-dimensional ultrasonography may be helpful in re-evaluating the endometrium completely topographically. Secondly, the retrospective nature of the study and the limited number of cases.

Conclusion

In daily practice, indication of endometrial sampling should be more selective, especially in the group of patients using anticoagulants or antiplatelets. The generally accepted endometrial thickness was not statistically observed in all three groups in this study. On the other hand when the groups were evaluated within themselves, the endometrial thickness was found to be thinner in the HCG and in the APG users compared to the patients using ACG.

## Disclosure

Authors have no potential conflicts of interest to disclose.

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