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CLINICAL ARTICLE

Threshold for endometrial sampling among postmenopausal patients without vaginal bleeding

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ABSTRACT

Objective: To provide an optimum threshold for endometrial biopsy sampling among postmenopausal women without vaginal bleeding and an incidentally-found endometrial lining of above 4 mm. *Methods:* A cohort of postmenopausal women (aged ≥50 years) who underwent pelvic ultrasonography at a tertiary US hospital for indications other than vaginal bleeding was retrospectively evaluated. Women were included if they had an endometrial lining of above 4 mm. Logistic regression was performed to determine the probability of endometrial carcinoma and atypical hyperplasia at each increasing millimeter of endometrial thickness from 4 to 20 mm. *Results:* Among 462 women, carcinoma was identified in 9 (1.9%) and atypical hyperplasia in 7 (1.5%). An endometrial thickness of or above 14 mm was significantly associated with atypical hyperplasia (odds ratio 4.29; 95% confidence interval 1.30–14.20; $P = 0.02$), with a negative predictive value of 98.3%. A thickness of or above 15 mm was associated with carcinoma (odds ratio 4.53; 95% confidence interval 1.20–17.20; $P = 0.03$), with a negative predictive value of 98.5% and a 0.06% risk of cancer. *Conclusion:* Irrespective of conventional risk factors, an incidentally-found thickened endometrial lining of less than 15 mm might not warrant endometrial biopsy sampling among postmenopausal women without vaginal bleeding.

1. Introduction

Endometrial carcinoma is the most common gynecologic cancer in the USA [1]. In the general population, the annual incidence of endometrial cancer was 25.1 per 100 000 women in 2008–2012, and has been increasing since then [1]. Several studies have demonstrated that transvaginal pelvic ultrasonography in women with postmenopausal bleeding yields a sensitive and cost-effective first assessment of the endometrium [2–6]. Endometrial sampling is deemed unnecessary when the endometrial thickness is 4 mm or less, because the risk of cancer below this threshold is extremely low, quantified as 0.07% in previous studies [4,5,7–11].

Although pelvic ultrasonography should not be used as a screening test for endometrial cancer [12–15], ultrasonography is commonly ordered for postmenopausal patients who have gynecologic complaints or abnormal physical examination findings. Endometrial lining thickness is generally measured routinely as part of the imaging study, and physicians can then have to manage a thickened endometrium in patients without postmenopausal bleeding. However, the management of postmenopausal women with a thickened endometrial lining identified incidentally has yet to be standardized.

Current guidelines state that the threshold of 4 mm for biopsy sampling in patients with postmenopausal bleeding should not be extrapolated to asymptomatic women because their risk of cancer and atypical hyperplasia is considerably lower [6,16]. Previous studies [4,17–19], all with fairly small sample sizes, have proposed biopsy thresholds of 4–15 mm. In a study of 283 postmenopausal patients without vaginal bleeding, Osmers et al. [17] reported no cases of endometrial cancer when the endometrial thickness was below 4 mm. A threshold of 6 mm was proposed by Schmidt et al. [18] in a prospective study of 304 asymptomatic postmenopausal women who underwent hysteroscopy after ultrasonography revealed an endometrial thickness of above 6 mm. Using a theoretical cohort of postmenopausal women aged 50 years and older, Smith-Bindman et al. [4] determined that a threshold of 11 mm yielded a similar risk of cancer as the 5-mm threshold in women with postmenopausal bleeding. Menzies et al. [19] confirmed the applicability of an 11-mm threshold in their retrospective chart review of 142 asymptomatic postmenopausal women. Through the use of a logistic regression model, they determined that the probability of endometrial cancer in women with postmenopausal bleeding and an endometrial thickness of 4 mm was the same as that in women without bleeding and a thickness of 15 mm.

The present study aims to evaluate a retrospective cohort to provide an optimal threshold for endometrial sampling among postmenopausal women with an incidentally-found endometrial lining thickness of more than 4 mm.

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2. Materials and methods

A retrospective cohort review was undertaken of all postmenopausal women who underwent transvaginal pelvic ultrasonography for indications other than vaginal bleeding at Magee-Womens Hospital, a tertiary referral hospital in Pittsburgh, PA, USA, between 2008 and 2013. Women were included if they were aged 50 years or more, were menopausal, had no history of postmenopausal bleeding, and had an endometrial thickness (maximum anterior–posterior thickness on a midline sagittal image of the uterus) of at least 4 mm. An age of 50 years was selected to efficiently identify postmenopausal patients. Candidates were considered to be postmenopausal if it was clearly reported in their medical record. Women were excluded if they had a history of endometrial hyperplasia or carcinoma, tamoxifen use, oral or transdermal hormone replacement therapy, endometrial ablation, or hereditary cancer syndrome. Cases of suboptimal imaging quality or women in whom the endometrial lining could not be accurately measured were excluded. Such cases included cavity distortion by uterine fibroids, acoustic shadowing by pelvic viscera such as bowel or adnexal masses, or a large habitus. Finally, patients were excluded when endometrial pathology results obtained from hysterectomy specimens or endometrial sampling (office biopsy sampling or dilation and curettage) were not available. Institutional review board approval with a waiver of informed consent was obtained.

A logistic regression analysis was applied to determine the probability of endometrial carcinoma and atypical hyperplasia at each increasing millimeter of endometrial thickness from 4 mm to 20 mm. Similar to the formula used by Smith-Bindman et al. [4], the risk of cancer or atypical hyperplasia for women with an endometrial lining at or below a specific thickness was defined as the false negatives divided by the sum of the false and the true negatives. Conversely, the risk of cancer or atypical hyperplasia for women with an endometrial thickness above a specific threshold was defined as the true positives divided by the sum of the true and false positives.

Epidemiologic variables were also collected, including age, gravidity, parity, body mass index, age of menopause, and histories of hypertension, diabetes mellitus, and hyperlipidemia. These factors were incorporated into a multivariable analysis to determine their association with endometrial thickness, hyperplasia, and carcinoma. The appearance of the endometrial lining as described in ultrasonography reports was also recorded and incorporated into a separate multivariable analysis to determine the association between ultrasonographic appearance and endometrial carcinoma and atypical hyperplasia.

Statistical analyses were conducted using Stata version 12.0 (Stata Corp, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

3. Results

Of the 2273 charts reviewed, 462 cases met the criteria for further analysis. The study cohort characteristics are summarized in Table 1. The five most common indications for pelvic ultrasonography were history of ovarian cysts (109 [23.6%]), pelvic pain (67 [14.5%]), previous abnormal imaging study (50 [10.8%]), history of uterine fibroids (46 [10.0%]), and history of both ovarian cysts and uterine fibroids (42 [9.1%]).

A total of 435 (94.2%) participants had benign pathology, including 192 (41.6%) women with endometrial polyps. Hyperplasia was found in 18 (3.9%) women, of which 7 (1.5%) had hyperplasia with atypia. Nine (1.9%) women were found to have endometrial carcinoma.

The mean endometrial thickness was 8.9 ± 4.2 mm (range 4.2–29.0). Participants with a histologic diagnosis of atypical hyperplasia had a mean endometrial thickness of 12.8 ± 7.7 mm (range 5.9–27.5). The mean endometrial thickness of those with endometrial carcinoma was 11.4 ± 5.6 mm (range 5.0–20.9).

Table 1
Patient characteristics (n = 462).[a]

Characteristic	Value
Age, y	59 ± 8 (50–87)
Gravidity	2.1 ± 1.6 (0–8)
Parity	1.7 ± 1.3 (0–6)
Ethnic origin	
White	426 (92.2)
African American	26 (5.6)
Asian	2 (0.4)
Hispanic	0
Other	8 (1.7)
Body mass index[b]	29.5 ± 6.2 (18–60)
Tobacco use	109 (23.6)
Diabetes mellitus	60 (13.0)
Hypertension	205 (44.4)
Hyperlipidemia	160 (34.6)

[a] Values are given as mean ± SD (range) or number (percentage).
[b] Calculated as weight in kilograms divided by the square of height in meters.

The logistic regression analysis indicated that an endometrial thickness of or above 14 mm was significantly associated with atypical hyperplasia (odds ratio 4.29; 95% confidence interval [CI] 1.30–14.20; $P = 0.02$). Further, an endometrial thickness of or above 15 mm was significantly associated with endometrial carcinoma (odds ratio 4.53; 95% CI 1.20–17.20; $P = 0.03$). Below these thresholds, there was no statistically significant risk of endometrial hyperplasia or carcinoma (data not shown).

The sensitivity of ultrasonography for atypical hyperplasia at a threshold of or above 14 mm was 36.4%, whereas the specificity, positive predictive value, and negative predictive value were 88.2%, 7.1%, and 98.3%, respectively. At a threshold of or above 15 mm, the sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonography for carcinoma were 33.3%, 90.0%, 6.4%, and 98.5%, respectively.

The number needed to treat for atypical hyperplasia at a threshold of 14 mm was 68 women, whereas below this threshold, 118 women would undergo endometrial biopsy sampling. In cases of carcinoma, 46 women would be subjected to biopsy at a threshold of 15 mm, whereas below this threshold, 1477 women would need to undergo endometrial sampling to detect one case of cancer.

The risk of cancer and atypical hyperplasia for each increasing millimeter of endometrial thickness between 4 and 20 mm is shown in Table 2.

Table 2
Risk of cancer or atypical hyperplasia.

Endometrial lining thickness, mm	Risk of cancer at or below threshold, %[a]	Risk of cancer above threshold, %[b]	Risk of atypical hyperplasia at or below threshold, %[a]	Risk of atypical hyperplasia above threshold, %[b]
5	0.02	2.11	0.03	2.53
6	0.03	2.26	0.03	2.79
7	0.03	2.79	0.03	3.09
8	0.03	2.86	0.03	3.28
9	0.03	2.82	0.03	3.32
10	0.03	2.79	0.03	2.74
11	0.03	3.70	0.04	3.63
12	0.04	3.62	0.05	4.74
13	0.05	4.34	0.07	5.68
14	0.06	5.40	0.08	7.07
15	0.06	6.41	0.11	8.40
16	0.06	5.86	0.12	11.50
17	0.09	6.41	0.18	12.60
18	0.12	9.76	0.24	19.20
19	0.08	12.00	0.23	23.70
20	0.11	9.32	0.34	27.40

[a] Risk of cancer or atypical hyperplasia with endometrial lining at or below a specific threshold = false negatives/(false negatives + true negatives).
[b] Risk of cancer or atypical hyperplasia with endometrial thickness above a specific threshold = true positives/(true positives + false positives).

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