Anatomic Pathology / THE EFFECT OF BETHESDA 2001 ON REPORTING OF ENDOMETRIAL CELLS

Reporting Endometrial Cells in Women 40 Years and Older
Assessing the Clinical Usefulness of Bethesda 2001

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Abstract

We assessed the usefulness of revised Bethesda System reporting of exfoliated benign endometrial cells (EMs) in postmenopausal women. Cervicovaginal cytology specimens with benign EMs in postmenopausal women and “out-of-phase EMs” in premenopausal women 40 years and older were identified. Cases with histologic follow-up within 12 months were selected.

There was tissue follow-up for 130 postmenopausal women: 10 (7.7%) had significant findings (endometrial adenocarcinoma, 6 [2 (33%) in asymptomatic women]; complex atypical endometrial hyperplasia [CAH], 3; leiomyosarcoma, 1); 20 were receiving hormone replacement therapy (HRT; n = 15) or tamoxifen (n = 5); 2 (10%) had significant pathology (endometrial adenocarcinoma, 1; CAH, 1). Eight not taking hormones (7.3%) had significant pathology (adenocarcinoma, 5; CAH, 2; leiomyosarcoma, 1). There were follow-up data for 96 premenopausal women; only 1 (who had vaginal bleeding) had significant pathology (CAH).

The difference in incidence of preneoplastic and neoplastic conditions after a cytologic interpretation of “benign EM” between postmenopausal and premenopausal women was significant (P ≤ .025); There was no difference between postmenopausal women receiving or not receiving HRT (P > .05). Reporting benign EMs for premenopausal women 40 years and older has no clinical significance but does for postmenopausal women, regardless of HRT and symptoms.

Benign-appearing endometrial cells commonly are seen in cervicovaginal cytologic (CV) specimens obtained from women of reproductive age in the proliferative phase (days 1-14) of the menstrual cycle. Historically, the presence of “cytologically benign-appearing” endometrial cells, outside the proliferative phase and in postmenopausal women, was reported to the clinician regardless of patient age. With the inception of the 1991 Bethesda System for the reporting of CV abnormalities, the reporting of benign endometrial cells was modified to state the presence of exfoliated endometrial cells only in postmenopausal women.1 This revision was based on the findings of several studies that suggested that spontaneously exfoliated benign endometrial cells might indicate endometrial pathology in postmenopausal women, necessitating endometrial sampling.2-7 Furthermore, it has been noted that while most women with endometrial adenocarcinoma are symptomatic, in a small portion of women, exfoliated benign endometrial cells in a CV specimen might be the only sign of underlying endometrial pathology; thus, their presence requires further investigation.2,6,8

In 2001, the reporting of benign endometrial cells was further modified (TBS 2001) to include all women 40 years and older.9 The rationale behind this change was that an individual woman’s risk factors for endometrial adenocarcinoma, the clinical symptoms, hormonal intake history, menopausal status, and the date of the last menstrual period (LMP) often are unclear or unavailable to the cytopathology laboratory. Thus, the significance of exfoliated benign endometrial cells can be interpreted only by the clinician.

A major concern with the reporting of cytologically benign-appearing endometrial cells in all women 40 years and older has been the potential for unnecessary clinical
concern and intervention because more recent outcome studies have shown that this finding in premenopausal women has no clinical relevance and, in many cases, creates a management dilemma for clinicians. In addition, many older studies showing the association of exfoliated benign endometrial cells with endometrial adenocarcinoma were based on data obtained before the widespread use of exogenous hormonal replacement therapy (HRT) and hormonal treatment with tamoxifen. Recently, HRT was shown to be associated with an increased prevalence of exfoliated benign endometrial cells on CV specimens and a lower incidence of endometrial pathology in comparison with specimens from women who did not use HRT. The converse was true for patients taking tamoxifen. In this group, the presence of benign endometrial cells on CV smears was associated with an increased risk of the development of endometrial adenocarcinoma.

We studied the clinical significance of modifying the reporting of endometrial cells in TBS 2001 by comparing the outcome in postmenopausal women with premenopausal women 40 years and older. We also evaluated the clinical significance of exfoliated benign endometrial cells in CV specimens in women receiving hormonal therapy.

Materials and Methods

The computerized databases of New York University Medical Center and Bellevue Hospital, New York, NY, were searched for cases from January 1998 to June 2002 with CV specimen (liquid-based cytology and conventional Papanicolaou smear) interpretations of “endometrial cells” in postmenopausal women and “endometrial cells out of phase” or “endometrial cells, not otherwise specified” in premenopausal women 40 years and older. The term endometrial cells, not otherwise specified was used for women with an unknown LMP date. Samples from postmenopausal women with unknown hormonal intake status and from women with atypical or malignant endometrial cells in CV specimens and menstrual smears with known LMPs were excluded from the study. Only samples from women with known follow-up histologic examination (endometrial curettage, endometrial biopsy, polypectomy, myomectomy, or hysterectomy) within 12 months of the CV specimen were included. Hormonal intake history and symptoms (eg, vaginal bleeding, pelvic mass) were obtained from CV specimen and surgical pathology requisition forms.

Two groups were created: group 1, samples from postmenopausal women with endometrial cells on CV specimens; group 2, samples from premenopausal women 40 years and older with endometrial cells out of phase or endometrial cells, not otherwise specified on CV specimens. The outcomes in groups 1 and 2 were compared. In addition, group 1 was divided into women receiving (group 1A) and women not receiving (group 1B) HRT or tamoxifen. The 2 subgroups in group 1 were compared. Statistical analysis was performed using the $\chi^2$ test.

Results

Clinical Data

We identified 576 cases in group 1. Follow-up histologic data were available for 130 women (22.6%). We identified 624 cases in group 2. Follow-up histologic data were available for 96 (15.4%). In group 1, 25 women had vaginal bleeding (4.3%); 1 woman was receiving HRT. In group 2, 12 women had vaginal bleeding (1.9%).

Cytohistologic Data

Group 1

Results are summarized in Table 1. Of 130 women, 25 (19.2%) had no pathologic findings, 95 (73.1%) had benign findings, and 10 (7.7%) had significant pathologic findings. The benign findings included 64 endometrial polyps and 31 leiomyomas. The significant findings included 6 cases of endometrial adenocarcinoma, 3 of complex atypical endometrial hyperplasia, and 1 of leiomyosarcoma. Of the 6 endometrial adenocarcinomas, 2 (33%) occurred in asymptomatic women.

Of 130 cases with follow-up data, 110 were included in group 1A and 20 in group 1B.

Group 1A

Results are summarized in Table 2. Of 110 patients, 14 (12.7%) had no pathologic findings and 88 (80.0%) had benign findings, including 58 endometrial polyps and 30 leiomyomas. Eight cases (7.3%) had significant pathology, including 5 cases of endometrial adenocarcinoma, 2 of complex atypical endometrial hyperplasia, and 1 of leiomyosarcoma.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Histologic Follow-up in Women With Benign Endometrial Cells on Cervicovaginal Smears: Comparison of Postmenopausal Women With Premenopausal Women 40 Years and Older*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n = 130)</td>
</tr>
<tr>
<td>No pathologic findings</td>
<td>25 (19.2)</td>
</tr>
<tr>
<td>Benign pathologic findings</td>
<td>95 (73.1)</td>
</tr>
<tr>
<td>Preneoplastic and neoplastic conditions†</td>
<td>10 (7.7)</td>
</tr>
</tbody>
</table>

* Group 1, postmenopausal women; group 2, premenopausal women 40 years and older. Data are given as number (percentage).
† P ≤ .005.
Results are summarized in Table 2. Eleven (55%) had no pathologic findings, and 7 (35%) had benign findings, including 6 endometrial polyps and 1 leiomyoma. Two (10%) had significant pathology, including 1 endometrial adenocarcinoma and 1 complex atypical endometrial hyperplasia. Both of these cases occurred in women receiving HRT. No preneoplastic or neoplastic lesions were detected in women taking tamoxifen.

Group 2
Results are summarized in Table 1. Of 96 cases, 48 (50%) had no pathologic findings, 47 (49%) had benign findings, and 1 (1%) had significant pathology. The benign findings included 27 endometrial polyps, 18 leiomyomas, 1 chronic endometritis, and 1 simple endometrial hyperplasia without atypia. The significant case showed complex atypical endometrial hyperplasia. This patient had vaginal bleeding.

Summary of Findings
The incidence of preneoplastic and neoplastic conditions after a cytologic interpretation of benign endometrial cells was higher in postmenopausal women than in premenopausal women 40 years and older (P ≤ 0.025). Only 1 woman had complex atypical endometrial hyperplasia in group 2, and she was asymptomatic with vaginal bleeding. A diagnostic procedure was done regardless of the CV specimen findings. There was no difference in the incidence of preneoplastic and neoplastic conditions in postmenopausal women receiving or not receiving hormonal therapy (P > 0.05).

Discussion
The 1991 Bethesda System recommended reporting of exfoliated benign endometrial cells in postmenopausal women only. The 2001 Bethesda System was revised to include reporting exfoliated benign endometrial cells in all women 40 years and older regardless of the date of the LMP. This change was deemed necessary because menstrual status, exogenous hormone therapy, and other clinical risk factors associated with endometrial adenocarcinoma often are unknown to the laboratory. However, the proper clinical management of exfoliated benign endometrial cells noted in CV specimens is controversial. This is due mostly to the markedly variable reported incidences (0.8%-12%) of atypical endometrial hyperplasia and endometrial adenocarcinoma detected in postmenopausal women after a cytologic finding of exfoliated endometrial cells in CV specimens. This issue becomes even more complicated for postmenopausal women who are asymptomatic or receiving HRT and for women who have not yet entered menopause. Thus, the clinical usefulness of reporting exfoliated endometrial cells as outlined in the TBS 2001 is being debated.

Our study indicated that the reporting of benign endometrial cells on CV smears in premenopausal women 40 years and older has no clinical relevance. Only 1 premenopausal woman (1%) in our study had significant endometrial pathology. This woman had vaginal bleeding, and, thus, further workup was initiated regardless of the CV smear finding. This contrasts with postmenopausal women in whom significant endometrial pathology was noted in 7.7%. Furthermore, 33% of the postmenopausal women with endometrial adenocarcinoma (2/6) were asymptomatic. Our results for postmenopausal women are in agreement with previously reported data.2,3,5,6,16-20

More recently, a review of the abstracts presented at the 2004 American Society of Cytopathology meeting revealed 5 studies that evaluated the clinical significance of reporting endometrial cells in women 40 years and older.21-25 All investigators unanimously reported the incidence of clinically significant endometrial lesions (hyperplasia and adenocarcinoma) in premenopausal women to be very low, ranging from 0% to 1.4%. In addition, all adenocarcinomas detected were associated with symptoms, and in each case, symptoms preceded the cytologic findings in defining the clinical management.23,24 TBS 2001 led to an increase in the number of women who underwent endometrial sampling as a result of decreasing the age cutoff for reporting of endometrial cells to 40 years.21,22 The increase in the number of endometrial sampling procedures occurred despite an educational note on the cytology report about the uncertain clinical implications of this finding in premenopausal women.22

The management of asymptomatic women with exfoliated benign endometrial cells in their CV specimens is not well defined. Most women with endometrial hyperplasia and adenocarcinoma have vaginal bleeding, but a minority are asymptomatic.2,5,8 In our study, in contrast with premenopausal women 40 years and older, one third of postmenopausal women with endometrial adenocarcinoma were asymptomatic.
The incidence of endometrial adenocarcinoma in asymptomatic women who have normal endometrial cells in their CV specimens ranges from 1% to 4.3%. Some recommend endometrial evaluation for all asymptomatic postmenopausal women with normal endometrial cells in their CV specimens. Others advocate no additional follow-up for asymptomatic women based on negative long-term follow-up. In a study of 44 asymptomatic women who had exfoliated endometrial cells in their CV smears with a 3-year follow-up, Gomez-Fernandez et al had no cases with endometrial hyperplasia or adenocarcinoma. The authors emphasized that the reporting of normal endometrial cells in CV specimens creates unnecessary patient anxiety and leads to unjustifiable diagnostic procedures. Ashfaq et al found significant pathology in 12% of postmenopausal women with normal endometrial cells in CV specimens, but all women had abnormal vaginal bleeding. Our study indicates that postmenopausal women who are asymptomatic and have exfoliated endometrial cells in CV specimens require further evaluation, whereas this finding may be ignored in asymptomatic premenopausal women.

Another controversial area is the significance of benign endometrial cells in CV specimens of postmenopausal women receiving HRT. We found no difference in the incidence of endometrial preneoplasia and neoplasia in postmenopausal women receiving HRT and those not receiving HRT. Our results are similar to those reported by Yancey et al. Others have reported a lower incidence of endometrial pathology in postmenopausal women receiving HRT. Ashfaq et al noted significant endometrial pathology (hyperplasia with atypia and adenocarcinoma) in 2% of postmenopausal women receiving HRT vs 9% of postmenopausal women not receiving HRT. Mount et al reported that despite the increased prevalence of benign endometrial cells in CV smears of postmenopausal women receiving HRT, the incidence of endometrial pathology was very low. It is noteworthy to clarify that these authors defined endometrial pathology to include endometrial polyps, simple and complex endometrial hyperplasia with and without atypia, and endometrial adenocarcinoma. In fact, there was no significant difference in the prevalence of endometrial adenocarcinoma between postmenopausal women with benign endometrial cells in CV smears who received HRT and those who did not (1.5% vs 3.7%; P = .175). Brogi et al did not identify any cases of atypical or complex endometrial hyperplasia or adenocarcinoma in 22 postmenopausal women who had endometrial cells in their CV specimens while receiving HRT.

A caveat of our study and of the study by Brogi et al is the low number of postmenopausal women receiving HRT for whom tissue follow-up was available. However, based on the data presented herein, it is our opinion that postmenopausal women receiving HRT who shed benign endometrial cells should undergo endometrial sampling.

The literature on follow-up of women who are taking tamoxifen and have exfoliated benign endometrial cells in their CV specimens is scant. Tamoxifen is a nonsteroidal antiestrogen used in the treatment of breast cancer. The presence of endometrial cells in the CV specimens of women taking tamoxifen is associated with a higher risk of development of endometrial adenocarcinoma. Abadi et al showed that the diagnosis of endometrial adenocarcinoma was preceded by exfoliated endometrial cells in CV specimens in 28% of women with breast cancer treated with tamoxifen in comparison with 7% of women with breast cancer and tamoxifen therapy who did not develop endometrial carcinoma. We did not find any cases of endometrial hyperplasia or adenocarcinoma in women who were taking tamoxifen in our study. However, the number of women taking tamoxifen was limited.

Our findings indicate that the reporting of benign endometrial cells in CV cytology specimens of premenopausal women 40 years and older has no clinical significance. This is in contrast with findings for postmenopausal women. Postmenopausal women who shed cytologically normal-appearing endometrial cells have a significant risk of preneoplastic and neoplastic endometrial disease regardless of their hormonal intake status and lack of symptoms. Therefore, although premenopausal women can be safely followed up conservatively in the absence of symptoms, all postmenopausal women with spontaneously exfoliated endometrial cells in their CV specimens should undergo endometrial sampling regardless of HRT status and symptoms.

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References


