Endometrial Cells in Cervical Cytology: Review of Cytological Features and Clinical Assessment

David L. Greenspan, MD, Marina Cardillo, MD, Diane D. Davey, MD, Debra S. Heller, MD, and Ann T. Moriarty, MD

1Department of Obstetrics and Gynecology, Maricopa Medical Center, Affiliate of The University of Arizona College of Medicine, 2601 East Roosevelt Street, Phoenix, AZ 85008; 2Anatomic Pathology, Quest Diagnostics, Teterboro, NJ; 3Department of Pathology and Laboratory Medicine, University of Kentucky, Medical Center, Lexington, KY; 4Department of Pathology and Laboratory Medicine, University of Medicine and Dentistry of New Jersey, Newark NJ; and 5Ameripath Indiana, Indianapolis, IN

Abstract: The 2001 Bethesda System for Reporting Cervical Cytology recommends reporting benign exfoliated endometrial cells in women age 40 and older, and a review of the literature supports this recommendation. Stromal cells and histiocytes do not need to be reported. The effect of hormonal therapy on endometrial shedding is reviewed. Clinical information should be provided to the laboratory so that appropriate educational notes can be appended to the cytology report. Benign endometrial cells in premenopausal women in the first half of the cycle are not associated with significant pathology and such women do not need additional evaluation. Significant pathology is also unlikely in the second half of the cycle and evaluation may not be required unless clinically indicated. Initial evaluation of other women with benign endometrial cells may include either endometrial sampling or transvaginal ultrasound. Atypical endometrial cells are associated with a higher rate of significant pathology and should lead to additional evaluation. Additional prospective studies on the management of patients with endometrial cells on Pap tests are needed.

Key Words: endometrial cells, atypical glandular cells, endometrial adenocarcinoma, cervical cytology (Pap test), Bethesda System, transvaginal ultrasound

The Pap test has performed most effectively in screening for squamous cervical carcinoma and its precursor lesions; reporting benign appearing/normal endometrial cells on Pap tests has been controversial. The Bethesda System (TBS) continues to update its recommendations and guidelines. The most current reporting system, TBS 2001, recommends reporting benign/normal endometrial cells in women 40 years or older [1]. This recommendation is controversial and challenged by recent reports. There are no rigorous scientific studies investigating the significance of endometrial cells identified in Pap tests. There are few prospective controlled studies addressing this issue. The studies are complicated by retrospective biases, lack of histological follow up in many cases, wide age ranges, unstated or varied criteria defining menopause, different definitions of lesions considered pathologically significant, and lack of documentation as to the type of endometrial cells being reported (glandular or stromal).
After an extensive review of the available literature in this area we address a number of issues related to endometrial cells detected on the Pap test:

1. The prevalence of endometrial cells on Pap tests
2. The morphologic differential diagnosis of endometrial cells including stromal cells, histiocytes, exfoliated versus abraded endometrial cells as well as atypical endometrial cells.
3. The significance of endometrial cells in the first or second half of the menstrual cycle in menstruating women and the effect of different sampling devices.
4. The endometrial lesions seen when exfoliated endometrial cells are detected on Pap tests and associated clinical risk factors
5. The significance of age, menopausal status, and symptomatic versus asymptomatic patients when endometrial cells are detected.
6. The effect and significance of hormone replacement therapy, tamoxifen, and some forms of birth control on endometrial cells on Pap tests.
7. Management options for patients with exfoliated endometrial cells on Pap tests
8. The evaluation of the current recommended guidelines in reporting endometrial cells on cervical cytology
9. Areas for further clinical studies.

**PREVALENCE**

It is difficult to get an accurate rate of endometrial cells recognized on the Pap test because the total population studied is not defined in many studies. The age of the screened population, which affects the prevalence of endometrial cells found in that population, is often not clarified. A study by Mount showed that of 52,662 Paps from postmenopausal women, 589 were identified with benign endometrial cells (1.1%) [2]. More recent abstracts reported endometrial cells on 1.8% and 0.5% of Pap tests in women 40 years and older [3, 4]. However, many of these women with endometrial cells on Pap tests (61%) had their Pap test collected in the first 14 days of the menstrual cycle [3]. Excluding women who were menstruating at the time of their Pap tests, Kerpsack et al identified endometrial cells in 61 of 119,00 Pap tests (0.05%) and of these 31 (60%) were benign endometrial cells [5]. A most recent report by Thrall et al examined 63,202 Pap tests and found 3% of women 40 years and older contained benign endometrial cells [6].

In a study by Cherkis, 440 of 700,000 Pap tests screened demonstrated benign endometrial cells either in the second half of the menstrual cycle or in postmenopausal women for a frequency of about 1/1600 [7]. Higher rates may be associated with symptomatic (bleeding) postmenopausal women [8]. In comparison, the median reporting rate for all types of atypical glandular cells, without regard to endometrial versus endocervical origin, was 0.2% in a recent large laboratory questionnaire survey [9]. Chihieng has reported atypical endometrial cells in 0.03% of Pap tests and that accounted for only 5.25% of all atypical glandular cells [10]. A recent report have also shown atypical endometrial cells in about 0.1% of Pap tests in women 40 and older [6].

**MORPHOLOGY**

Endometrial cells, as described in Bethesda 2001 terminology, include both glandular and stromal cells exfoliating in ball or gland-like clusters, rarely as single cells [11]. Abraded endometrial cells from the lower uterine segment, and cells that can be identified as histiocytes or stromal in origin should not be reported as endometrial cells as they do not carry the same risk for endometrial pathology. In the first half of the menstrual cycle, endometrial cells often have a double contour with glandular cells surrounding a core of stromal cells (“exodus”). Normal endometrial nuclei are small, no larger than an intermediate nucleus, and are either round or bean-shaped. The chromatin pattern may be difficult to discern in the cell groups, but nucleoli are usually inconspicuous and nuclei may be degenerated [11]. Cytoplasm is scant, basophilic, and often wispy or occasionally vacuolated. Cell borders are not well defined, and the cells frequently appear to be packed together [12] (Fig. 1). The background is often bloody and may contain histiocytes and endometrial stromal cells. In liquid based preparations, three-dimensional cell clusters are common, with the plane of focus often above the plane of the normal squamous cells [11]. Single cells may be more commonly seen, and the background is usually cleaner with less blood. Nuclear chromatin detail may be more easily discerned, and single cell necrosis (apoptosis) is common within exfoliated cell groups. The differential diagnosis of exfoliated endometrial cells includes abraded endometrium, endocervical cells, inflammatory cells, stromal cells, and parabasal or reserve cells. Directly sampled or abraded endometrium is more common with vigorous sampling of the cervical canal and after excisional procedures; biphasic tissue fragments showing branching glands admixed with stroma containing vessels are observed [11].
Endocervical cells are generally larger than endometrial cells, columnar in shape with apical nuclei, and present in honeycomb sheets or strips. The nuclei are round to oval, slightly larger than intermediate nuclei, and exhibit a vesicular chromatin pattern [12]. Lymphocytes are distinguished from endometrial cells by their distinct coarse chromatin pattern. Histiocytes occur as individual cells or loose clusters, have bean-shaped nuclei, and may contain debris; they may vary in size and number of nuclei. Endometrial stromal cells include both superficial and deep varieties. Superficial stromal cells are indistinguishable from loose clusters of histiocytes and have oval or bean-shaped nuclei. Deep stromal cells are spindle-shaped with scant cytoplasm and may show nuclear grooves. Parabasal cell clusters have nuclei resembling other squamous nuclei and more distinct and dense cytoplasm. Parabasal cells are usually present in sheets or small clusters instead of balls. Some older women may have clusters of bare “naked” nuclei that may be confused with endometrial cells. Such naked nuclei have a bland chromatin pattern and are thought to arise from reserve or parabasal cells [11]. These naked nuclei have been described in patients receiving Tamoxifen therapy; they are easily identified in contrast to the relative estrogenization of the background squamous cells.

Atypical endometrial cells generally occur in small three-dimensional clusters of about 5–20 cells [13, 14]. Nuclei are mildly to moderately enlarged and may be slightly hyperchromatic. However, nuclei are generally smaller than atypical endocervical cells and adenocarcinoma cells. Small nucleoli may be present. Cell borders are usually poorly defined and cytoplasm may be vacuolated [13, 14]. In liquid based preparations, hyperchromasia and nucleoli are more frequent, and chromatin pattern is more easily discerned.

It may be difficult to differentiate benign and atypical endometrial process, especially when cells show degradative features. This should not be surprising as endometrial cells may be shed in a broad spectrum of benign to malignant lesions. The differential diagnosis of atypical endometrial cells includes benign exfoliated endometrial cells, other types of atypical glandular and squamous processes, and adenocarcinoma. There is considerable interobserver variability in diagnosis of atypical glandular cells in general [15, 16]. Some studies have also documented high-grade squamous cervical lesions or squamous carcinomas in women with reports of atypical endometrial cells [10].

Benign exfoliated endometrial cells may show more pleomorphic nuclei in liquid based preparations, and may lead to overcalling benign cells as atypical endometrial cells. Although atypical endocervical cells are more frequently present as sheets and strips of cells with palisading, studies have shown that there is not reliable interobserver identification of the site of origin of atypical glandular cells [16]. In liquid based preparations, both atypical endocervical and endometrial cells frequently present in 3-dimensional groups, making such differentiation even more challenging. High-grade squamous processes may also present with 3-dimensional crowded hyperchromatic cell groups, and it is helpful to look for single cells in the background to determine cell type. Endometrial adenocarcinoma shows a spectrum of appearance depending on grade and subtype. Carcinomas are more likely to show large nuclei, prominent nucleoli, hyperchromatic nuclei with chromatin clearing, and a watery tumor diathesis compared to benign processes. Cytoplasm is generally cyanophilic and may be vacuolated or contain neutrophils [14] (Fig. 2). Well-differentiated endometrioid adenocarcinoma generally shows slight nuclear enlargement and atypia, and is frequently reported as “atypical endometrial cells” by cytology. Higher grade and serous carcinoma are more likely to be classified as malignant by cytology based on the nuclear features and, therefore, not mistaken for benign appearing endometrial cells. Salomao et al. compared women with atypical endometrial cells on Pap tests and adenocarcinoma on biopsy versus those with atypical cells but benign follow-up. They found that nuclear size increased at least two times that of an intermediate cell nucleus and absence of cell clusters with irregular borders were more indicative of adenocarcinoma than a benign endometrial process. Nuclear size was seen as an especially important cytotologic feature, and it was postulated that carcinomas were more often characterized by small cell clusters or single cells [17]. Many women with proven endometrial adenocarcinoma will have negative cervical cytology or only bland endometrial cells [17, 18]. However, studies have shown that those women with malignant cells on cytology are more likely to have higher grade and advanced stage tumors [18, 19].

**STROMAL CELLS**

The significance of histiocytes on Pap tests has been controversial. In a case-control study, Blumenfeld et al attempted to quantify the numbers of histiocytes on
smears, and found that when moderate or heavy numbers were present (5-10/HPF, and >10 HPF respectively), histiocytes were more sensitive but less specific than endometrial cells on Pap tests as predictors for carcinoma [20]. However, in a study of 102 menopausal women with Paps showing features raising concern for an endometrial lesion (inflammatory changes including histiocytes, blood, elevated squamous maturation, endometrial glandular cells), Zucker et al found that neither mononucleated nor multinucleated histiocytes were predictors of endometrial pathology [21]. This is in agreement with Nguyen et al, who found that the presence of histiocytes on Pap alone did not predict endometrial hyperplasia or carcinoma [22]. Tambouret et al also found that the presence of histiocytes alone, in the absence of clinical symptoms or risk factors, did not indicate hyperplasia or carcinoma in their series of peri- and postmenopausal women, and was not an indication for an endometrial biopsy [23]. Nassar et al also reported that histiocytes alone were a poor predictor of endometrial pathology. In their study, the positive predictive value (PPV) was 5.5% for significant endometrial pathology and 1.3% for endometrial carcinoma [24].

Wen et al separated histiocytes seen on Pap tests into three types, foamy histiocytes, histiocytes resembling superficial stromal cells, and variably sized histiocytes alone or in association with inflammatory or multinucleated cells. Only the foamy histiocytes were associated with carcinoma in 2/13 (15.3%) patients [25]. There were polyps found in all three groups, and both patients with carcinoma presented with abnormal uterine bleeding. Silver et al noted that foam cells were present in a significant percentage of the cervical cytology of women with endometrial pathology, but were histologically indistinguishable from those seen in benign endometrial breakdown [26].

**ENDOMETRIAL CELLS, THE MENSTRUAL CYCLE, AND SAMPLING DEVICES**

In premenopausal women, benign endometrial cells are mostly found in the first half of the cycle, corresponding to the menstrual and early proliferative phases. Most normal endometrial cells are found during active bleeding. In a study from 1963, endometrial cells were identified only in the presence of well-preserved erythrocytes [27]. In the absence of red cells, regardless of the day of menstrual phase in which the smear was obtained, no endometrial cells were seen. Earlier studies are confounded by the type of screening used; cervicovaginal smears, vagina smears alone or endocervical aspirates.

It has been demonstrated by several studies that the use of endocervical brushing devices has improved the specimen adequacy and sampling of endocervical cells, as well as the detection of intraepithelial neoplastic lesions and glandular abnormalities in Pap tests [28]. With the use of the endocervical brushing devices it is possible to achieve a more efficient sampling of the cells from the transition zone, the endocervical canal, and inadvertent sampling of the lower uterine segment (LUS). As consequence of the sampling of the LUS, there was an increase in the incorrect interpretation of the cells from this area as glandular atypia and/or squamous lesions. Currently, most cytologists have developed more experience and are now comfortable with the appearance of the LUS (see morphology section). Since LUS is abraded endometrium, it does not have the same implications for endometrial pathology as identifying exfoliated endometrial cells. TBS recognizes this difference and recommends reporting only exfoliated endometrial cells [11].

**ASSOCIATED LESIONS, DEMOGRAPHICS AND RISK FACTORS**

Normal endometrial cells on cervical cytology are most often associated with the finding of benign endometrium. In most published studies a large percentage of patients are not evaluated, resulting in a significantly lower denominator, skewing the rates of endometrial pathology. Shedding of normal endometrial cells has been associated with the following conditions: polyps, hyperplasias with and without atypia, low and high grade adenocarcinomas, leiomyomata, atrophy, proliferative endometrium, immediate postpartum state, impending or early post abortion, acute endometritis, recent intrauterine instrumentation, IUD use, and cervical and vaginal endometriosis [29, 30]. Most high grade carcinomas or other malignant endometrial lesions will also have malignant cells or atypical cells on the Pap tests, not only benign appearing endometrial cells [18, 19, 31, 32].

In one study of 297 postmenopausal women with benign endometrial cells on Pap, 14 of 132 women undergoing subsequent endometrial biopsy (9%) were found to have endometrial lesions, of which only 3 were clinically significant (1 polyp, 5 simple hyperplasias, 5 complex hyperplasias, 2 atypical hyperplasias, one
carcinoma) [33]. In most of these cases, the endometrial cells were of histiocytic origin (stromal). In 27% of the cases, endometrial glandular cells were present either alone or along with stromal cells. The presence of endometrial glandular cells was found to indicate a five times greater risk of endometrial disease, although the sensitivity and positive predictive values were low in this study [33]. In the same paper, the authors noted that several older studies had shown higher rates of endometrial disease with benign endometrial cells on Pap tests, but pointed out that these studies only reported on women who had subsequently undergone endometrial biopsy, suggesting a selection bias.

Endometrial cells on Pap tests have been associated with normal endometrial findings in 22–97% of women, polyps in 1–41%, hyperplasias 1–20%, atypical hyperplasia in 0.6–8%, and carcinoma in 1–15% [2, 7, 33–39]. Higher rates of pathology are reported when significant lesions include benign findings such as polyps, and hyperplasia without atypia. Studies involving older patients will also have a greater frequency of carcinoma. The evaluation of the prevalence of endometrial pathology has been complicated by the fact that many studies do not have adequate controls for comparison.

While recent studies have reported endometrial disease in postmenopausal women when there were benign endometrial cells on cytology [38–40], the prevalence of endometrial pathology for premenopausal women age 40 and over are low in most series. Simsrc et al reviewed cases of both postmenopausal women with endometrial cells on Pap tests and premenopausal women age 40 and older with out-of-phase endometrial cells on Paps. Of 130 premenopausal women with subsequent endometrial biopsy, 10 (7.7%) had significant pathology (6 endometrial adenocarcinomas, 3 complex atypical endometrial hyperplasias, and 1 leiomyosarcoma). Of 96 premenopausal women, only one had significant pathology and in this case the patient presented with abnormal vaginal bleeding, which would have triggered further evaluation [41]. Gomez-Fernandez et al retrospectively reviewed Pap tests from women who had endometrial biopsies showing hyperplasia or carcinoma. This group was a mixture of premenopausal and postmenopausal women, with an age range of 31–84 years, and a mean age of 53.6. The control group was composed of postmenopausal women (36–83 years) with diagnosis other than hyperplasia or carcinoma. The authors found no significant difference in the prevalence (2% vs. 5%) of benign endometrial cells on Paps between the two groups [34].

Gomez-Fernandez also looked at a group of 206 women age 35 and over who had normal endometrial cells reported on their Pap tests. Of the 206 women, 162 had presented with abnormal bleeding, and had undergone endometrial sampling, with the finding of 10 hyperplasias and 7 carcinomas. Of the asymptomatic women who were followed for at least 3 years, none were found to have significant disease [42]. They concluded from their findings that it is appropriate for clinicians to evaluate symptomatic patients, but often disregard the presence of benign endometrial cells in the absence of symptomatology. Based on their study, Karim et al suggest that the reporting of benign endometrial cells in Pap tests of premenopausal women has little practical value [43]. A recent retrospective study found no significant difference in endometrial hyperplasia or malignancy when comparing women 40 and older or 50 and older with no endometrial cells with women with benign endometrial cells on Pap tests [6]. However, the comparison group in this study was not a true control group because the histological follow up rate for the comparison group was much lower than for the group with endometrial cells on Pap tests.

Several abstracts from the 2004 American Society of Cytopathology meeting have also reported very low rates of significant endometrial pathology in women 40 and older with benign endometrial cells on Pap tests [3, 4, 44–46]. However, an increase in performance of biopsy was noted by some, in spite of educational comments in the cytology reports. It appears that significant endometrial pathology is uncommon in premenopausal women when benign endometrial cells are present on Pap tests.

There is no literature evaluating the significance of benign endometrial cells detected in women under 40 but who have risk factors for endometrial carcinoma such as obesity, type 2 diabetes, hypertension anovulation/Polycystic Ovary Syndrome (PCOS), long term use of unopposed estrogens, tamoxifen, and genetic factors such as defects in DNA mismatch repair genes. It may be postulated that certain high risk women under 40 are at greater risk for a significant lesion if shedding endometrial cells out of phase. Studies with this stratification and sub analysis are lacking in the literature.

Associated symptoms will vary in women with significant endometrial lesions. Some women will be asymptomatic or have abnormal premenopausal bleeding and others will have postmenopausal bleeding. Many studies report groups as symptomatic or asymptomatic, but do not define the symptoms.
While the focus of this review is not about atypical endometrial/glandular cells, it is important to note that the presence of atypia increases the risk of an underlying endometrial malignancy. Atypical endometrial cells in postmenopausal women may be associated with endometrial carcinoma in 9–50% [5, 47, 48]. Cherkis showed a prevalence rate of atypical endometrial cells of about 1/1700 from a pool of 300,000 pap smears. In addition, this study noted that women over 59 had an increased frequency of carcinoma [47]. Thus, when endometrial cells are reported as atypical, women need additional evaluation.

**HORMONE REPLACEMENT THERAPY, TAMOXIFEN, AND BIRTH CONTROL**

There is controversy about the effect of hormone replacement therapy (HRT) on postmenopausal women and the presence of normal appearing endometrial cells on Pap tests. Many studies examining postmenopausal women with endometrial cells on Pap tests have lacked control groups and did not account for the presence or absence of symptoms, type, duration and dosage of HRT, and differing sampling methods. In some older studies sampling was sometimes obtained with endocervical aspiration, a procedure not used in screening. Also, past studies used vaginal pool sampling in addition to the exo and endocervix.

In a recent study (2005) Samsir et al compared pre and postmenopausal women over 40 who had endometrial cells on Pap tests and did not find any difference in endometrial pathology in the postmenopausal group using HRT. They also did not observe any cases of endometrial pathology in the group of women taking tamoxifen [41]. Cai et al reported HRT in 11 of 103 postmenopausal women that had benign endometrial cells or foamy histocytes on Paps. Only 1/11 had endometrial pathology and this was in a woman receiving tamoxifen; no endometrial pathology found in the remaining 10 [49].

Kerpsack et al reported a multivariate analysis to determine factors that impact on the diagnosis of carcinoma or hyperplasia in a group of 61 patients with endometrial cells on Pap test. Benign endometrial cells were present in 31 of these Pap tests. In the 47 patients with histological follow up there were nine with hyperplasia and 7 with carcinoma; two of the patients with benign endometrial cells had a subsequent diagnosis of carcinoma. In this study, 12 of 61 women (23%) with endometrial cells on Paps were taking estrogen therapy.

None of the carcinomas were in the patients on HRT. Independent predictors of carcinoma or atypical endometrial hyperplasia were found to be age (60 or older) at the time of the Pap, abnormal bleeding, and Pap test results(atypical or malignant endometrial cells) [5]. In a series of women with endometrial cells on Pap tests reported by Sarode, 91 of 220 women were receiving HRT and 129 were not taking HRT. Endometrial pathology was found in 43% of cases without HRT compared to 20% of those using HRT. Endometrial carcinoma was also found less frequently in the HRT group; 3.3% (1 case) compared to those without HRT 5.8% (3 cases) [37]. However, this study was limited because only 39.5% of those without HRT and 32.9% of those with HRT had histological evaluation of the endometrium.

A retrospective review of endometrial cells on Pap tests obtained during the secretory phase or in postmeno- pausal women found no significant difference in carcinoma or hyperplasia between estrogen users and non-users [35]. Montz examined 93 postmenopausal asymptomatic women on HRT noted to have endome- trial cells on Pap tests. In this study results were stratified by HRT regimen, and specific histological findings. This study reported 4% of cases with significant disease but lacked a comparison group. There was no significant difference in rate of pathology found in the group with continuous or sequential regimen. However, asymptomatic women on unopposed estrogen and shedding benign endometrial cells had a significantly greater rate of underlying endometrial pathology, but no cancer. Of the 93 asymptomatic postmenopausal women on HRT there were 2 with atypical hyperplasia, and 1 with adenocarcinoma. The one case of adenocarcinoma would have not otherwise been diagnosed except for the finding of benign endometrial cells on the Pap test [39].

Brogie et al reported endometrial pathology in 33 postmenopausal women not on HRT (18%) with endometrial cells on Pap tests and in 8.5% of women using a variety of HRT. The 2 cases of adenocarcinoma were found in the group of women not using HRT [40].

Endometrial cells may be more common on Pap tests in HRT users compared to non-users. Mount reported a large study of 52,662 Pap tests from postmenopausal women including 31% of women using HRT and 63% not using HRT (6% unknown). While there was a significant increase in the prevalence of benign endome- trial cells in the women receiving HRT compared to those not using HRT (1.52% vs. 0.097%, relative prevalence of 1.56), a higher frequency of endometrial
pathology was found in those not using HRT compared to HRT users (7.4% versus 2.6%) [2]. Although not statistically significant, more endometrial carcinomas were diagnosed in those not using HRT compared to HRT users (3.7% versus 1.5%) [2]. Other studies have found no difference in the rate of endometrial cells on Pap tests in postmenopausal women using HRT compared to those not using HRT. Ashfaq et al reported that the use of HRT did not affect the presence of benign endometrial cells on Pap tests. However, comparing a group of postmenopausal women on HRT to a group of women not on HRT, they also found that significant pathology was higher in those not using HRT (2% vs. 9%) [50]. Endometrial cells may be more frequently found on pap tests of postmenopausal women on HRT but the significance of such a finding is not useful to indicate endometrial pathology. It seems that there may even be a slightly higher rate of pathology, including carcinoma, in women not using HRT. These conclusions are based on studies that are limited by differing criteria used to define postmenopausal status, different age ranges, and lack of follow-up evaluation of the endometrium.

As for other hormonal effects, Depo-Provera (DP) use has been compared to oral contraceptive pills (triphasil-TP). Endometrial cells were not found in Pap tests of 50 DP users but were present in 1 (2%) of triphasil oral contraceptive users [51]. IUD using women were reported to have an increase in the presence of endometrial cells in Pap tests (17.2% in IUD users compared to 8.7% in those without IUD) especially during the second half of the menstrual cycle [52].

Tamoxifen use has been associated with an increased risk of endometrial pathology including hyperplasia and carcinoma especially with extended use of greater than 5 years. There is limited data suggesting that benign endometrial cells on Pap tests are significantly more frequent in patients on tamoxifen who developed endometrial carcinoma. Abadi et al examined the effects of tamoxifen in breast cancer patients and found greater number of cases with benign endometrial cells in patients on tamoxifen that subsequently developed endometrial carcinoma (10 of 36) compared to the group not on tamoxifen (4 of 34) and in the group on tamoxifen that did not develop carcinoma of the endometrium (3 of 44). In this study, the number of cases with benign endometrial cells in each group was small [53]. They conclude that all women on tamoxifen should continue to receive Pap tests and that detection of benign endometrial cells should lead to further evaluation.

There are no data available evaluating aromatase inhibitors (AI), which are being used increasingly in breast cancer treatment, and the prevalence or significance of benign appearing endometrial cells in Pap tests.

**MANAGEMENT**

If follow up is recommended, what is the appropriate management? Studies evaluating the clinical follow up of benign appearing endometrial cells on Pap tests have relied on various diagnostic methods. Considering the high rate of benign endometrial findings, most authors agree that a less invasive and costly procedure should be attempted first in the evaluation of women with benign endometrial cells on Pap tests. Therefore, endometrial sampling, hysteroscopic dilation and curettage (D&C), and transvaginal ultrasound with or without sonohysterography are the options available for immediate follow up. In-office endometrial sampling remains the initial evaluation for many women with abnormal bleeding and correlates well with dilation and curettage [54–57]. However, postmenopausal women may have inadequate sampling, non diagnostic material, or inability to be sampled due to a stenotic cervical os. Studies have evaluated the use of transvaginal ultrasound as a means to evaluate the endometrium in postmenopausal women. Karlsson et al noted no malignant endometrium thinner than 5 mm and an endometrial thickness of less than or equal to 4 mm had a 5.5% risk of endometrial pathology in postmenopausal bleeding patients [58]. A meta-analysis noted that an endometrial thickness of less than or equal to 5 mm excludes significant endometrial pathology in most postmenopausal women with bleeding, regardless of HRT. In this analysis of symptomatic postmenopausal women, 96% of cases with endometrial cancer and 92% with endometrial disease (cancer, polyps, atypical hyperplasia) had an endometrial thickness of greater than 5 mm. While the sensitivity for detecting significant endometrial pathology was not affected by HRT use, the number of women with normal endometrial histology and abnormal endometrial thickness (>5 mm) did vary with HRT (specificity of 93% for those not using HRT versus 73% for those using HRT) [59]. There were more women taking HRT with an endometrial thickness greater than 5 mm than those not receiving HRT.

Transvaginal ultrasound evaluation of endometrial thickness has also been used as an initial evaluation in postmenopausal symptomatic women, regardless of HRT use. Lofallah et al evaluated transvaginal ultrasound as the initial screen for postmenopausal bleeding.
They noted that women with an endometrial thickness of 4 mm or less did not need further evaluation and that those women with greater than 4 mm endometrial thickness should be evaluated with hysteroscopy [60]. Studies have shown that screening asymptomatic women with transvaginal ultrasound is not an effective screening tool. In one study screening asymptomatic postmenopausal women had a 93% false positive result thus leading to unnecessary cost and invasive procedures [61]. Other studies have supported this finding [62–65].

There is no study that has examined the predictive value of transvaginal ultrasound in asymptomatic postmenopausal women with benign endometrial cells on Pap tests. In evaluating these women, The Kelly Gynecologic Oncology service at Johns Hopkins performs an in office sampling with endometrial biopsy. In cases where the biopsy is inadequate or non-diagnostic, or cervical stenosis prohibits endometrial sampling, a transvaginal ultrasound is performed. If the ultrasound with or without sonohysterography shows an endometrial stripe equal or greater than 5 mm, or findings suggestive of a polyp or other lesion, a hysteroscopy dilation and curettage is performed [38]. However, a cost benefit analysis of this approach has not been done.

While we know evaluation of the endometrium is important and recommended in postmenopausal women with endometrial cells on Pap tests, the most predictive and cost effective method remains to be determined. We have no data to support evaluation, and certainly none indicating which type of procedure should be performed in premenopausal asymptomatic women with one or more risk factors associated with endometrial carcinoma.

**GUIDELINES**

In the past, benign endometrial cells on Pap tests were reported only in women if it occurred after the first half of the cycle/outside the proliferative phase or in postmenopausal women. The 1991 Bethesda System Guidelines for reporting Cervical Cytology recommended reporting exfoliated endometrial cells in postmenopausal women as an epithelial abnormality [66].

The Bethesda System 2001 revised its recommendation to include reporting benign endometrial cells in all women 40 years and older and these endometrial cells are not considered an epithelial cell abnormality [1]. This recommendation is based on the lack of significant lesions in anyone less than 40 years old when benign endometrial cells were reported on Pap tests, most of the time endometrial cells detected on Pap tests are associated with normal endometrium, and the pathologist is often not given information regarding menopausal status, use of HRT, and clinical symptoms. As such, while continued reporting of endometrial cells in women age 40 and over appears indicated, more specific educational notes in the cytology report and other educational efforts directed towards the clinician may

![Figure 1. High power view of benign endometrial cells from a liquid based preparation. The cells are in a three dimensional cluster. Cells are small without nucleoli or pleomorphism and the chromatin is granular. Nuclear details are easier to see than in conventional preparations. Single cell necrosis (apoptosis) is present deep in the cell group. (Papanicolaou stained preparation, 100×).](image1)

![Figure 2. Endometrial adenocarcinoma. There is nuclear and cellular enlargement. Nuclear irregularity and pleomorphism are present. Nucleoli can be seen from this power. The three dimensional array is still apparent in these exfoliated cells of endometrial adenocarcinoma. (Papanicolaou stained liquid based preparation, 40×).](image2)
impact on the frequency of unnecessary endometrial evaluation. A recent extensive review by Fadare et al also concluded that reporting benign endometrial cells on Pap tests in women 40 years and older was the most practical, prudent and reasonable approach based on the current evidence. Relying on clinical information often not available when the Pap test is screened such as menopausal status, or clinical symptoms would create non-uniformity in reporting endometrial cells [67].

**CONCLUSIONS**

We have addressed many of the issues that have surrounded the controversy that continues about the reporting benign endometrial cells on Pap tests. After extensive evaluation of the literature we recommend the following:

1. We support the current ASCCP guidelines and TBS 2001 in reporting benign endometrial cells on Pap tests in all women 40 and over. While it appears that the prevalence of this finding is low (1–3/100 to 1/1600 or less), patients over 40 may be at an increase risk for significant endometrial pathology.

2. Educational notes should be specific. Clinicians should be advised of the current evidence that supports further evaluation in all postmenopausal women with benign endometrial cells in Pap tests regardless of the presence of symptoms (bleeding) (1–15% risk of carcinoma).

3. Normal exfoliated endometrial cells in premenopausal women in the first half of the menstrual cycle are not associated with any significant endometrial pathology and need not be evaluated unless otherwise clinically indicated.

4. Benign endometrial cells in the second/half of the menstrual cycle in asymptomatic menstruating women over 40 are also rarely associated with significant pathology and do not need further evaluation.

5. Clinicians should be continually encouraged to provide the best demographic and clinical information to the pathologist, so that more specific educational notes can be rendered. However, it is unrealistic to expect that this will happen in all cases and diagnosis should not be delayed until such information becomes available.

6. The initial evaluation of the endometrium is an in-office endometrial sampling or transvaginal ultrasound. Transvaginal ultrasound screening appears useful in the follow-up of symptomatic postmenopausal women. While the most effective evaluation for asymptomatic postmenopausal women with endometrial cells on Pap tests still needs to be determined (endometrial sampling versus uterine cavity imaging), some form of evaluation needs to occur in these women.

7. The presence of endometrial stromal cells/histiocytes in most cases has no significance. Currently these cells do not need to be reported under TBS 2001 and do not require further evaluation.

8. HRT may increase the rate of benign endometrial shedding. All postmenopausal women, regardless of HRT, should be evaluated when endometrial cells are reported on the Pap test.

9. Women under 40 years old are at very low risk of significant endometrial pathology, therefore endometrial cells should not be reported in their Pap tests.

10. There are no data to suggest that women under 40 years old with certain high risk factors (obesity, DM, hypertension, anovulatory cycles, PCOS, genetic factors, or infertility) and who have benign endometrial cells on their Pap tests should be further evaluated. Since benign endometrial cells in women under 40 will not be reported, the best recommendation for these at high risk younger women would be to evaluate them only if clinically indicated.

11. Atypical endometrial cells should always be reported regardless of patient’s age and further evaluation is required as per the current ASCCP Guidelines.

12. Prospective studies with adequate controls, defined menopausal status, age stratification, risk factors, and specifically described symptoms are needed. Attempts should be made to evaluate the endometrium in all patients studied. Significant pathology should be defined as atypical complex hyperplasia and carcinoma or other malignancies. Asymptomatic postmenopausal women with exfoliated benign appearing endometrial cells on Pap tests need to be randomized to various types of endometrial evaluation. This will determine which is the most predictive and cost effective method in detecting disease at a stage when a cure can be obtained. These studies are needed to provide evidence to answer many of the questions remaining in this area and to establish future guidelines.

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