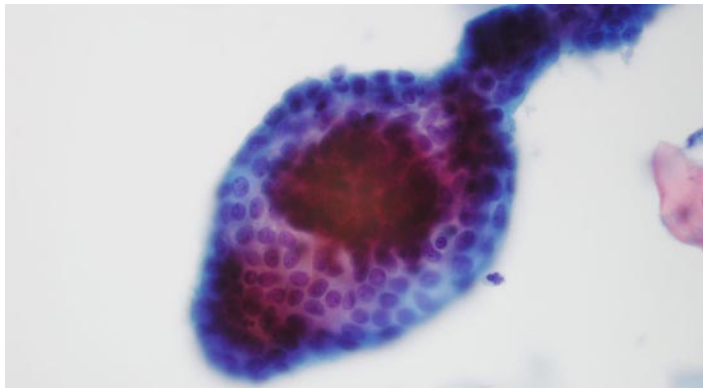


Significance of Benign Endometrial Cells in Women Over 40 Years of Age (EM 40+) Detected in Cervical Cytology

By Felix Martinez, M.D., and David Hoak, M.D.

Why do laboratories utilize the reporting category “Endometrial Cells Present in a Woman over 40 Years of Age”?

The Bethesda System For Reporting Cervical Cytology, in its 2001 workshop, chose to retain the category of “*Exfoliated Endometrial Cells in a Woman Greater Than 40 Years of Age*” (EM 40+) based upon reports in the literature showing increased risk for endometrial pathology with benign endometrial cells seen in cervical/vaginal cytology preparations of postmenopausal women or outside of the proliferative phase of the menstrual cycle. The decision to retain the category was controversial.



Benign cluster of endometrial cells on a Sure-Path Pap in a 41-year-old with unknown menstrual history.

If endometrial cells are benign in appearance (free of cytologic atypia) why might they signal the presence of endometrial pathology?

Benign exfoliated endometrial cells are commonly seen in specimens obtained during the proliferative phase of the menstrual cycle. The finding of benign endometrial cells without atypia in a woman having endometrial pathology is actually an *epiphenomenon* – a separate finding associated with another condition – and is the consequence of increased shedding of benign cells.

How is it determined whether endometrial cells are “in-cycle” or “out-of-cycle”?

Correlation of the Pap finding is based upon the patient’s last menstrual period (LMP). In women under 40, exfoliated endometrial cells during the patient’s proliferative phase of her menstrual cycle or during her menses are commonly seen, and are interpreted as “in-cycle” normal findings. Such cells are the consequence of nor-

mal increased shedding of the endometrial lining during these phases. If the cells are present beyond two weeks from the LMP, they are interpreted as “out-of-cycle.”

Why is a patient’s last menstrual period and birth date important information in the interpretation of benign endometrial cells in a Pap smear?

Benign endometrial cells, both glandular and stromal, appear morphologically the same during any phase of the patient’s menstrual cycle.

Correct birth date and last menstrual period information provided by the submitting office are essential to assess the Pap finding. If the needed information is not provided or is incorrect, the laboratory assessment is not valid.

Why are “out-of-cycle” findings significant in a woman over 40?

Some studies have shown there to be increased likelihood of endometrial pathology in menopausal women with this finding. This perspective is primarily based upon retrospective reviews performed in the 1970s and 1980s on the significance of endometrial cells detected in cervical smears. In the largest of these early studies, biopsy follow-up showed that women over 40 years of age occasionally demonstrated endometrial abnormalities, whereas women under 40 did not have endometrial pathology (^{1,2}).

In follow-up biopsies of women with “EM 40+” Pap findings, what are the most common biopsy findings?

Most follow-up biopsies in this setting are benign. The most common cause of benign endometrial cells in a Papanicolaou collection from a woman over 40 years of age is hormone replacement therapy (HRT). For women who are not on HRT, the most common pathologic condition encountered in follow-up biopsy is endometrial polyp, followed by atrophy. In a small number of women, endometrial hyperplasia and carcinoma are identified – conditions often associated with abnormal bleeding (See Table 1).

Recent studies suggest that most women with endometrial carcinoma have bleeding symptoms at the time of presentation, and some studies note that the presence of endometrial cells as the only abnormal finding (i.e., the patient is asymptomatic) occurs in only a small proportion of asymptomatic women in whom endometrial adenocarcinoma is subsequently detected.

Table 1: . Four studies with endometrial biopsy follow-up on women who were postmenopausal or greater than a specific age (40, 45, or 55) who had normal appearing endometrial cells on a Pap smear

Patient type	>45 yrs	>55 yr w HRT	>55 no HRT	Postmenopausal	Postmenopausal	> 40 yrs not PM, but "out of phase" endometrial cells
Study (see ref. below)	1. Karim et al.	2. Sarode et al.	3. Sarode et al.	4. Chang et al.	5. Sinsir et al.	6. Sinsir et al.
Biopsy Finding in % of patients						
Benign endometrium	78.5%	63.3%	29.4%	89.4%	19.2%	50%
Insufficient or non-diagnostic	3.9%	16.6%	27.4%	NS	0%	0%
Endometrial polyp	4.9%	16.6%	27.4%	0.75%	49.2%	28.1%
Leiomyoma	3.9%	0%	1.9%	NS	23.8%	18.8%
Simple or complex endometrial hyperplasia	4.6%	0%	7.8%	9.1%	2.3%	2%
Endometrial carcinoma	4.2%	3.3%	5.8%	0.75%	4.6%	0%

1. Karin, B.O. et al. Diagn Cytopathol. 2002 Feb; 26(2):123-7. Study design: Of 1162 women > 45 yrs with normal endometrial cells on a Pap test, 430 had follow-up biopsy
- 2-3. Sarode, V.R. et al. Acta Cytol.2001: 45(2) 152-6. Study design: 220 women > 55 yrs with normal endometrial cells on a Pap test. 81 patients had biopsy follow-up with results (30 on HRT and 51 no HRT).
4. Chang, A. et al. Gynecol Oncol. 2001 Jan:80(1): 37-43. Study design: 297 post menopausal women with benign appearing endometrial cells on Pap test. 132 women (44%) had follow-up biopsies and 165 had routine Gyn exams.
- 5-6. Sinsir, A. et al. Am J Clin Pathol. 2005 123 (4):571-575. Study design: 130 women post menopausal with normal endometrial cells on a Pap test compared to 96 women > 40 yr but not post menopausal with normal endometrial cells "out-of-phase" on a Pap test.

How sensitive is a Pap smear for the detection of endometrial carcinoma?

Not very. Cervical cytology is a screening test for squamous intraepithelial lesions and squamous cell carcinoma. It occasionally detects endocervical adenocarcinoma, but it is unreliable for the detection of endometrial lesions and should not be used to evaluate causes of suspected endometrial abnormalities.

What does the literature after 1990 show regarding the significance of EM 40+?

The findings in the literature are mixed. In reports prior to 1990 – an era before widespread use of hormone replacement therapy – up to 15% of studied women were found to have associated endometrial hyperplasia or endometrial carcinoma. These early studies recommended endometrial biopsy as follow-up to the finding of EM 40+.

In more recent reports, the proportion of women with EM 40+ having endometrial hyperplasia or endometrial carcinoma is significantly less than earlier reports and, in some instances, very low. In some studies, the finding of the EM 40+ in women who later are found to have endometrial carcinoma or hyperplasia did not differ significantly from that in women without these conditions. The authors concluded that "Reporting normal endometrial cells in Papanicolaou smears according to the recommendation of the Bethesda System 2001 may lead to unnecessary procedures and patient anxiety." In another study, women who presented with

abnormal uterine bleeding were followed and worked up regardless of their Pap findings, and led authors to conclude that, in this setting, "Reporting the presence of normal endometrial cells in Pap smears is of no clinical relevance and may, in fact, create a management dilemma for clinicians."

Because follow-up biopsy is so often negative in clinically asymptomatic patients, practitioners often disregard the finding of normal endometrial cells in a Pap smear report, and there are studies to support this approach.

An individual woman's risk factors for endometrial carcinoma, clinical symptoms, hormone therapy, and menopausal status determine the true significance of EM 40+ in Pap smears. This information is often unclear, inaccurate, or unknown to the laboratory (See Table 2).

Table 2. Relative risk factors for finding a significant endometrial abnormality in a patient greater than 40 with endometrial cells on a Pap test

Lower risk	Higher risk
On Hormone Replacement Therapy	No Hormone Replacement Therapy
Still cycling or perimenopausal	Post menopausal
Asymptomatic	Vaginal bleeding
Benign appearing endometrial cells	Abnormal appearing endometrial cells

Prior to the Bethesda 2001 Workshop, nine forum groups, each consisting of 6 to 10 individuals, initiated a lengthy process designed to provide wide input via an Internet-based "discussion." Forty-four international organizations with interest in cervical cytopathology co-sponsored the Bethesda 2001 Workshop, along with the National Cancer Institute. Literature review, expert opinion, large input from a worldwide panel of experts, and responses to an Internet Bulletin Board were all considered in developing the recommendations. The strength of evidence of the scientific data was considered of paramount importance. In the comments posted on the Internet Bulletin Board, many practitioners were critical of continuing to report the presence of benign endometrial cells in a menopausal woman because, in the absence of bleeding, the yield of either endometrial hyperplasia or endometrial carcinoma in follow-up biopsies was extremely low.

Is there a general consensus on how to manage patients with EM 40+ path findings?

No. There is general consensus that endometrial biopsy should be performed if EM 40+ Pap findings are associated with vaginal bleeding. There is still controversy regarding follow-up of an asymptomatic patient. As mentioned, the literature has reports recommending follow-up biopsy to this Pap finding, but other studies contradict an association with endometrial hyperplasia or carcinoma.

In our outpatient experience over the past forty years, we have found that the presence of endometrial hyperplasia or carcinoma in follow-up biopsies in women with EM 40+ Pap findings is *very* low (approximately 1%) and, in the absence of clinical signs or symptoms, we agree with the reports in the literature that downplay the clinical significance of the findings.

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WE PASSED!

InCyte Pathology has successfully passed the national gynecologic cytology proficiency test required by The Centers for Medicare and Medicaid Services (CMS). This test was administrated by Midwest Institute for Medical Education as defined by the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

In order to maintain scoring files for all pathologists and cytotechnologists who evaluate Pap tests, CMS designed a complex computer database called Cytology Personnel Recording System (CYPERS). This system will be used to follow participants during their cytopathology career.

According to the mandate, all laboratories performing cytology testing must ensure that each individual (cytotechnologist and pathologist) involved in the examination of gynecologic cytology be enrolled in a CMS-approved cytology proficiency testing program and successfully achieve a passing score (90%). Mandated remedial actions must be taken following a testing event failure to ensure quality

assurance. As a consequence of this Federal statute, pathologists, even after board certification, are the only physician specialty that must demonstrate proficiency through testing every year.

The cytology community has not had this much excitement since 1987 when Walt Bogdanich wrote a series of articles in the Wall Street Journal that exposed serious problems with Pap smear collection and high-volume, low-quality laboratories ("Pap mills"). The outrage that ensued from Mr. Bogdanich's Pulitzer Prize-winning exposé, in part, helped craft the Clinical Laboratory Improvement Amendment (CLIA '88). One of the regulations mandated by CLIA was a stipulation for a national cytology proficiency test. The difficulties of instituting such a test were seemingly insurmountable but, thirteen years later, the test is here.

InCyte Pathology is proud to be the first laboratory in the Inland Northwest in which every cytotechnologist and pathologist passed the national proficiency test on the first try.

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FREQUENTLY ASKED QUESTIONS

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InCyte Pathology is an independent professional service company of pathologists that provides interpretation of biopsies and cytology preparations.

Circulation List

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Frequently Asked Questions has items of interest for office personnel and assistants as well as for physicians, nurse practitioners, nurses and physician assistants. We recommend that, upon completion of circulation, your copy of **Frequently Asked Questions** be filed in the InCyte Pathology *Anatomic Pathology Services Manual* for future reference.

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