THE IMPORTANCE OF FINDING ENDOMETRIAL CELLS IN CERVICO-VAGINAL SMEARS IN RELATION TO ENDOMETRIAL CANCER AND ITS PRECURSORS

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SUMMARY

Abnormal desquamation of the endometrium, indicated by the presence of normal endometrial cells in smears obtained from women during the second half of their menstrual cycle or after menopause, could be associated with an endometrial carcinoma or its precursors. The frequency of exfoliation increases with advancing age. These data could be of great use in the screening of patients with cancerous or precancerous lesions of the endometrium.

INTRODUCTION

Under normal circumstances one finds endometrial cells in cervico-vaginal smears only during the first half of the menstrual cycle, occasionally during the second half ([2]). The presence of endometrial cells during the second half of the cycle at any time after menopause is a sure indication of abnormal endometrial desquamation ([1]). Patients with endometrial cancer of precancerous endometrial lesions often show characteristically abnormal cells in their cervico-vaginal smears ([1, 2, 3]). In any case, we should remember that cervico-vaginal smears may show completely normal endometrial cells even in presence of certain endometrial lesions, such as hyperplasia and carcinoma.

There are very few articles dealing with the frequency of carcinoma or endometrial hyperplasia in women whose cervico-vaginal smears contain only normal endometrial cells.

The purpose of our research is to illustrate the endometrial changes found in histological examinations of women whose cervico-vaginal smears contained flaked-off normal endometrial cells during the second half of their menstrual cycle or during the post-menopausal period.

MATERIAL AND METHODS

From 1973 to 1979 we have examined 836 women whose cervico-vaginal smears contained normal endometrial cells and who subsequently underwent surgery for endometrial curettage, total hysterectomy, or partial hysterectomy. Cytological specimens were obtained from each patient by means of scraping and cervical tampons. The results from cellular and tissue studies of each patient were compared. The cellular and histopathological criteria for cystic hyperplasia, adenomatous hyperplasia, atypical hyperplasia, adenocarcinoma *in situ*, and adenocarcinoma infiltrating in the endometrium have been described in other papers ([1, 2, 4, 5, 6]).

Of the 836 cervico-vaginal smears taken, exfoliated endometrial cells were seen during the first half of the menstrual cycle in 140 cases, during the second half of the cycle in 453 cases, and during the post-menopausal period in 243

cases. Endometrial cells observed during the first half of the cycle can be considered in relation to the normal physiological sloughing process, and their presence in the smears at this time is certainly less important than when they are found during the second half of the cycle or after menopause. The presence of endometrial cells in smears taken during the second half of the cycle or after menopause is, in fact, considered a sign of abnormal exfoliation and demands subsequent histological tests. We found 696 such cases in our study.

Patients with physiological and abnormal exfoliation of endometrial cells were studied within the framework of the incidence of endometrial carcinoma and its precursors, of the patient's age, of the menopausal stage, and of the presenting symptoms.

RESULTS

Of the 140 patients who had normal endometrial cells in smears obtained during the first half of their cycle, histological examination revealed proliferating endometrium in 66 cases, secreting endometrium in 47 cases, menstrual endometrium in 5 cases, anovulatory endometrium in 3 cases, endometrium treated with progestins in 3 cases, and an atrophic endometrium in 5 cases. The endometrium was found to be within normal limits in 129, that is 92.2%, of the 140 cases. Only 11 of the 140 cases showed pathological alterations. Adenomatous polyps were found in 10, that is 7.1%, of the cases, and one patient suffered from adenomatous hyperplasia of the endometrium. We did not find any endometrial adenocarcinomas (table 1).

We found no significant relationship between the type of endometrium and the age of the patient.

Of the 453 patients who had normal endometrial cells in smears obtained during the second half of their cycle, 9 (2%) had invasive endometrial adenocarcinoma or adenocarcinoma "in situ", 22 (4.9%) had endometrial hyperplasia, and 98 (21.6%) had adenomatous polyps in the endometrium (table 1). Of the 9 endometrial carcinomas, 4 were adenocarcinomas "in situ" and 5 were initially invasive adenocarcinomas, with infiltrations limited to the internal myometrial layers.

These diagnoses were reached after examination of surgically removed specimens consequent to hysterectomy. Of the 22 cases with endometrial hyperplasia, 7 had cystic hyperplasia, 11 had adenomatous hyperplasia, and 4 had atypical hyperplasia. In the remaining 324 patients we have observed proliferating endometrium in 154 cases, secreting endometrium in 108 cases, menstrual endometrium in 9 cases, endometrium treated with progestins in 7 cases, anovulatory endometrium in 16 cases, and atrophic endometrium in 30 cases.

Of the 243 patients who had exfoliated endometrial cells after menopause, 14 (5.2%) had an adenocarcinoma of the endometrium, 32 (13.2%) had endometrial hyperplasia, and 86 (35.4%) had adenomatous polyps of the endometrium (table 1). There was 1 adenocarcinoma "in situ" among the 14 endometrial cancers. In the 13 cases of invasive adenocarcinoma, infiltration into the myometrium was limited in 10 cases and extensive in 3 cases. Of the 32 cases of endometrial hyperplasia, 8 had cystic hyperplasia, 17 had adenomatous hyperplasia, and 7 had atypical hyperplasia. Of the remaining 111 women, 18 had proliferating endometrium, 4 had secreting endometrium, 1 had menstrual endometrium, 8 had anovulatory endometrium, and 80 had atrophic endometrium.

The presence of endometrial cells in smears obtained from women during the second half of their menstrual cycle or after menopause is considered a sign of abnormal exfoliation. We had 696 women with this abnormal exfoliation of endometrial cells. The abnormal desquamation of endometrial cells was found to be associated with a significant number of endometrial carcinomas and their precursors.

Of these 696 cases (table 2), endometrial adenocarcinoma was observed in 23 (3.2%) cases, endometrial hyperplasia in

Table 1. — *The importance of endometrial cells in pre- and post-menopausal women.*

Histological diagnosis	First half of cycle		Second half of cycle		Post-menopause	
	No.	%	No.	%	No.	%
Normal endometrium	129	92.2	324	71.5	111	45.7
Adenomatous polyps	10	7.1	98	21.6	86	35.4
Endometrial hyperplasia	1	0.7	22	4.9	32	13.2
Adenocarcinoma	0	0	9	2	14	5.7
TOTAL CASES	140		453		243	

54 (7.8%) cases and adenomatous polyps of the endometrium in 184 (26.5%) cases. Of the 23 endometrial carcinomas, 5 were "in situ" and 18 were invasive. Of the 52 cases of endometrial hyperplasia, 15 were cystic hyperplasia, 28 were adenomatous hyperplasia, and 11 were atypical hyperplasia. We did not note any significant endometrial alterations in the remaining 435 women (62.5%). We have observed 172 cases of proliferating endometrium, 112 cases of secreting endometrium, 10 cases of menstrual endometrium, 7 cases of endometrium treated with progestins, 24 cases of anovulatory endometrium, and 110 cases of atrophic endometrium.

In table 2 the ages of patients presenting abnormal exfoliation of endometrial cells have been compared with the results of histological tests. The youngest patient was 20 years old and the oldest one 69.

The endometrium was within normal limits in 89.8% of the 195 cases of the 20-39 year-old group. Adenomatous polyps were noted in 18 (9.2%) cases, and endometrial hyperplasia was present in only 2 (1%) cases. Adenocarcinoma was not observed in this age group. There were 237 patients in the 40-49 year-old age group, and the endometrium was within normal limits in 148 (62.4%) cases. Adenomatous polyps were observed in 67 (28.3%) cases, endometrial hyperplasia in 17 (7.2%) cases, and endometrial adenocarcinoma in 5 (2.1%) cases. Of the 17 women with hyperplasia, 6 had cystic hyperplasia, 7 had adenomatous hyperplasia, and 4 had atypical hyperplasia. 3 of the 5 endometrial neoplasms were adenocarcinoma "in situ". 82 (43.6%) cases of the 188 patients in the 50-59 year-old age group had a normal endometrium. We observed adenomatous polyps in 77 (41%) cases, endometrial hyperplasia in 21 (11.2%) cases, and carcinoma in 8 (4.2%) cases.

Of the 21 endometrial hyperplasias, 4 were cystic, 12 were adenomatous, and 5 were atypical. 1 of the 8 endometrial neoplasms was an adenocarcinoma "in situ" and 7 were infiltrating. Of the 76

Table 2. — *Abnormal desquamation of endometrial cells in relationship to age.*

Histological diagnosis	Total		39 years		40-49 years		50-59 years		+59 years	
	No.	%	No.	%	No.	%	No.	%	No.	%
Normal endometrium	435	62.5	175	89.8	148	62.4	82	43.6	30	39.5
Adenomatous polyps	184	26.5	18	9.2	67	28.3	77	41	22	28.9
Endometrial hyperplasia	54	7.8	2	1	17	7.2	21	11.2	14	18.4
Adenocarcinoma	23	3.2	0	0	5	2.1	8	4.2	10	13.2
TOTAL CASES	696		195		273		188		76	

Table 3. — *Abnormal desquamation of endometrial cells in relationship to symptoms.*

Histological diagnosis	Asymptomatic patients No.	%	Symptomatic patients No.	%
Normal endometrium	303	64.3	132	58.7
Adenomatous polyps	117	24.8	67	29.8
Endometrial hyperplasia	38	8.0	16	7.1
Adenocarcinoma	13	2.9	10	4.4
TOTAL CASES	471		225	

women over 59 years of age, only 30 (39.5%) had a normal endometrium. 22 (28.9%) had adenomatous polyps, 14 (18.4%) had endometrial hyperplasia, and 10 (13.2%) had invasive carcinoma. Of the 14 endometrial hyperplasias, 4 were cystic, 8 were adenomatous, and 2 were atypical. There were 9 invasive carcinomas and 1 adenocarcinoma "in situ". These figures show that endometrial carcinoma and its precursors were found in about 1/3 of the women over 59 years of age, and in 15% of the women in the 50-59 year-old age group.

As shown in tables 3, 4, and 5, there is no significant difference in the frequency and the nature of the endometrial alterations among patients with abnormal exfoliation of endometrial cells who have the same symptoms. One possible exception is adenocarcinoma, which seems to be more frequent in post-menopasual women with symptoms. Symptoms were observed in 225 (32.3%) of the 696 cases, while 471 (67.7%) of the women were asymptomatic. Abnormal metrorrhagia was observed in over 90% of the patients while spotting or pelvic pain were less frequent. 10 (43.5%) of the 23 women with adenocarcinoma were symptomatic, while 13 (56.5%) were asymptomatic. Of the 54 women with endometrial hyperplasia, 38 (70.3%) were asymptomatic, only 16 (29.7%) presenting symptoms. 67 (36.4%) of the patients with adenomatous polyps in the endometrium presented with symptoms, while 117 (63.6%) had none. Of the 435 patients with endometrial alterations other than endometrial neoplasms or hyperplasia, 132 (30.3%) were symptomatic, while 303 (69.7%) were not.

Different types of endometrial cells were observed in the 54 cellular samples obtained from patients with endometrial hyperplasia (table 6).

Glandular cells of endometrial origin were identified in 32 samples (59.3% of the cases), glandular as well as stromal cells were found in 17 (31.5%) cases, and

Table 4. — *Abnormal desquamation of endometrial cells in relationship to symptoms among premenopausal women.*

Histological diagnosis	Asymptomatic patients No.	%	Symptomatic patients No.	%
Normal endometrium	238	71.9	86	70.5
Adenomatous polyps	68	20.6	30	24.6
Endometrial hyperplasia	18	5.4	4	3.3
Adenocarcinoma	7	2.1	2	1.6
TOTAL CASES	331		122	

Table 5. — *Abnormal desquamation of endometrial cells in relationship to symptoms among post-menopausal women.*

Histological diagnosis	Asymptomatic patients No.	%	Symptomatic patients No.	%
Normal endometrium	65	46.4	46	44.7
Adenomatous polyps	49	35.0	37	35.9
Endometrial hyperplasia	20	14.3	12	11.7
Adenocarcinoma	6	4.3	8	7.7
TOTAL CASES	140		103	

only stromal cells were recognized in 5 (9.2%) cases. Certain differences became evident when we have considered the type of endometrial cells in relation to the type of endometrial hyperplasia. Of the 15 patients with cystic hyperplasia, 8 had glandular cells, 5 had glandular and stromal cells, and 2 had stromal cells. Of the 28 patients with adenomatous hyperplasia, 15 had glandular cells, 11 had glandular and stromal cells, and 2 had only stromal cells. Of the 11 patients with atypical hyperplasia, 9 had glandular cells, 1 had glandular and stromal cells, and 1 had only stromal cells.

5 of the 23 endometrial carcinomas were "in situ" and 18 were invasive. The endometrial cells were of glandular origin in 3 of the 5 adenocarcinomas "in situ", while 2 had glandular and stromal cells. Of the 18 cases of invasive adenocarcinoma, 12 showed endometrial cells of glandular origin, 5 had glandular as well as stromal cells, and 1 had cells of stromal origin (table 6).

DISCUSSION

Papers have been written ([2]) which show that normal endometrial cells observed in cervico-vaginal smears obtained from women during the first half of their menstrual cycle are usually the result of physiological desquamation, endometrial carcinoma and its precursors being rarely observed. The results of our work confirm this conclusion. Data were scarce, however, on the importance of normal endometrial cells found in cellular samples obtained from women during the second half of their cycle or after menopause. Endometrial cells observed during these periods reflect an abnormal endometrial desquamation. Endometrial cells in specimens obtained from women with hyperplasia or carcinoma usually present characteristic morphological traits ([1, 2]). In any case, the results of our research indicate that in certain cases the desquamated endometrial cells from carcinoma or its precursors could be relatively normal. These endometrial cells sloughed off in non-physiolo-

Table 6. — *Types of endometrial cells in relationship to endometrial pathology.*

Type of cell in cervico-vaginal smear	Histological Diagnosis: Normal No.	%	Polyps No.	%	Hyperplasia No.	%	Carcinoma No.	%
Epithelial	226	51.9	95	51.6	32	59.3	32	59.3
Epithelial and stromal	146	33.6	74	40.2	17	31.5	7	30.4
Stromal	63	14.5	15	8.2	5	9.2	1	4.4

gical phases of the cycle. The frequency and nature of the endometrial lesions observed were related to the age or the menopausal stage of the patient. The frequency of endometrial carcinoma and its precursors increased with the age of the patient. The frequency was higher in post-menopausal women than in pre-menopausal women. In addition, adenomatous polyps were often observed. In women with invasive carcinomas, the neoplasms were usually well differentiated and confined to the internal layers of the myometrium, the middle and external portions being free of infiltrations.

The frequency and nature of the endometrial alterations was not significantly different in women with and without symptoms. Abnormal desquamation of the endometrium can be observed in patients with disfunctional metrorrhagia, submucosal myomas, endometritis, endometriosis. hormone therapy, I.U.D. abortions ([1]). Data concerning these variables were not considered in our research.

The number of endometrial cells in cellular preparations from abnormal desquamations was variable. Generally speaking, the number of endometrial cells was higher in samples from women with endometrial neoplasms. In any case, in women with hyperplasia or endometrial carcinoma the number of normal endometrial cells was much lower than the number of hyperplastic or carcinomatous cells.

It was possible to identify the various types of endometrial cells. Regardless of the state of the endometrium, normal endometrial glandular cells were more frequently observed alone, glandular and stromal cells together were less frequently observed, and stromal cells alone were rarely found in the cellular samples. Stromal cells alone were observed in about 5% of the cases of endometrial carcinoma, in 10% of the cases of hyperplasia or polyps, and in 15% of the women without appreciable pathological lesions in the endometrium.

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