Research Article

Atypical squamous cells of undetermined significance (ASCUS) for papanicolaou smears in perimenopausal and postmenopausal women and its significance: a retrograde study

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Abstract

The diagnostic category of atypical squamous cells of undetermined significance (ASCUS) varies in threshold and significance among individual pathologists and among cytology laboratories. The rate of concurrent and subsequent squamous intraepithelial lesions (SIL) in patients with ASCUS found on Papanicolaou (Pap) smears shows a wide range in the literature.1–8 The significance of this diagnosis in perimenopausal and postmenopausal women is particularly unclear.4, 9, 10 We therefore compared the ASCUS-to-SIL ratio and the rate of subsequent SIL diagnoses in premenopausal, perimenopausal, and postmenopausal women.

Key Words: Pap smear, ASCUS, premenopausal, postmenopausal,postmenopausal.

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INTRODUCTION

The diagnostic category of atypical squamous cells of undetermined significance (ASCUS) varies in threshold and significance among individual pathologists and among cytology laboratories. The rate of concurrent and subsequent squamous intraepithelial lesions (SIL) in patients with ASCUS found on Papanicolaou (Pap) smears shows a wide range in the literature.[1–8] The significance of this diagnosis in perimenopausal and postmenopausal women is particularly unclear.[4,9,10] We therefore compared the ASCUS-to-SIL ratio and the rate of subsequent SIL diagnoses in premenopausal, perimenopausal, and postmenopausal women.

MATERIAL AND METHODS

The reports of all Pap smears were viewed in retrograde manner over a 24 –months period (May 1 2011 to June 30, 2013) in the Cytology Laboratory of People's college of medical sciences. Women were then divided arbitrarily into premenopausal (age $\leq$ 45 years), perimenopausal (ages 46–54 years), and postmenopausal (age $\geq$ 55 years) categories. All women who had abnormal Pap smears during this period were identified. The abnormal rate and the ASCUS-to-SIL ratio were determined for each age category. Those women who had undergone a hysterectomy were excluded from the study. Follow up data was then reviewed for all women with diagnosis of ASCUS for next 1 subsequent years of our data collection (i.e. up to May 2014). Women who were diagnosed as ASCUS continued for follow up and again gone for Papsmear, which were then examined accordingly. Based on the follow-up Pap smear, the patients were characterized as "no follow-up," "SIL on follow-up," or "no SIL on follow-up" on Pap smear. A review of the slides without knowledge of the menopausal status or age of the patient (blinded) was made on two tiers. The first was an assessment of the overall slide to determine "obvious" air-drying artifact, "obvious" atrophic change,

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predominant cell type, and the presence of significant inflammation. The term "obvious" was used to indicate an overall subjective impression on rapid review at low magnification. Due to a lack of standardization of the "maturation index" of cervical Pap smears, the predominant cell type was assessed to corroborate with the subjective impression of atrophy. The second tier of review was restricted to the previously dotted areas from primary screening. Because not all dots were for ASCUS (others were for Candida, endocervical glandular component, etc.), all dotted areas were reviewed and those individual cells on which a diagnosis of ASCUS most likely was based were assessed for nuclear size, nuclear-cytoplasmic (N: C) ratio, chromatin pattern, nuclear membrane irregularities, nucleoli, koilocytic change, multinucleation, and metaplasia.[11,12] An exact age-matched control was selected from women with negative Pap smears for every perimenopausal woman with ASCUS in the current study. These slides were reviewed for "obvious" air-drying artifact, "obvious" atrophic change, predominant cell type, and the presence of significant inflammation. Clinical information that was available from the requisition form was recorded for patients with clinical follow-up as well as for perimenopausal controls.

RESULTS

The total number of Pap smears collected over the study period was 4067 out of which 34 women had history of hysterectomy, hence excluded from our study, so a total of 4033 smears were included in study. As shown in Table 1, the total number of smears from women in the premenopausal, perimenopausal, and postmenopausal categories was 2850, 603, and 580, respectively. The mean (median) age was 39 years (37 years) overall and32 (32 years), 49 (49 years), and 64 (63 years), respectively, for

Table 1: Overall Population Divided by Menopausal Status (n =4033)

	Pre	Peri	Post
Total	**2850**	**603**	**580**
Mean age (yrs)	32	49	63
Abnormal (%)	193 (6.7)	26 (4.3)	16 (2.7)
Total ASCUS (%)	120 (4.2)	21 (3.4)	10 (1.72)
Total SIL (%)	62 (2.17)	3 (0.49)	3 (0.51)
ASCUS-SIL	**1.93**	**7**	**3.33**

Pre: premenopausal; Peri: perimenopausal; Post: postmenopausal; ASCUS: atypical squamous cells of undetermined significance; SIL: squamous intraepithelial lesion.

The premenopausal, perimenopausal, and postmenopausal groups. The total number of abnormal Pap smears in the premenopausal, perimenopausal, and postmenopausal categories was 193, 26, and 16, respectively; of these abnormal Pap smears, there were 120, 21, and 10 diagnoses of ASCUS, respectively, and 62, 3, and 3 diagnoses of SIL, respectively. The remainder of the diagnosis was atypical glandular cells of undetermined significance (AGUS). The distribution of ASCUS favour reactive was 17%, 33%, and 22%, respectively; that for ASCUS unqualified was 53%, 47%, and 49%, respectively; and that for ASCUS favour SIL was 30%, 21%, and 29%, respectively (Fig. 1). The prevalence rate of ASCUS per age category was 4.2%, 3.4%, and 1.72%, respectively, and that of SIL was 2.17%, 0.49%, and 0.51%, respectively; the abnormal rate decreased with increasingage. The ASCUS-to-SIL ratio was 2.22 overall and 1.9, 7, and 3.3, respectively, for the premenopausal, perimenopausal, and postmenopausal groups ($P < 0.001$) (Table 1).

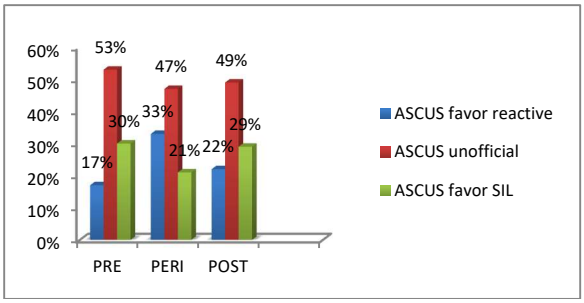

Figure 1: Distribution of qualifiers of atypical squamous cells of undetermined significance (ASCUS). SIL: squamous intraepithelial lesion

Due to the relatively large size of the premenopausal group (120 cases), follow-up data were obtained for only one randomly chosen month (April (of two years); 17 cases) for this group. Therefore, the number of patients with ASCUS examined for each age category was 17, 21, and 10, respectively (48 cases in total). Of these 48 cases, the number of cases percategory with Pap smear follow-up was 14, 17, and 8, respectively (n = 39) and for cervical biopsy follow-up was 7, 8, 4 (n = 19) respectively andthe number of cases per category with Pap smear or cervical biopsy follow-up was15, 20, 9 respectively (n = 44)(Table 2). Of the cases with follow-up, the number of cases with subsequent SIL in each category was 4 (26.7%), 3 (15%), and 3 (33%), respectively ($P = 0.062$)(Table 2).Pap smear and biopsy results were available for 15, 20, and 9cases, respectively; of these, 4, 3, and 4 cases, respectively, had SIL. The positive predictive value (PPV) for SIL was 26.7%, 15%, and 33%, respectively ($P = 0.17$) (Table 2).

Table 2: Results of Follow-Up in Patients with ASCUS by Menopausal Status (n = 48)

	pre	peri	post
Total	**17**	**21**	**10**
Mean age (yrs)	32	51	62
Pap follow up	14	17	8
Biopsy follow up	7	8	4
Either (%)	15 (88)	20 (95.2)	9 (90)
SIL-Pap	1	2	2
SIL - Biopsy	2	1	1
SIL- Either (%)	4 (26.7)	3 (15)	3 (33)
No follow up	**2**	**1**	**1**

Pre: premenopausal; Peri: perimenopausal; Post: postmenopausal; Pap: Papanicolaou; SIL: squamous intraepithelial lesion; LG: low grade; HG: high grade.

Table 3 shows the percentage of women with ASCUS in each category that had the feature examined in the study.

It was observed that the premenopausal group showed a significantly lower percentage of atrophy (5.8%; P < 0.001), a higher percentage of increased N:C ratio (64.7%; P = 0.03), and a greater percentage of nuclear membrane irregularity (47 %; P = 0.02) in the ASCUS cells compared with the other categories. The perimenopausal group demonstrateda greater percentage of ASCUS in metaplastic cells (51.8%) compared with the other categories (P = 0.03).In all 3 categories, the intermediate cell was the predominant ell type in the majority of cases (approximately 75% of the time), with the parabasal cell predominating in only 5.89% of premenopausal women and the superficial cell predominating in only 5 % of postmenopausal women (P = 0.012) (Table 3).

Table 3: Results of ASCUS Slide Review

	Pre Group	Peri Group	Post Group	P value[a]
Total cases	**17**	**21**	**10**	
Air-drying artifact	23.56	19.04	20	0.65
Atrophy	5.8	23.8	30	0.0001
Predominant cell type				
Superficial	17.64	18.1	5	—
Intermediate	76.47	69.9	70	—
Parabasal	5.89	12	20	—
Significant inflammation	58.82	53	60	0.62
N:C ratio increase	64.7	43.4	50	0.03
Granular chromatin	41.17	32.5	40	0.48
Irregular nuclear membrane	47	27.7	20	0.02
Nucleoli				0.35
Absent	58.82	66.3	50	—
Small	41.1	27.7	40	—
Large	5.8	6	5	—
Koilocytic change	29.41	27.7	10	0.49
Multinucleation	58.8	59	50	0.71
Metaplastic cells	**29.4**	**51.8**	**30**	**0.03**

ASCUS: atypical squamous cells of undetermined significance; Pre: premenopausal; Peri: perimeno- pausal; Post: postmenopausal; N:C: nuclear to cytoplasmic. ; [a]P values derived from chi-square test.; Numbers represent the percentage of category total.

A direct comparison between individual categories for given criteria was made by selective deletion of categories. A significant difference was noted between the premenopausal and postmenopausal groups and the premenopausal and perimenopausal groups interms of the presence of “obvious” atrophy (P < 0.001 and P = 0.01, respectively), but not between the perimenopausal and postmenopausal groups (P = 0.08). A significant difference also was noted with regard to the predominant cell type between the premenopausal and postmenopausal groups (P = 0.002) but not between the perimenopausal and postmenopausal groups and the premenopausal and perimenopausal groups (P = 0.07 and P = 0.11, respectively). Other significant differences noted in the current study results included a higher percentage of ASCUS cells with increased nuclear size and N:C ratio in the premenopausal group compared with the perimenopausal group (P = 0.02 and P = 0.01, respectively); greater nuclear membrane irregularity in the premenopausal group compared with the postmenopausal group and in the premenopausal group compared with the perimenopausal group (P = 0.02 for both) but not between the perimenopausal and postmenopausal groups (P = 0.51); and more koilocytic change in the premenopausal group compared with the postmenopausal group and in the perimenopausal group comparedwith the postmenopausal group (P = 0.04 and P = 0.05, respectively) but not between the premenopausal and perimenopausal groups (P = 0.86).To verify internal consistency in the slide review, a correlation between

"obvious" atrophy and the predominantcell type was determined and showed statistical significance (P < 0.001).

Table 4: Comparison of Age-Matched Negative (n = 21) and ASCUS (n = 21) Diagnostic Groups in Perimenopausal Patients

	ASCUS	Control	P value [a]
Air-drying artifact	4	1	0.004
Atrophy	3	7	0.012
Predominant cell type			0.33
Superficial	4	2	
Intermediate	14	15	
Parabasal	2	3	
Significant inflammation	**11**	**9**	**0.35**

ASCUS: atypical squamous cells of undetermined significance. a P value derived from chi-square test.

On review patients with ASCUS and control group, a significant difference was noted with regard to air-drying artifact and atrophy between these two groups (P = 0.004 and P = 0.012, respectively)but no significant difference was observed between the predominant cell type and significant in flammationin these two groups (P = 0.33 and P =0.35, respectively) (Table 4).

DISCUSSION

The results of the current study demonstrate that the abnormal rate decreases with increasing age, with a particularly dramatic decrease in the rate of SIL. In addition, the perimenopausal and postmenopausal groups were found to have elevated ASCUS-to-SILratios. Despite the increased ASCUS-to-SIL ratio in the postmenopausal group (3.33), the PPV for SIL (33%) was greater than that in the premenopausal group (26.7%), a finding that, if anything, suggests that SIL is being under diagnosed in the postmenopausal group. The perimenopausal group was found to have the highest ASCUS-to-SIL ratio (7) as well as a particularly low PPV for SIL (15%); therefore, it is likely that ASCUS also is overcalled in this category of patients. Other authors also have shown a low abnormal rate of Pap smears in older women.[10,13] Although the PPV for neoplastic lesions of squamous atypia in women age >40 years was reported to be lower than that in women age ≤40 years in a study by Kaminski *et al*. (6.3% vs. 23%),[13] 2 other more recent studies showed a PPV for SIL of ASCUS in older women (33%and 22%, respectively) that was comparable to the value in postmenopausal women in the current study(33%).[9,10] The authors of the later two studies concluded that squamous cell abnormalities in postmenopausal women could be significant and carry a real risk of an underlying intraepithelial lesion. Therefore, overcalling ASCUS (squamous atypia) in older women most likely is no longer an issue. Instead, the underdiagnosis of SIL may occur because of over adjustment for age-related changes in these women.[14]Based on the results of the current study, overcalling ASCUS now appears to be a problem in perimenopausal women. The slide review in the current study showed that cells are designated as ASCUS for a number of reasons. Although the majority of these "abnormal" features were present in comparable percentages among the three age categories, a significantly higher percentage of ASCUS smears in the premenopausal group showed an increased N:C ratio and irregular nuclear membranes in the abnormal cells, features that are associated with SIL.[15] Conversely, abnormal cells in perimenopausal women were most likely to bemetaplastic (i.e., atypical squamous metaplastic cells of undetermined significance). Atypical squamousmetaplastic cells on Pap smears are known pitfalls.[4,8,16] Although they may represent high grade SIL, they also may represent atrophy. In perimenopausal women, adjustment for age-related changes may not be made as often as in postmenopausal women, thus accounting for the apparent overcalling of ASCUS as manifested by the increased ASCUS-to-SIL ratio and low PPV for SIL reported in the current study. To test our hypothesis of ASCUS being overcalled in perimenopausal women, we compared the slide review results in the perimenopausal ASCUS cases with that of the negative Pap smears in an exact age matched control group. Although the ASCUS cases were more likely to have air-drying artifact on the smears, the control Pap smears were more likely to show "obvious" atrophy. When atrophy is apparent on a smear, the pathologist is more apt to take age-related changes into consideration and to adjust the diagnostic criteria and threshold. Conversely, when only subtle atrophy is present (especially when with superimposed air-drying artifact), the pathologist may overinterpret the atrophy and thus overcall ASCUS.

CONCLUSION

The results of the current study confirmed other authors' findings of a low rate of abnormal Pap smears in older women. The current study also suggests that pathologists are aware of age-related changes and appear to make appropriate adjustments with regard to the diagnostic criteria and threshold when rendering a diagnosis in postmenopausal women or on Papsmears with "obvious" atrophy. There might even bean over adjustment because the PPV of ASCUS for SIL appears to be higher in postmenopausal women. However, smears from perimenopausal women appear to receive an overcalled ASCUS diagnosis, similar to that received by postmenopausal women approximately a decade ago. By paying attention to the patient' sage and evidence of

subtle atrophy when examining Pap smears, pathologists also may reduce the problem of overcalling ASCUS in this age group.

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