



A prospective study of 86 cases of ASCUS (atypical squamous cells of undetermined significance) over two year

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OBJECTIVE(S) : To determine clinical significance and prediction of neoplasia among patients with persistent atypical squamous cells of undetermined significance (ASCUS) on Pap smear.

METHOD(S) : Out of a total of 1866 patients who underwent Pap smear over a year, 86 patients with report of ASCUS were followed up for 2 years. A repeat Pap smear was done 4 to 6 months later and depending on this report, further management with colposcopy was decided.

RESULTS : ASCUS was detected in 100 (5.3%) of the 1866 patients in the first Pap smear report. Fourteen of them were lost to follow up. 75.4% lesions regressed whereas 19.7% patients had a repeat ASCUS on Pap smear after 4 to 8 months; 64% of patients with a repeat ASCUS had a normal biopsy. But 52% of the patients with normal biopsy had ASCUS for the third time after 4 to 8 months.

CONCLUSION(S) : Colposcopy can be reasonably deferred till the second Pap smear. Patients with second time ASCUS should be meticulously followed up as a large number of them may have a underlying persistent disease.

Key words : atypical squamous cells of undetermined significance (ASCUS), colposcopy, cervical cancer

Introduction

With the adoption of the Bethesda system in 1989, a new definition has emerged in cervical pathology, the borderline diagnosis termed as atypical squamous cells of undetermined significance (ASCUS) ¹. The significance and clinical management of women with such cytological modification remain controversial ². Some investigators have advocated its elimination due to overusage and low reproducibility ². ASCUS was the most common epithelial abnormality diagnosed in cytology laboratories in some countries ⁴. But in our country, many cytology laboratories are not using the Bethesda system and therefore a large number of them may be labeled as inflammatory. Subsequently these women may not be followed up meticulously leading to severe cervical pathologies. Metaanalysis has shown that over a period of 2 years the rate of progression from ASCUS to invasive cancer

is 0.25% and to HSIL 7.13%, while the rate of regression is 68.19% ⁵. As a result of clinical and economic pressures, attempts have been made to distinguish between cytological atypia due to benign reactive process and atypia associated with preneoplastic lesions prone to progression ⁵. We prospectively analyzed 86 cases of ASCUS over 2 years to determine the clinical significance and prediction of neoplasia among patients with a persistent ASCUS on Pap smear.

Methods

This prospective study was carried out over a period of 3 years between January 2002 and December 2004 at the Gynecology department of our Institute of Science and Research. A total of 1866 patients underwent a routine Pap smear in the first year of the study. Patients with a diagnosis of ASCUS were reevaluated after local treatment with a repeat Pap smear after 4-6 months and followed up for a period of 2 years. Further protocol depended on the repeat Pap smear report. If the repeat Pap smear was normal and the cervix looked healthy, patients were asked to come for follow up after one year. However, if the repeat Pap smear showed ASCUS or higher lesions, or if the patient had gross

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appearance of unhealthy cervix and Pap smear showed benign cellular changes, a colposcopy was done followed by cervical biopsy when indicated. Further follow up of patients depended upon the severity of cytological pathology and the treatment offered. Colposcopy was performed after applying 3% acetic acid solution and after painting the cervix with Lugol's iodine solution. All cytology and histology specimens were screened by the same laboratory. Standard demographic variables were entered prospectively into a computerized database. Age, history of contraception, sexually transmitted disease, smoking, parity, menopausal status, hormone replacement therapy, Pap smear, colposcopy, and cervical biopsy result were recorded for each patient. The student t test was used for statistical analysis.

Results

ASCUS was detected in 100 (5.3%) of the 1866 patients in the first Pap smear report. A second Pap smear was recommended to them but 14 patients were lost to follow up. Results of the distribution of first Paper smear onwards are shown in the flow chart in Figure 1. Thus 86 patients were followed up over 2 years. The mean age was 36 (range 25-75) years. Of these 73 (85%) were premenopausal. The mean parity was 1.5 (range 0-4). Eight (9%) of these were nulliparous. Out of the 13 (15.1%) postmenopausal patients, three were receiving hormone replacement therapy. Out of the 86 patients, 39 (45.8%) had a normal Pap smear, 17 (20%) had ASCUS and 3 (3.4%) had high grade squamous intraepithelial lesion (HSIL) on repeat Pap smear evaluation (Figure 1 and Table 1).

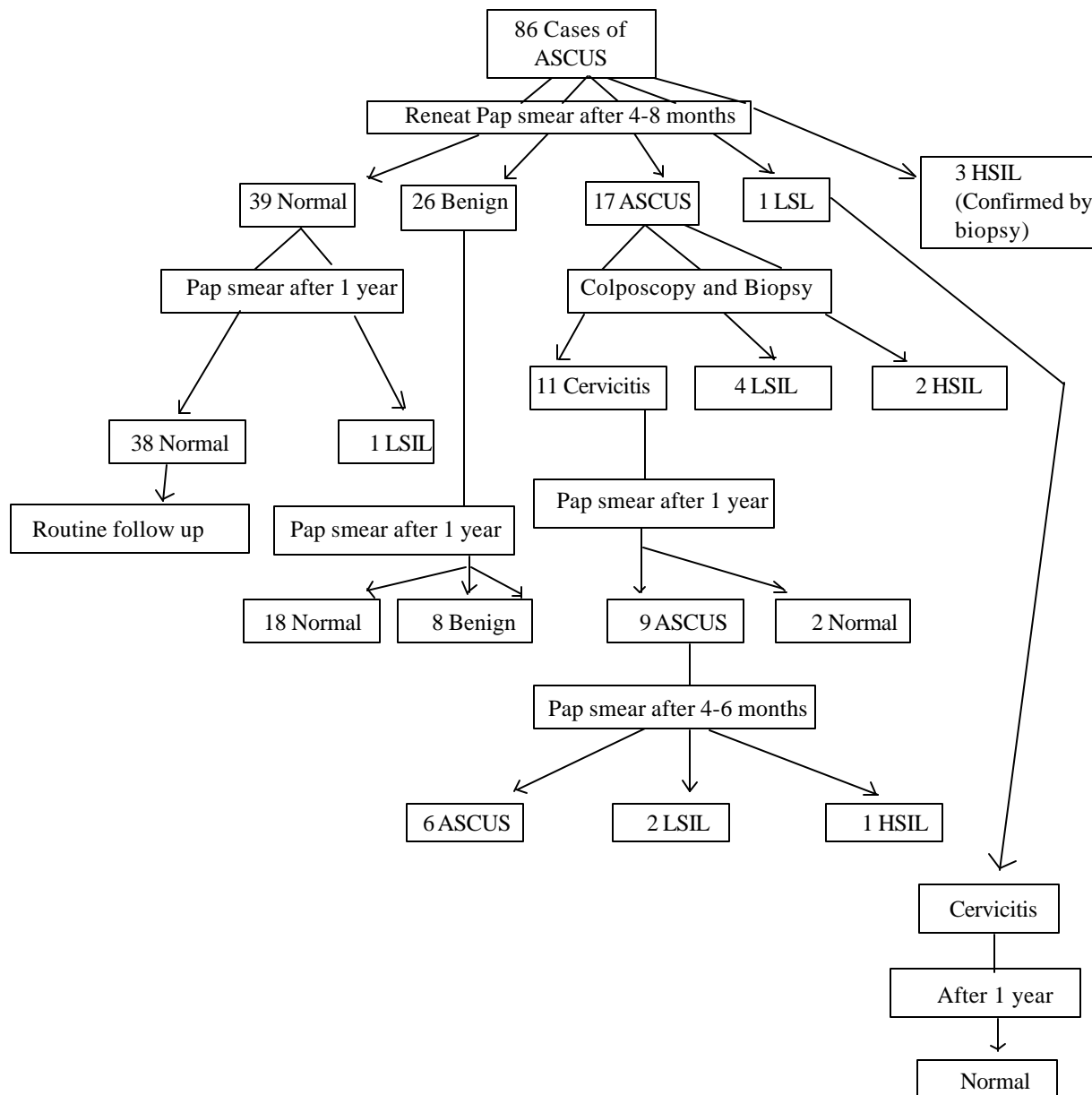


Figure 1. The schematic flow chart depicting the follow up of 86 ASCUS patients over two years.

Table 1. Diagnosis on second Pap smear (n=86).

Paper smear	Number	Percentage
Normal	39	45.3
Benign cellular changes	26	30.2
ASCUS	17	19.7
LSIL	1	1.16
HSIL	3	3.4

Twenty one patients showing ASCUS or low grade intraepithelial lesion (LSIL) or HSIL were subjected to

colposcopy and biopsy. Histology in the 17 women with ASCUS revealed 4 LSIL (23%) and 2 HSIL (11%) while the remaining 11 patients had only chronic cervicitis. Nine (52%) of these 11 patients showing cervicitis on biopsy had ASCUS for the third time on Pap smear after 4-8 months. These 11 women were further followed-up after 4-6 months when 6 showed ASCUS, 2 LSIL, and 1 HSIL. All patients with HSIL were treated by conization or hysterectomy. Patients with ASCUS or LSIL were treated with antibiotics and were followed up. Out of 17 cases of second time ASCUS only two were ultimately normal on a 2 year follow-up.

Table 2. Comparison of various studies.

Study	Incidence of ASCUS	Normal Pap smear	3rd ASCUS	LSIL on biopsy	HSIL on biopsy
Selvaggi and Haefner (1995) ²	1	70	3	19	8
Taylor et al (1993) ⁴	2	71	9	14	6
Kline and Dakey (1996) ¹⁶	6	55	19	19	
Williams et al (1997) ⁸	5	78		14	8
Nyirjesy et al (1998) ¹¹	3	70		25	5
Alanen et al (1998) ⁷	5	78	11	7	4
Gerber et al (2001) ¹²	5	49	21	21	9
Sheil and Wilbur (1997) ¹³	4	81		14	5
Lindheim and Simith-Nguyen (1990) ¹⁵		70		13	17
SBISR (2005)	5	75.4	52.9	23.5	11.76

The table has been modified from Gerber et al ¹². All figures indicate percentage.

Table 3. Patient characteristics with repeat ASCUS and normal Pap smear after 6 months

	Second ASCUS (17)	Second normal (39)	P value (Significant <0.05)
Age > 30 years	14	30	0.648
Nulliparity	2	11	0.18
Oral contraception	1	3	0.30
Smoking	1	0	0.12
Postmenopausal status	0	5	0.12
Multiple sexual partners	3	0	0.007

Discussion

ASCUS was found in 5.3% of Pap smears done for screening. The incidence was similar to that in other studies ⁶. Opting to carry out colposcopy only after ASCUS on repeated Pap smears allowed us to avoid a great number of colposcopies as 45.2% ASCUS returned to normal when a repeat smear was done and 30.2% showed only benign cellular changes. Thus overall 75.4% smears regressed. This

rate is comparable to figures in other studies whose normal results ranged between 55% and 81% ⁷. In a private clinic in our country, a colposcopy costs rupees, 2000 to 3000 and a Pap smear costs rupees 300 approximately. Applying this strategy, we saved a lot of money and did not overload colposcopy consultations. The disadvantage was that we had to perform a second Pap smear on the remaining 21 cases who ultimately required a colposcopy. We can consider

the time lost is not a significant factor because the interval time between the first Pap smear and colposcopy or treatment was less than 6 months. The additional cost of the second Pap smear is insignificant compared with the savings on the avoidable colposcopies.

Both the groups (normal and benign cellular changes on second Pap smear) showed no ASCUS or higher lesions excepts one LSIL on follow up for 1 year. 19.8% cases had persistent ASCUS on second Pap smear. It has been reported that between 10% and 30% of histological LSIL or HSIL are diagnosed when women with ASCUS are followed up⁸. In a retrospective study of 19,215 Pap smears conducted in a cancer hospital in Gujarat, the rate of CIN III in cytologically detected ASCUS was 38.89%⁹. We found a rate of 23% LSIL vs 7% to 25% in other studies¹⁰ and 11.7% HSIL vs 4% to 17% in other studies¹¹ after second ASCUS. However, the rate of third ASCUS was 52.9% in comparison to 9-12% in other studies¹² (Table 2). This was surprising as the third Pap smear was done only 4 to 8 months after the biopsy report which was normal. This may indicate a propensity for recurrent infections and therefore puts this category of patients with second time ASCUS at high risk of future cervical precancerous and cancerous lesions. The risk of HSIL among ASCUS cases cannot be ignored and needs further evaluation. We consider the delay of 4 to 6 months between the first Pap smear and colposcopic evaluation to be cost effective. In order to determine the high-risk characteristic, we compared the second ASCUS group (17) with second normal (39) group (Table 3). Multiple sexual partners is the only prognostic factor found to be significant in the ASCUS group (P=0.007). Other authors have tried to define a risk group with different categories of ASCUS reactive, pre-malignant or unqualified¹³. But the results are not conclusive and better criteria of triage of patients are necessary. It would be interesting to include screening of HPV, the relationship of HPV to cervical neoplasia being well established.

Conclusion

As the regression rate of ASCUS is as high as 75% the need for colposcopic evaluation arises only if ASCUS persists. This also helps in reducing the burden on the colposcopic consultations. However, as the progression to higher lesions is a known entity, it is of utmost importance that these patients are diligently followed up and biopsied when indicated.

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