

# Management of ASCUS findings in Papanicolaou smears. A retrospective study

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## Summary

**Aim:** Atypical squamous cells of undetermined significance (ASCUS) are a cervical cytologic finding category suggestive but not definitive of squamous intraepithelial lesions. ASCUS remains an incompletely described entity and accounts for even 5%-10% of reported Papanicolaou (Pap) smears. The management of women with such cytologic findings remains controversial. The aim of this study was to evaluate the cytology laboratory findings with regards to ASCUS diagnosis, using cervical Pap smears, and colposcopic biopsies, as well as their management. **Materials and Methods:** This is a retrospective study of patients with ASCUS Pap smears taken during the period January 2010 – December 2010 in the Second Department of Obstetrics and Gynecology, Aretaieion Hospital. **Results:** During the study period, 657 Pap smears were examined at the Aretaieion Hospital; moreover, seven patients, whose Pap smears were cytologically diagnosed with ASCUS, were referred from other clinics, providing a total of 42 cases with a descriptive diagnosis of ASCUS for review. Of the 42 cases, eight were not studied because they were either lost in follow-up or they did not have available data. The remaining 34/42 patients were evaluated by colposcopic examination and directed biopsies where necessary. The ratio of ASCUS to low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous cell intraepithelial lesion (HGSIL) or squamous cell carcinoma (SCC) was 5/34, 1/34, and 0/34, respectively. In the 34 ASCUS cases evaluated by colposcopy, the age distribution varied from 22 to 54 years. Eight of 34 cases did not have a child, 7/34 were primigravida, 18/34 were secondigravida, and 1/34 had four children. Four out of 34 cases were postmenopausal, 3/34 referred no history of abnormal bleeding, 21/34 were smokers, 6/34 used oral contraceptives, 2/34 used intrauterine devices, 1/34 took replacement of hormones, 4/34 had prior abnormal Pap smears human papillomavirus (HPV), or 1/34 had previous cancer (breast cancer). Colposcopy was inconclusive in 4/34 patients, while 8/34 cases were negative for Schiller and acetic acid tests and also had normal colposcopy. Infectious organisms were found in 8/34 patients with ASCUS, including actinomyces (1/8), trichomonas (5/8), and candida albicans (2/8). Histologic tests revealed 16/34 koilocytosis cases, 5/34 LGSIL, 1/34 HGSIL, and 0/34 SCC. **Conclusion:** The dilemma in the management of patients with an ASCUS diagnosis still exists as a significant problem for clinicians

**Key words:** ASCUS; Papanicolaou smear; Colposcopy; Management.

## Introduction

Human papillomavirus (HPV) is considered the primary etiologic agent for cervical cancer in women worldwide [1-3]. Over 100 subtypes of HPV are known with approximately 50 infecting the urogenital tract. Fifteen to 20 of these are associated with cervical cancer and types 16, 18, 31, 45, and 58 cause the majority of all cervical dysplasias and carcinomas [2-5]. Although HPV infection is considered a necessary precursor for the development of the majority of cervical carcinoma, only a small percentage of women with persistent infection progress from low- to high-grade lesions [6]. A significant percentage of cervical cytologic examinations do not yield a definitive diagnosis of dysplasia or a diagnosis within normal limits. These are designated as atypical squamous cells of undetermined significance (ASCUS).

More specifically, the ASCUS category is a cervical cytologic finding that is suggestive, but not definitive, of squamous intraepithelial lesions (SILs). ASCUS remains an incompletely described entity and accounts for even 5%-10% of reported Papanicolaou (Pap) tests [7-8, 4].

ASCUS diagnosis may indicate the presence of histological lesions ranging from cervical intraepithelial neoplasia (CIN) I to cancer in 5% - 17% and 0.2% of cases, respectively [9]. Aside from being commonly found in Pap smears, ASCUS should be considered because it can mask a higher-grade lesion, and the management of these patients remains controversial [10].

The management of women with such cytologic modifications also remains debatable [10-12]. According to the American Society for Colposcopy and Cervical Pathology, women with an initial cervical cytologic diagnosis of ASCUS should be managed by using a program of two repeated cervical cytology tests at six month intervals, immediate colposcopy, or DNA testing for high-risk types of HPV [4, 13]. These three proposed management strategies for patients with ASCUS diagnoses have been compared by using results from the randomized ALTS group trial. This comparison determined that Hybrid Capture II (HCII) testing for cancer-associated HPV DNA has a greater sensitivity to detect high-grade lesions than does cytologic testing and has a comparable specificity to a single additional cervical cytology [14]. In an earlier study, Wright *et al.* [4] compared the cost per case of detecting high-grade squamous intraepithelial lesions (HGSILs) in women with ASCUS or low-grade squamous intraepithelial lesions (LGSILs) in initial cervical

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cytology. In this study, the patients were managed by repeat cervical cytology or HCII and then followed up by colposcopic examination.

The option of reflex HPV DNA testing in triaging ASCUS for colposcopy seems sensible, particularly in settings where compliance to follow up Pap schedules is a challenge. It may also assure women negative for high-risk HPV, that they do not have a significant lesion, and offer an opportunity for prompt management of those with high-risk results [15].

The practice of regular Pap smear screening to detect premalignant changes in the cervix has been proven to be an effective means of preventing cervical carcinoma. These abnormalities are of concern because approximately 10%-15% of patients with LGSIL [16, 17] and an uncertain proportion of women with ASCUS [18-22] will be found to have a higher-grade lesion at colposcopy. Although immediate referral to colposcopy is advocated by some, it remains to be proven that this is necessary and cost-effective [10, 23, 24]. There are also valid concerns that many women with minor cervical abnormalities are being tested repeatedly or treated unnecessarily, resulting in costs to the healthcare system, estimated to be more than six billion annually in the US alone [10].

The aim of this study was to evaluate the cytology laboratory performance with regard to ASCUS diagnosis, using cervical Pap smears, and colposcopic biopsies obtained from a referral colposcopy clinic over a one-year period. The objectives of this study were: 1) to determine the ASCUS rate and ASCUS/SIL ratio in the laboratory; 2) to compare the colposcopy clinic and referring Pap smear results.

## Materials and Methods

A retrospective study of patients with ASCUS Pap smears, taken during the period January 2010 – December 2010, was performed. Most patients enrolled in the present research had an ASCUS report following a Pap smear in the Second Department of Obstetrics and Gynecology, Aretaieion Hospital, and the remainder was referred to this Hospital from other clinics. The study protocol was approved by the Ethical Committee of the Hospital. Women who had been previously diagnosed with SIL or cervical carcinoma, and pregnant women were excluded. Cytological criteria for diagnosis of ASCUS focused on nuclear enlargement, variation in size and shape of the nucleus, mild nuclear hyperchromasia with evenly distributed chromatin, and regularly smooth nuclear outlines. More specifically, ASCUS was established as a diagnostic category to allow the reporting of cervico-vaginal smears that could not be definitively assigned to the normal and benign cellular changes or to SIL categories. ASCUS refers to cellular abnormalities that are more marked than those resulting from reactive alterations but are quantitatively and/or qualitatively insufficient for a definitive diagnosis of SIL [10]. The diagnostic criteria for ASCUS included: bland nuclear enlargement (two- to three-fold the area of squamous cells nuclei), smooth nuclear membranes, nuclear hyperchromasia, cellular shape, and dimensional changes. These cytological abnormalities are characterized by epithelial changes associated with reactive/inflammatory processes, sampling artifacts, or SIL [10].

All women underwent a colposcopic examination by an experienced colposcopist. Colposcopic examination was performed with a binocular colposcopic device after applying 5% acetic acid solution and painting of the cervix with Lugol's solution. The examination was considered satisfactory when the entire squamocolumnar junction (SCJ) and the margin of any visible lesion could be visualized with the colposcope. A colposcopy was considered positive when a flat or slightly elevated, mostly well-demarcated, aceto-reactive lesion, a punctuate capillary pattern, or a mosaic pattern could be found after acetic acid application. Colposcopies were defined non-satisfactory if SCJ was not visible during the examination. If the examination suggested any cervical abnormality, a directed biopsy was conducted.

The medical records of all ASCUS patients were reviewed and the retrieved data consisted of the woman's age, gravidity, parity, menopausal status, as well as any history of abnormal bleeding, smoking, use of oral contraceptives, intrauterine devices, hormonal replacement, prior abnormal Pap smear, or previous cancer. The surgical-pathological files were searched, and clinic records and subsequent cervical vaginal cytologies were checked to determine follow-up diagnosis. Clinicians following and treating these patients were contacted when records were incomplete or not available in colposcopy or in the gynecology clinic. The pathologic material was reported by three pathologists using relatively uniform criteria and terminology. In cases without tissue biopsies, diagnoses were based on the colposcopic examination. Then final diagnoses were correlated to the ASCUS smears. For the patients followed only by cytology, the outcome diagnosis was determined by the most recent Pap smear. For the patients who underwent colposcopic evaluation, the outcome diagnosis was the more significant of either the biopsy or Pap smear taken at the time of colposcopy.

Data was analyzed by SPSS software. When a probability was less than 0.05, the comparison was documented to be significant.

## Results

During the study period, 657 Pap smears were examined at the Aretaieion Hospital. Moreover, seven patients, whose Pap smears were cytologically diagnosed with ASCUS, were referred from other clinics, providing a total of 42 cases with a descriptive diagnosis of ASCUS for review. Of the 42 cases, eight were not studied because were either lost in follow-up or did not have available data. The remaining 34/42 patients were evaluated with colposcopic examination and with directed biopsies if necessary. The ratio of ASCUS to LGSIL, HGSIL, or SCC was 5/34, 1/34, and 0/34, respectively.

In the 34 ASCUS cases evaluated by colposcopy, the age distribution varied from 22 to 54 years. Eight of 34 cases did not have a child, 7/34 were primigravida, 18/34 were secondigravida, and 1/34 had four children. Four out of 34 cases were postmenopausal, 3/34 referred no history of abnormal bleeding, 21/34 smoked, 6/34 used oral contraceptives, 2/34 used intrauterine devices, 1/34 took hormonal replacement, 4/34 had prior abnormal Pap smears (HPV), or 1/34 previous cancer (breast cancer).

Colposcopy was inconclusive in 4/34 patients, while 8/34 cases were negative for Schiller and acetic acid tests and also had normal colposcopy. Infectious organisms were found in 8/34 patients with ASCUS, including actin-

Table 1. — Final histological diagnoses of atypical squamous cells of undetermined significance (ASCUS).

Final diagnosis	ASCUS n
Cervicitis	8/34
Koilocytosis	16/34
LSIL	5/34
HSIL	1/34
SCC	0/34
Total	34

omyces (1/8), trichomonas (5/8), and candida albicans (2/8). Histologic tests revealed 16/34 cases with koilocytosis, 5/34 LGSIL, 1/34 HGSIL and 0/34 SCC. The results for the 34 patients with ASCUS are presented in Table 1.

With regards to the time needed for the discovery of subsequent LGSIL or HGSIL after ASCUS was diagnosed, the final cytologic diagnosis was made three months after the first ASCUS diagnosis in 5/6 of patients; for 1/6 of patients, the diagnosis was made six months after the initial diagnosis.

No correlation was demonstrated between age, smoking, parity, contraceptive method, or menopausal status at detection of ASCUS, and subsequent detection of LGSIL or HGSIL in any group ( $p > 0.05$ )

## Discussion

In the current study, the authors attempted to evaluate outcomes in the largest group of women diagnosed with ASCUS according to cervical smear reports.

The prevalence of ASCUS varied from 1.8% to 10% in different studies [25-27]. In the present study, ASCUS was found in 42/664 of the Pap smears performed for screening. Such a wide variation may be due to differences in population characteristics and differences in the characteristics of the samples studied. In the current study, the specimens for cytopathologic evaluation were collected at clinics for the purpose of cervical carcinoma screening. Most patients were asymptomatic and were representative of a population at low-risk for cervical carcinoma. It has been claimed that the Thin Prep method lowers the percentage of borderline Pap smear diagnoses such as ASCUS, and increases the percentage of more accurate Pap smears diagnoses such as SILs [28].

In general, the Bethesda System (TBS) recommends that the frequency of ASCUS diagnoses should not exceed two or three times the rate of SIL in any given laboratory [10]. In the present study, the authors found those values to be 42/664 for ASCUS and 12/664 for SIL (4/12 LGSIL, 8/12 HGSIL), which are in accordance with TBS guidelines.

The optimal method for managing a patient diagnosed with ASCUS has not yet being established. Conservative follow-up with repeated cytologic evaluations at shortened intervals has been used as standard practice. The interim guidelines published by the National Cancer Institute suggest that a patient should be referred for col-

poscopy after the second ASCUS diagnosis within two years [10]. The American College of Obstetrician and Gynecologists however, suggests that patients with at least two consecutive ASCUS diagnoses, or one ASCUS diagnosis with the presence of high-risk factor (such as HPV infection, cigarette smoking, or multiple sexual partners) should be referred for further evaluation [29].

Most reports agree that patients whose cervical smears fall within the ASCUS diagnostic category have a significant incidence of SIL on follow-up biopsies, with rates varying from 13.5% to 58% and the majority being LGSIL [25, 30, 36]. This was also confirmed in the present study. Manos *et al.* [37] have proposed that the rate of progression from ASCUS to HGSIL is significant, but substantially less than the rate of progression from LGSIL to HGSIL. These same authors suggested that the risk of progression (within two years) from ASCUS to HGSIL is greater than the risk of progression from normal or reactive findings to HGSIL, but less than the risk of progression from LGSIL to HGSIL [37]. ASCUS, therefore, truly is an intermediate cytologic category.

In the present study, among patients with ASCUS who were followed for two years, approximately 5/34 developed LGSIL and 1/34 developed HGSIL. All the diagnoses were confirmed histologically. The incidence of carcinoma in situ or invasive cervical cancer among patients with ASCUS varied between 0.14 and 0.46% [28]. In the present study, the authors did not identify such a patient.

No correlation was found in the present study regarding LGSIL or higher-grade findings with age, parity, menopausal status, smoking, contraceptive methods, or hormonal replacement treatment. This interpretation, however, is limited by the small number of women detected with LGSIL or HGSIL in this segment of the study population.

It should be mentioned that in the postmenopausal period, most common diagnostic tools (Pap smear and colposcopy) used for the diagnosis of CIN have several limitations. Postmenopausal hypoestrogenism could be followed by atrophic changes in the urogenital female tract, such as the involution of cervical tissue. A common finding in postmenopausal women is an increase in the number of diagnosis of ASCUS with a higher ASCUS/LGSIL ratio. However, in postmenopausal women ASCUS has a low-positive predictive value. Mature squamous cells with enlarged nuclei have been classified as ASCUS. However, in postmenopausal women, as opposed to younger women, this bland nuclear enlargement is relatively common and rarely associated with a significant histologic abnormality [38]. This bland nuclear enlargement due to atrophic changes might be the cause of the increased number of ASCUS diagnosis in menopause. Therefore, with a single course of local estrogen replacement therapy, it may be possible to distinguish between benign chorionic villus sampling mimicking atrophy and true preneoplastic changes. Estrogen therapy will often cause enough ectropion of the endocervical cells so that the entire SCJ can be visualized. Moreover, it may reduce

the number of endocervical curettage or loop excision or cone procedure for women with inadequate colposcopic examination [38].

From the study of Rader *et al.* [26], the association of a diagnosis of ASCUS and the presence of HPV infection also seems clear. Although, the authors did not perform HPV-DNA testing due to the high cost, a number of studies have shown the advantages of using HPV DNA testing to determine which patients with a cytologic diagnosis of ASCUS should be referred to colposcopy and biopsy [4, 13, 14, 38]. These studies have demonstrated that HPV testing is the preferred triage technique for ASCUS specimens. Prior studies have generally investigated ASCUS triage by HPV DNA testing, using the HCII method. Kim *et al.* [13] pointed out that HPV testing in patients with ASCUS smears may provide the best prognostic information and thus may be the most cost-effective management strategy for these women. For women with ASCUS cytology interpretations, the ALTS data demonstrate that HPV triage is at least as sensitive as immediate colposcopy in the detection of underlying CIN III, while nearly halving the number of women referred for colposcopy. Repeat cytology with colposcopic referral at an ASCUS threshold is also sensitive in detecting CIN III but requires repeated visits and leads to significantly more colposcopic examinations than does a single HPV test [14].

HPV testing was highly-sensitive for detecting cancer in women ASCUS, especially in older women [29]. Thus, HPV testing should be used as a triage test if the cost is not considered. In a situation where follow-up care is uncertain and the patient might be at increased risk, immediate colposcopy could be more effective [10].

## Conclusion

The management of patients with an ASCUS diagnosis remains controversial and a significant problem for clinicians. The dilemma in the management of ASCUS patients also stems from the uncertain clinical significance of this diagnosis and the variable prevalence of SIL in these patients.

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