AGUS and ASCUS: different incidence in pre- and post-menopausal women

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Summary

Purpose of investigation: The aim of this study was to determine the incidence of AGUS (atypical glandular cells of undetermined significance), ASCUS (atypical squamous cells of undetermined significance) and SIL (squamous intraepithelial lesion) in the cytologic diagnosis in pre- and postmenopausal women.

Methods: We did a retrospective study selecting 183 patients who were screened for cervical pathology. Ninety-six patients were in postmenopausal age. We determined the incidence of cytologic abnormalities defined as ASCUS, SIL, and AGUS in pre- and postmenopausal women.

Results: We expected a marked incidence of low-grade SILs in the fertile population, while the postmenopausal group was thought to be affected more by AGUS and ASCUS. We obtained different results. In our population study, premenopausal women presented more AGUS and ASCUS; the two subgroups presented the same incidence of low-grade SILs; postmenopausal women were more affected by high-grade SILs.

Conclusions: The significance of the new categories introduced by the Bethesda System is still uncertain for different authors. As we look to the future new markers that more specifically identify individuals at-risk can be expected.

Key words: CIN; Bethesda system; Precancerous lesion.

Introduction

Every year 10% of advanced age patients reveal abnormal bleeding. Pap-smears, colposcopy and hysteroscopy are important diagnostic steps in the presence of abnormal bleeding in postmenopausal patients. The vaginal bleeding in 50% of these patients is not due to malignant or premalignant lesions. In the remaining cases several abnormalities were revealed ranging from precancerous lesions to invasive cancer.

The Pap test has been the best method of screening for every kind of cervical lesion. International screening has given evidence of a high percentage of abnormal Pap smears with an incidence of abnormal smears ranging from 0.3% to 1.1% patients [1-4].

The Bethesda System introduced new terminology to define the classes of Papanicolau CIN (cervical intraneoplasia): squamous intraepithelial lesion (SIL), divided in low-grade (LSIL-corresponding to coilocytosis and/or CIN I) and high-grade (HSIL-corresponding to CIN II or CIN III).

The Bethesda System [5-8] in 2001 revised the guidelines for the management of patients with low-grade abnormal cervical cytology: after initial follow-up they revert to three yearly screenings. The concept of "specimen adequacy" for cervical cytology is another new aspect stressed by the Bethesda System terminology. The recognition of inadequate specimens has reduced the incidence of false-negative tests. On the other hand the introduction of two other classes for reporting borderline cytological changes in cervical cytology, ASCUS (atypical squamous cells of undetermined significance) and AGUS (atypical glandular cells of undetermined significance), can induce other problems related to recognition of "real" ASCUS and AGUS, including the risk of downgrading the specimens.

In the 2001 Bethesda System classification ASCUS lesions have been split into two categories: ASC-US and ASC-H which correspond respectively to LSIL and HSIL.

Our study was undertaken in order to retrospectively evaluate Pap smears eprformed in 2001, to obtain the incidence of cervical lesions in premenopausal and postmenopausal women.

Materials and Methods

A laboratory database was used to identify all cervical specimens obtained at the Department of Gynecology and Obstetrics of the II University of Naples from January to December 2001 and data were extracted from patient records retrospectively. Data were analyzed for 1,012 patients who were at least 17 years old (mean = 49 years) with satisfactory baseline Pap tests; 183 presented cervical lesions defined as ASCUS, AGUS and SILs.

The criteria for the diagnosis of ASCUS [9, 10] for squamous cells were: slightly increased nuclear-cytoplasmic ratio, increased nuclear dimension (not more than twice a normal nucleus) and slight hyperchromic chromatin. The diagnosis of AGUS on glandular cells was based on the presence of nuclear atypia that was more remarkable with respect to an inflammatory reaction. SILs were defined in the presence of HPV cytopathic effects, dysplasia and Richart's CIN classes [11, 12]. The specimens were obtained using common Pap smears colored with hematoxylin-eosin.

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The population study included 183 patients; 96 were in postmenopausal age and 87 in premenopausal age. The percentage of AGUS, ASCUS and SIL in the different subgroups was determined. The data of each patient was collected including weight, infertility, parity, previous cervical infections, abnormal menstrual bleeding, duration of menstruation (> 7 days), number of partners and smoking habits.

Results

Of the total 1,012 cervical pap smears processed from January to December 2001 in our department, 183 were included in this study because they were positive for AGUS, ASCUS and SIL. The ages of the patients ranged from 17 to 62 years (median age 49 years). The 183 patients were divided into pre- and postmenopausal age. Ninety-six were in postmenopause (group A) and 87 were still fertile (group B). The different incidences in the two groups were calculated and are shown in Table 1. In the postmenopausal group (Group A), one patient (1.04%) presented a Pap smear with AGUS; three (3.13%) presented ASCUS; five SILs (5.2%) were identified. The percentage of LSIL and HSIL in group A was calculated: one patient (1.04%) was positive for LSIL; four patients presented HSIL lesions.

Table 1. — *The incidence of AGUS, ASCUS and SIL (Bethesda System) in our population study.*

	Postmenopausal (Group A)	Premenopausal (Group B)
ASCUS	3 (3.13%)	5 (5.75%)
AGUS	1 (1.04%)	1 (1.15%)
LSIL	1 (1.04%)	2 (2.30%)
HSIL	4 (4.17%)	1 (1.15%)

In the premenopausal group (Group B), AGUS was present in one patient (1.15%). Five patients revealed ASCUS (5.75%) on Pap smears and three patients were affected by SIL (3.45%), two of which presented LSIL.

In postmenopausal women, one case of CIN I was found, two CIN II, and two CIN III and two coilocytosis were found in the premenopausal group, corresponding to two cases of LSIL and one CIN II. The correspondence between the Bethesda System and Richart's classification is shown in Table 2.

Table 2. — *Correspondence between Richart's classes and Bethesda System.*

	LSIL		HSIL	
	Group A	Group B	Group A	Group B
Coilocytosis	0	2	0	0
CIN I	1	0	0	0
CIN II	0	0	2	1
CIN III	0	0	2	0
Total	1	2	4	1

Table 3 displays the distribution of risk factors among study participants which included the following: weight > 80 kg (26.7%), parity (73.7%), infertility (7.1%), prolonged menstrual bleeding of > 7 days' duration (32%), previous cervical infections (38.2%) and number of partners > 3 (15.8%).

Table 3. — *Incidence of risk factors in the study population.*

Risk factors	No. of patients	Percentage
Weight > 80 kg	49	26.7%
Parity	135	73.7%
Infertility	13	7.1%
Menstual bleeding > 7 days	58	32.0%
Previous cervical infections	70	38.2%
Number of partners > 3	30	15.8%
Smokers	75	40.1%

The median duration of infertility was 8.5 years (range 1-23 years).

Discussion

Before the advent of mass screening for cervical cancer precursors, approximately 3% to 4% of women developed cervical cancer [13, 14]. During the last 50 years the incidence of cervical cancer and mortality has decreased more than 75%. The reasons for this medical success lie in the early detection of precancerous lesions and the less invasive methods of treatment such as traditional ablative or excisional treatment options.

Moreover, studies on the etiology and natural history of cervical cancer precursor lesions and the immune response to them has given new direction to management options that include preventive measures and healthy dietary habits [9].

Todays cancer of the cervix presents an incidence of 3,700 new cases yearly and still represents 3.6% of female cancers in Italy. Five-year survival has increased from 63% to 65% in the last decade.

Differently from other countries, the screening for cervical carcinoma in Italy has not been applied homogeneously, collecting most adhesions among women over 50 years of age.

The significance of the new categories introduced by the Bethesda System is still uncertain for different authors. The definitions of AGUS and ASCUS, in particular, are not well defined. According to some authors they represent a "wastebasket" for uncertain cytologic diagnoses [15, 16]. The risk of Bethesda System classes is the overdiagnosis and consequently the overtreatment of patients, when several patient data (such as age, hormonal therapy, tamoxifen therapy) are incomplete [17, 18].

Conclusion

The actual guidelines recommend that the cases of ASCUS be limited to 5% of the cytologic diagnoses; even AGUS must not be more than 0.3-0.5%. These percentages are necessary to minimize the equivocal diagnosis. The debate does not concern just terminology but even economics: the patients whose pap smears present the diagnosis of ASCUS must be studied through colposcopy, thus becoming more expensive [15].

Considering the increasing life-time expectancy and the aims of the Bethesda System, it is worthwhile, in our opinion, to review our cytologic diagnoses.

The two groups in this report were studied similarly. The two populations presented a similar incidence of minor cervical precancerous lesions. The incidence of LSIL in group A was 1.04%, which was not so different from 2.30% in group B. As we expected, the cytopathic effect of HPV was found in premenopausal women.

The incidence of ASCUS in premenopausal women, considering both the relative and absolute frequency, was higher with respect to postmenopausal women. The percentages were 3.13% vs 5.75% The incidence of AGUS appeared similar between the two groups: although the absolute frequency was the same, the relative one was different (1.04% vs 1.15%). The different percentages between the two groups can be due to two reasons: a) increasing inflammatory diseases in fertile age; b) higher prevention among younger women.

We expected different results, considering the physiologic changes in the genital tract in postmenopausal age such as dystrophy and alteration af the T-zone. According to Flynn and Rimm [14], the diagnosis of ASCUS in the elderly is 2.3 times less reliable than in younger women. It should thus be advisable, to repeat the Pap smears in elderly women after estrogenic therapy.

This result agrees with that of Herrero *et al.* [11], who noted a spike of HPV infection in fertile women. It is interesting to note that all 30 patients who asserted to having had more than three partners belonged to group B.

As we look to the future we can expect new markers that more specifically identify individuals at-risk.

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