

Reclassification and analysis of clinical significance of atypical glandular cells on ThinPrep using The Bethesda 2001: Geneva experience

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Summary

Background: The category “atypical glandular cells” (AGC) in The Bethesda System (TBS) 2001 represents equivocal glandular atypia. The objective was to determine the clinical significance of diagnosing AGC using new TBS 2001 on ThinPrep. There is scant information on the diagnosis of AGC and its outcome on ThinPrep using TBS 2001.

Methods: 174 “ThinPrep®” Pap tests reported as atypical glandular cells of unknown significance (AGUS) using TBS 1991 during the period (2001–2004) were reclassified using AGC subcategories of TBS 2001. Follow-up histology was correlated with AGC subcategories of TBS 2001 and in women <40 and ≥40 years of age.

Results: The mean AGC rate significantly decreased from 0.7% to 0.3%. ($p < 0.02$). The frequency of clinically significant lesions on follow-up was higher with AGC diagnosis (51%, 21/41) than AGUS diagnosis (36%, 37/103). It was significantly higher for atypical endocervical cells

favouring neoplasia (AEC-FN) (67%, 4/6) and AGC with concurrent squamous intraepithelial lesions (SIL) (67%, 8/12) than for the atypical endocervical cells, not otherwise specified (AEC-NOS) subcategory (12.5%, 2/16). All clinically significant lesions were high grade squamous intraepithelial lesions (HSIL) in women <40 years but in women ≥40 years, the majority (70%) were glandular. In categories atypical glandular cells favouring neoplasia (AGC-FN) and atypical endometrial cells (AEMC) all women had clinically significant glandular lesions.

Conclusions: AEC-FN, AGC-FN, AEMC and AGC with concurrent SIL subcategories represented high risk diagnoses. The sequence of further investigations may vary by age and presence of postmenopausal bleeding.

Key words: The Bethesda System 2001; atypical glandular cells; ThinPrep

List of abbreviations

ADCA	Adenocarcinoma
AEMC	Atypical endometrial cells (as used under the 2001 Bethesda system)
AEC-FN	Atypical endocervical cells favour neoplasia (subcategory of atypical glandular cells as under the 2001 Bethesda system)
AEC-NOS	Atypical endocervical cells, not otherwise specified (subcategory of atypical glandular cells as under the 2001 Bethesda system)
AGUS	Atypical glandular cells of unknown significance (as used under the old 1989 and 1991 Bethesda system)
AGC	Atypical glandular cells (as under the 2001 Bethesda system)
AGC-FN	Atypical glandular cells favouring neoplasia (subcategory of atypical glandular cells as under the 2001 Bethesda system)

AIS	Adenocarcinoma in situ (as used under the 2001 Bethesda system)
CS	Conventional smear
ECC	Endocervical curettage
HSIL	High grade squamous intraepithelial lesion (as under the 1991 Bethesda system)
LSIL	Low grade squamous intraepithelial lesion (as under the 1991 Bethesda system)
SIL	Squamous intraepithelial lesion
PPV	Positive predictive value
TBS	The Bethesda System
TP	ThinPrep

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Introduction

Glandular cells in Pap samples have increased due to the rising incidence of glandular lesions and better sampling techniques [1, 2]. Thus it has become necessary for cytologists to be familiar with cytological features of various glandular lesions and their mimics, and to be aware of the clinical significance of different categories under the reporting system in use.

The term atypical glandular cells of unknown significance (AGUS) was first introduced into The Bethesda System (TBS) in 1988. It is defined as endocervical or endometrial glandular cells exhibiting changes beyond reactive or repair, but lacking unequivocal features of invasive adenocarcinoma (ADCA) [3]. In 1991, the qualifier “favour reactive” and “favour neoplasia” were added to help differentiate between AGUS of benign appearance and those more likely to result in malignant pathology [4]. In 2001, radical changes were made. AGUS was changed to atypical glandular cells (AGC) and the category “favour reactive”, considered misleading, was eliminated. Distinction of atypical endocervical cells favouring neoplasia (AEC-FN) and atypical endocervical cells, not otherwise specified (AEC-NOS) was advocated. Also, it was held that AGC should whenever possible be further characterised by the cell of origin as endocervical or endometrial. Two separate categories for adenocarcinoma in situ (AIS)

and exfoliated endometrial cells in women over 40 were created [5].

The cytological criteria are now better established, with good interobserver agreement for the diagnosis of high grade glandular abnormalities such as AIS and ADCA as compared to AGC, which represents equivocal glandular atypia. There is scant published data on experience in the diagnosis of AGC on liquid based cytology as compared to conventional smear (CS) [6, 7]. Our laboratory changed to ThinPrep (TP) in 1997. Revised TBS 2001 terminology is gradually being implemented and the clinical relevance for AGC is under study in other centres [8, 9]. The management guidelines are not universally followed [10, 11]. In response to these emerging challenges and as a preparation for laboratory adaptation of TBS 2001 for AGC, this retrospective study was done with analysis of follow-up histology. The objective was to determine the clinical significance of different subcategories of AGC under TBS 2001 in the Geneva population, thus helping to formulate the most appropriate follow-up guidelines and avoid unnecessary investigations. This would also create awareness of cytological features of different subcategories of AGC under TBS 2001 on TP, identify areas of difficulty and increase diagnostic accuracy.

Materials and methods

The diagnosis of AGUS was rendered in 185 cases out of 26,919 Papanicolaou (Pap) tests screened during the 4-year period (2001–2004). These were retrieved along with the clinical data. Cases with cytodagnosis of AIS or ADCA were not included. 11 cases were excluded due to unavailability of slides or previous hysterectomy (as slides did not represent the cervix).

During the study period all Pap samples were obtained by cervix brush (CombiPlus, Trimastek Medical, Neuchâtel, Switzerland) and were processed to make ThinPrep® (Cytoc Europe S.A., Lausanne, Switzerland) slides. Qualifiers recommended by TBS 1991 “favouring reactive” and “favouring neoplasia” were not in use, but qualifiers for site of origin of cells and notes to exclude high grade squamous intraepithelial lesion (HSIL) were added wherever appropriate.

TP slides of 174 patients were reviewed retrospectively and reclassified using the TBS 2001 terminology without knowledge of follow-up data. Features based on criteria chosen from the literature [5, 6] and agreed by consensus were used, and are as follows:

Criteria	Cytological features
Architecture	Cell strips, 3D groups, sheets, syncytium, single atypical cells, feathering and rosettes
Cytoplasm	Quantity, vacuoles, cell border, cilia

Nucleus	Nuclear overlapping, hyperchromasia, size, shape, anisonucleosis, N/C ratio, chromatin, nuclear membrane thickening and regularity, naked nuclei, mitosis
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Nucleoli	Prominence, size (macro or micro)
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Reactive endocervical cells were characterised as having minimal nuclear overlap, mild variation in nuclear shape, enlarged nucleus 3–5 times normal size, mild hyperchromasia, presence of nucleoli and abundant cytoplasm. AEC-FN were characterised by flat sheets, strips and rosettes, high N/C ratio, ill-defined cell borders, marked nuclear overlap and crowding, hyperchromasia with granular chromatin and indistinct or distinct nucleoli. AEC-NOS had features overlapping with reactive endocervical cells and AEC-FN. Atypical endometrial cells (AEMC) appeared in small groups with slight nuclear enlargement, mild hyperchromasia, small nucleoli, ill defined cell borders and scant vacuolated cytoplasm.

The cases were divided into two groups by age, i.e. women <40 years and ≥40 years. Correlation with histology was done. The predictability of “clinically significant lesions” was studied among AGC subcategories. Under “clinically significant lesions” we included high grade SIL (CIN 2, CIN 3, and CIS), endocervical AIS, and all invasive cancers classified as cervical, endometrial or ovarian.

Results

The patients' age range was 17–89 years with a mean of 47 years and median 57 years. 66 women were <40 years and 108 were ≥40. The patient population consisted of asymptomatic women receiving annual Pap test, high risk women and symptomatic women. The most common symptom was metrorrhagia, which was present in 14 patients, followed by postmenopausal bleeding in 7 patients. Six were pregnant and eight were HIV positive.

The annual AGUS rate steadily increased from 0.4% to 0.9% over the 4-year period. Using revised TBS 2001 terminology, the AGC rate increased initially for the first three years and declined slightly in the last year. The mean AGC rate was 0.3% as compared to a mean AGUS rate of 0.7% (figure 1).

Only 37% (64/174) AGUS cases were reclassified as AGC, the remainder were low or high grade SIL (14%, 25/174), reactive glandular cells (44%, 76/174) and tubal metaplasia with atypia in glandular cells (2%, 3/174). Among AGC, 86% (55/64) were classified as of endocervical origin i.e. AEC-FN (13%, 8/64), AEC-NOS (47%, 30/64) and AEC with concurrent SIL (HSIL or LSIL) (27%, 17/64). In 8% of cases (5/64) the cells of origin could not be determined and were reclassified as AGC-FN. Another 6% (4/64) were reclassified as AEMC. In women over 40, 3% (6/174) were diagnosed as having endometrial cells.

Cytological features: Three-dimensional groups of crowded cells with hyperchromatic nuclei formed the low power trigger for a diagnosis of AGC. As compared to CS, these cells in the TP slide showed ill defined cytoplasmic borders, enhanced nuclear shrinkage, rounding up of cells leading to tight clustering and formation of hyperchromatic 3-dimensional cell groups. In addition, mitosis was frequent and nucleoli were often distinctly visible in contrast to CS. We had difficulty in distinguishing normal endometrial cells from endocervical cells and reserve cell hyperplasia. Sometimes the atypical glandular cells could not be further characterised by the cell of origin. Cytohistological correlation showed that HSIL was often interpreted as AEC-FN (figure 2 A–F).

A total of 103 out of 174 women (59%) had a

histological follow-up, out of whom only 41 were reclassified as AGC on cytology. 16% of women (28/174) were followed up by cytology alone without biopsy evaluation. The frequency of clinically significant lesions with AGUS diagnosis was 36% (37/103), which after review using TBS 2001 rose to 51% (21/41) (table 1). The proportion of squamous and glandular lesions remained almost the same in both classification systems. All glandular lesions were located in the uterine body and comprised predominantly endometrial carcinomas (11%) and a few ovarian carcinomas (3%). There was no case of endocervical ADCA or AIS. Three out of 38 cases considered negative on review showed clinically significant glandular lesions.

The predictability of clinically significant lesions varied among AGC subcategories (table 2). The AEC-FN category showed higher predictability for clinically significant lesions (67%, 4/6) as compared to AEC-NOS (13%, 2/16). AEC-FN showed predominantly HSIL (75%), while AEC-NOS showed one HSIL and one endometrial ADCA. Concurrent SIL (low or high grade) was highly predictive of subsequent SIL, as all the lesions were squamous in AEC-NOS+ SIL and HSIL was detected in 67% (8/12) cases.

All cases of AGC-FN (5/5) and AEMC (2/2) showed clinically significant lesions of glandular origin and were located in the uterine body (5 endometrial and 2 ovarian ADCA). Five women with exfoliated endometrial cells ranged in age from 55 to 90 years. Three of them had lesions endometrial in origin (1 endometrial ADCA, 1 atypical complex hyperplasia and 1 endometrial polyp) while two were negative.

The distribution of clinically significant lesions in two groups of women based on age (women <40 and ≥40 with AGC) is shown in table 3. This further highlights that the origin of these lesions is determined by age. There was no difference in the proportion of clinically significant lesions, which was almost the same in both age groups under both systems. However, it is noteworthy that among women <40 years with diagnosis of AGC, all clinically significant lesions were HSIL. Among women ≥40 years with a diagnosis of AGC, the majority of 69% (9/13) were

Figure 1

Annual rate for cyto-diagnosis of AGUS (TBS 1991) and AGC (TBS2001) on thin prep Pap test over 4 years.

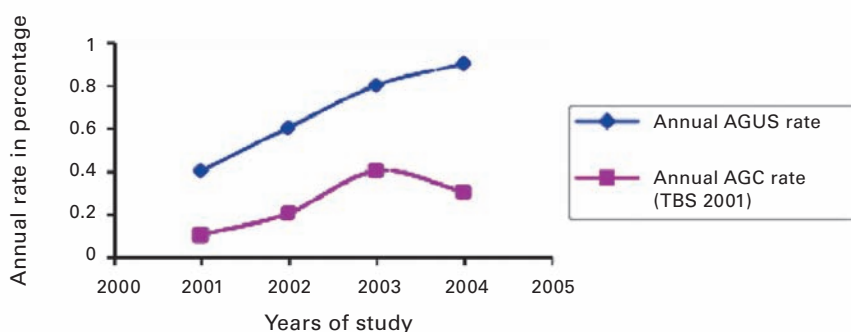
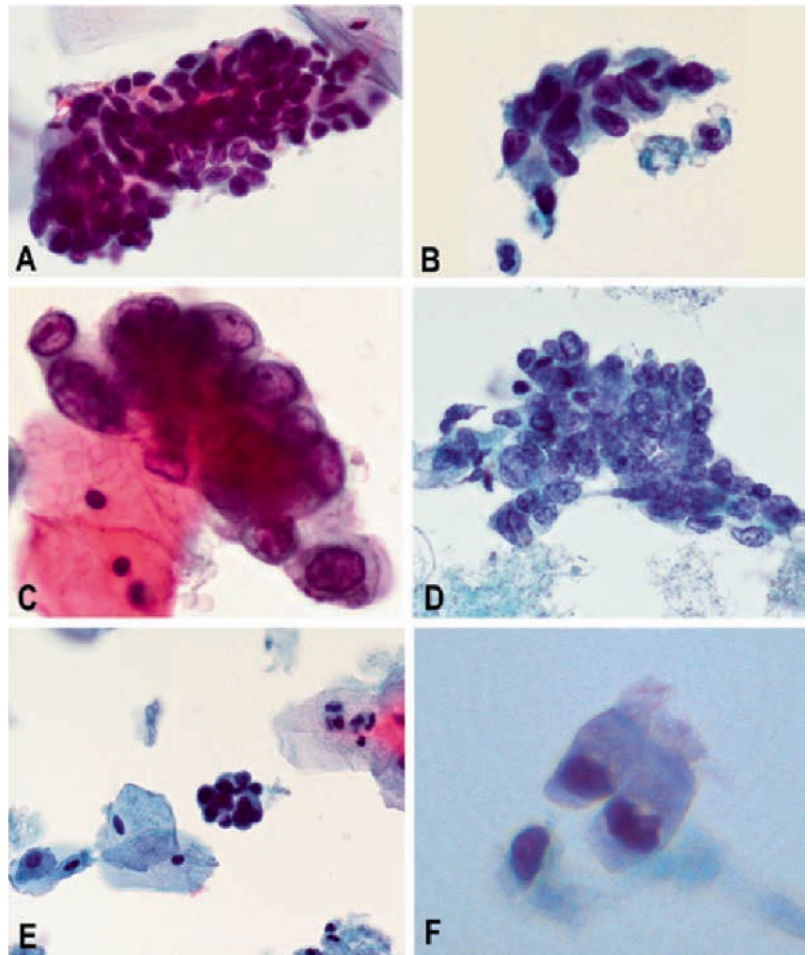


Figure 2

- A HSIL misdiagnosed as AEC-FN. Crowded group of cells with mild nuclear overlapping, loss of central polarity, hyperchromatic nuclei, high NC ratio, marked pleomorphism, coarse chromatin, absent nucleoli, moderate cytoplasm (34/F, cone biopsy-CIN 3 involving endocervical gland) (ThinPrep, $\times 400$, Papanicolaou stain).
- B AEC-NOS. Sheet of cells with mild disarray, minimal nuclear overlap, enlarged nucleus, mild hyperchromasia, small inconspicuous nucleolus, slight variation in size and shape (37/F, follow up was CIN1) (ThinPrep, $\times 400$, Papanicolaou stain).
- C AGC-FN: Three dimensional group of cells with rounded margin, marked nuclear overlap, hyperchromatic, enlarged round to oval nuclei, prominent nucleolus (follow-up was endometrial carcinoma) (ThinPrep, $\times 600$, Papanicolaou stain).
- D Atypical endometrial cells. Crowded group of small cells with mildly hyperchromatic round nuclei, slight anisonucleosis, small nucleoli, scant cytoplasm (80-year-old with postmenopausal bleedings) (follow-up was endometrial well differentiated adenocarcinoma) (ThinPrep, $\times 400$, Papanicolaou stain).
- E Endometrial cells/endocervical cells/reserve cell hyperplasia. Three-dimensional tight cluster with scalloped border, scant cytoplasm, small hyperchromatic nuclei and absent nucleoli. (Follow-up was endometrial polyp) (ThinPrep, $\times 400$, Papanicolaou stain).
- F Reactive (benign) atypia. Columnar cells with atypical nuclei, cilia noted on review (follow-up histology was tubal metaplasia) (ThinPrep, $\times 400$, Papanicolaou stain).



glandular, comprising predominantly (78%, 7/9) endometrial ADCA with the remainder ovarian ADCA. This distribution was the same with the previous AGUS diagnosis, although predictability for significant lesions was higher with AGC diagnosis (52% vs 32%).

The origin of lesions also appeared to be related to a history of postmenopausal bleeding. Seven patients who had postmenopausal bleeding were found to have endometrial ADCA ($n = 6$) and ovarian ADCA ($n = 1$).

Nearly half, viz. 44% (76/174) of cases from the previous AGUS category were characterised as negative or reactive on cytology after review. 46% (35/76) had histological follow-up and showed clinically significant lesions in 9% (3/35). (2 endometrial and 1 ovarian ADCA.) All these 3 ADCA which were downgraded to negative on review were symptomatic. None of HSIL was downgraded. Initial investigations such as colposcopy, directed biopsy or endocervical curettage were negative in 71% of women (25/35) in

the negative category and possibly represent unnecessary investigations due to previous overdiagnosis of AGUS.

Previous history of SIL (histology or cytology) was strongly predictive of subsequent SIL even after diagnosis of AGC. 16% of women (10/64) with a diagnosis of AGC had antecedent SIL. Among those who had follow-up, 89% (8/9) had SIL (4HSIL, 4 LSIL). The number of women with a previous history of extruterine malignancy or conisation and current cytodiagnosis of AGC was too small for analysis.

58% of women (38/66) in group <40 and 60% (65/108) in group ≥ 40 yrs underwent histological follow up. Not all women underwent uniform clinical evaluation. Some had more than one investigation. Women with an AGUS diagnosis on cytology were initially investigated by colposcopy and directed cervical biopsy ($n = 29$), endocervical curettage (ECC) ($n = 50$) and endometrial sampling ($n = 61$). Colposcopic cervical biopsy was the predominant method in women <40 and endometrial sampling the predominant method in women ≥ 40 yrs (fig. 3). Secondary evaluation consisted of cone biopsy ($n = 17$) and hysterectomy ($n = 17$). A total of 35 SIL were diagnosed by all procedures. ECC detected only 23% SIL (8/35). Among ECC negative cases 8 had HSIL and 1 had LSIL on follow-up cone biopsy. In 7 cases the ECC material was insufficient. Colposcopic biopsy detected 54% SIL cases (19/35).

Table 1

Clinically significant lesions in AGUS and AGC diagnosis.

Histology	Cytology AGUS (old system) N = 103(%)	Cytology AGC (TBS2001) N = 41(%)
Total significant lesions	37/103 (36)	21/41 (51)
Squamous lesions	23/37 (62)	12/21 (57)
Glandular lesions	14/37 (38)	9/21 (43)

AGUS: Atypical glandular cells of unknown significance;
AGC: Atypical glandular cells

Table 2
Clinically significant lesions (HSIL, ADCA) in AGC subcategories.

Subcategory by cytology review (Bethesda 2001)	LSIL N (%)	HSIL N (%)	ADCA EM N (%)	ADCA Ovary N (%)	Benign N (%)	Negative N (%)	Total cases
AEC-FN	1 (17)	3 (50)	1(17)	–	–	1 (17)	6
AEC-NOS	2 (13)	1 (6)	1(6)	–	3 (19)	9 (56)	16
AEC-NOS + LSIL/ASCUS/ASC-H	4 (50)	4 (50)	–	–	–	–	8
AEC-NOS + HSIL	–	4 (100)	–	–	–	–	4
AGC-FN	–	–	3 (60)	2 (40)	–	–	5
AEMC	–	–	2 (100)	–	–	–	2
Total	7	12	7	2	3	10	41

Figures in parenthesis represent percentages.

AEC-FN: Atypical endocervical cells favour neoplasia; AEC-NOS: Atypical endocervical cells, not otherwise specified; AGC-FN: atypical glandular cells favouring neoplasia; AEMC: Atypical endometrial cells; LSIL: Low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion; ASCUS: Atypical squamous cells of unknown significance; ASC-H: Atypical squamous cells cannot exclude high grade lesion; ADCA EM: Adenocarcinoma endometrial

Table 3
Clinically significant lesions in AGUS vs. AGC in women <40 and in women ≥40.

Histology	Women <40		Women ≥40	
	Cytology AGUS N (%)	Cytology AGC N (%)	Cytology AGUS N (%)	Cytology AGC N (%)
Total significant lesions	16/38 (42)	8/16 (50)	21/65 (32)	13/25 (52)
Squamous	15/16 (94)	8/8 (100)	8/21 (38)	4/13 (31)
Glandular	1/16 (6)	–	13/21 (62)	9/13 (69)

Figures in parenthesis represent percentages.

AGUS: Atypical glandular cells of unknown significance; AGC: Atypical glandular cells

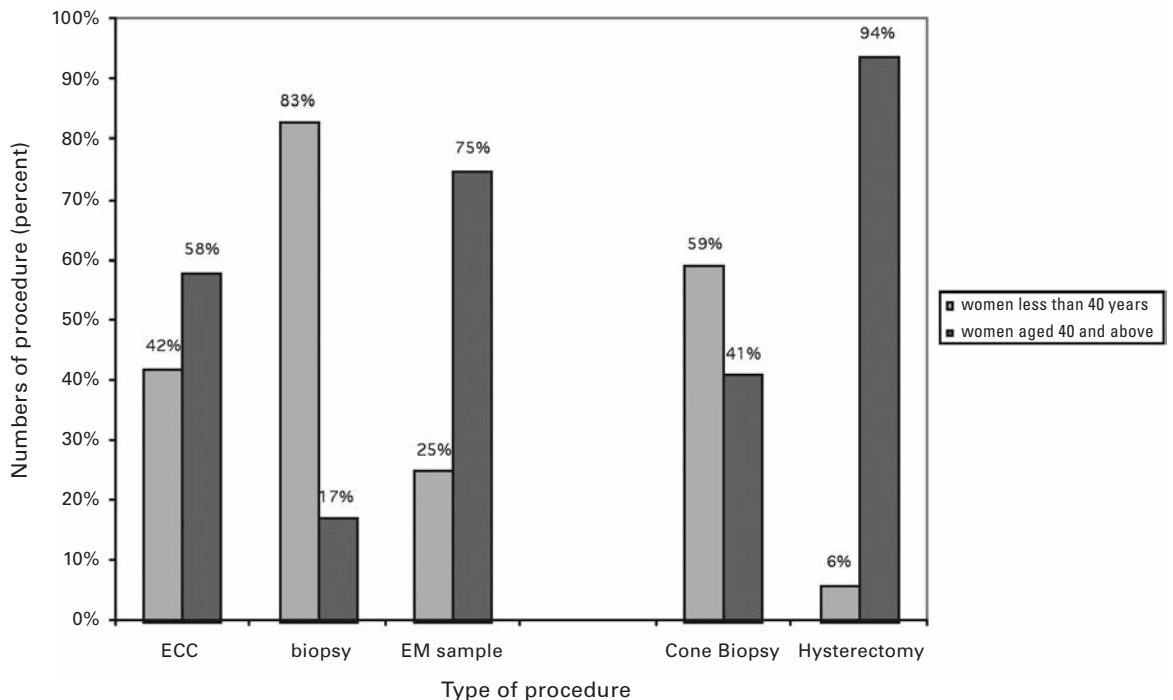
Discussion

In our study the AGUS rate was within the reported range in CS (0.1–1.8%) and in TP (0.14–0.65%) [12–15]. None of these studies used TBS 2001 terminology. In the present study, the initial rise in AGC rate up to 2003 followed by a fall in the year 2004 was probably due to an improved learning curve of revised TBS 2001. The

optimal rate of AGC on TP has not yet been determined. The significant drop in mean AGC rate as compared to mean AGUS rate is due to the exclusion of reactive atypia as per TBS 2001.

Published experience with the use of TBS 2001 for diagnosis of AGC consists of three retrospective studies [9, 16, 17] All these were done on

Figure 3
Investigations in women aged below 40 (N = 38) and aged 40 and above (N = 65) with cytodiagnosis of AGC.



CS. One study [17] showed significantly improved detection of significant lesions with use of TBS 2001 over old TBS 1991 (28.9% in AGUS and 50% in the AGC). Two other studies did not compare the two systems [9, 16]. Although in our study the increase in the rate of significant pathologies in AGC (50%) from AGUS (36%) was not statistically significant, but this, along with the significant fall in mean AGC rate, does indicate a slightly increased specificity of AGC diagnosis under TBS 2001.

In AGC of endocervical origin it was useful to separate FN from the NOS subcategory and a thorough evaluation of women can be recommended with diagnosis of AEC-FN, in view of its higher predictability for a significant lesion than AEC-NOS, which is similar to that reported earlier in CS [9]. No data are available for AGC subcategories using TBS 2001 on TP. In previous studies the detection rate of clinically significant lesions in the AGUS category (TBS 1991) was slightly higher in TP than CS, but none of these studies have reported a statistically significant difference [14, 15, 18].

As also reported previously in CS, AEC with concurrent SIL (low or high grade) represented a higher risk of clinically significant HSIL as compared to those without SIL [18]. In our study, 67% of HSIL and 33% of LSIL were correctly predicted due to squamous dysplastic component coexisting with AGC elsewhere in the slide. This indicated that a careful search for scattered dysplastic squamous cells of any grade is necessary. Parellada et al. found no statistical difference in subcategories using TBS 2001 and associated SIL to predict the nature of lesions on CS [16]. AEC-NOS category resulting in over- and under-interpretation, with follow-up histology negative in 75% and positive in 13% respectively, represented ambiguous morphology.

Subclassification by cell of origin of AGC in TBS 2001 is not always feasible. We had difficulty in distinguishing atypical endocervical from atypical endometrial cells in 5 cases even with the criteria described in a previous study [19]. In our experience, and also that of other workers, presence of tight 3D groups with much smaller nuclei and a much higher NC ratio than endocervical cells, and scalloped cytoplasmic border rather than round border outside the cell group, favoured exfoliated endometrial cells, but the distinction was not always possible [20]. The location of significant pathology was not well correlated in our or previous studies [14, 21].

There was no statistical difference in the proportion of clinically significant lesions by TBS 2001 in two groups of women (women below 40 and ≥ 40 years) as also reported by Parellada et al. [16]. However, women ≥ 40 years showed more diversity of lesions including SIL, ADCA endometrium and ovary. All the categories AEC-FN, AEC-NOS, AGC-FN and AEMC had endometrial ADCA. But the categories AGC-FN,

AEMC and endometrial cells in women ≥ 40 , and presence of postmenopausal bleeding, were highly predictive of neoplastic endometrial lesions. Published follow-up data on AEMC is scant [19, 22]. When interpreting the Pap test from women with postmenopausal bleeding, diligent search for AGC or AEMC should be made in order to improve diagnostic accuracy [23].

The present study shows that using TBS 2001, unnecessary investigations could (possibly) be avoided in a high proportion (71%) of patients with reactive but atypical-looking glandular cells, which are considered negative in TBS 2001. Three cases of ADCA on histology with AGUS on initial cytology were downgraded to negative on cytology after review. However, it may not represent a false negative, since conventionally the Pap test is not intended to diagnose endometrial or ovarian pathology [4]. But caution must always be exercised when excluding benign mimics of AGC.

Recognition of the variations in cytological features on TP from CS is critical if misinterpretation is to be avoided. We concur with previous studies that the flat sheets and distinct cell borders seen in glandular cells in CS were less common in TP, as cells were more tightly clustered. In TP nuclear shrinkage caused hyperchromasia and nucleoli were more often distinct [6, 7]. Probably all the three features were responsible for a tendency to overcall AGUS in our study. 83% (10/12) of our HSIL cases with cytodiagnosis of AGC showed involvement of endocervical glands, which can be misinterpreted as AGC. Cytological features of HSIL involving endocervical glands are now emerging [5, 20, 23–25]. With the additional experience in using TBS 2001 and awareness of interpretative pitfalls, diagnostic accuracy can be improved.

The rate of histological evaluation (59%) in our study is similar to the previously reported range of 45–88% [11]. A comprehensive initial evaluation comprising colposcopy, directed cervical biopsy and endocervical curettage (ECC) with or without endometrial sampling was not done uniformly in all women, as also reported by Sharpless et al. [11]. Considering the poor detection rate of SIL by ECC in our series and previous studies, and the high PPV for FN category in our study, it is evident that cytodiagnosis of AEC-FN, if negative on both ECC and colposcopic biopsy, should mandate cone biopsy.

Long duration of follow-up despite initial negative findings, especially in high-risk groups, may also increase diagnostic accuracy, as pointed out in a study which reported clinically significant uterine lesions in 13% of women after a mean follow-up of 37 months [26]. In one of our cases atypical endometrial hyperplasia was detected after 38 months. Long follow-up of a larger number of cases may provide guidance as to the optimum period of follow-up.

To conclude, with TBS 2001, AEC-FN,

AGC-FN, AEMC and AGC with concomitant SIL subcategories are high-risk diagnoses. This necessitates prompt and thorough investigations, including colposcopy, directed biopsies and ECC, uniformly in all women. Cone biopsy should be mandatory in cases with cytological diagnosis of FN category, if the initial investigations are negative. Frequency of clinically significant lesions was the same in both age groups, but in women ≥ 40 the diversity of lesions was seen. Because cytological prediction of the cell of origin is not perfect, we recommend that it be viewed as a probabilistic approach to identifying disease rather than a specific lesion. Thus, choice in sequence of investigations may vary by age and presence of postmenopausal bleeding.

The study is limited by its retrospective nature. Single institutional data due to a low AGC rate will mean a small number of cases in each group and may not have sufficient statistical power. Hence observational data from more studies is necessary to refine management guidelines.

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