Atypical glandular cells and the real significance in clinical practice: experience of a university hospital in the municipality of Niterói, RJ, Brazil

Células glandulares atípicas e o real significado na prática clínica: experiência de um hospital universitário no município de Niterói, RJ, Brasil

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ABSTRACT

Introduction: Atypical glandular cells (AGC) are rare but clinically significant due to their association with cervical and endometrial lesions. Although human papillomavirus (HPV) is the main etiological agent of cervical lesions, not all AGC are HPV-related, particularly those of endometrial origin. Given the heterogeneity of associated findings, their characterization is essential to guide clinical management. **Objective:** To describe the distribution of AGC subcategories and evaluate subsequent diagnostic findings, comparing findings between AGC (not otherwise specified) NOS and AGC (favor neoplastic) FN in women evaluated at a Brazilian university hospital. **Methods:** This is an observational, retrospective, analytical study with a retrospective cohort design, based on the review of cytology reports with an AGC diagnosis and their subsequent diagnostic investigation. Associations between categorical variables were assessed using Fisher's exact test, with a significance level of 5%. **Results:** Among 22,246 cytology samples, 161 showed AGC (0.72%). After exclusions, 126 cases were included: 85.7% AGC-NOS and 14.3% AGC-FN. Neoplasia at any site was identified in 22.2% of women and was more frequent in AGC-FN (55.6%) than in AGC-NOS (16.7%) (p=0.001). A statistically significant difference was observed in the distribution of cervical findings between groups (p=0.003), with a higher proportion of neoplastic lesions in AGC-FN. No significant difference was found for endometrial findings (p=0.400). Endocervical cytology was performed in 68 women, showing a significant association between the initial AGC classification and subsequent cytological findings (p=0.003), although 44.4% of AGC-FN cases had negative results. **Conclusion:** AGC represents a heterogeneous clinical entity, with a higher frequency of neoplastic findings in AGC-FN compared to AGC-NOS, particularly in the cervix. These findings reinforce the importance of a comprehensive diagnostic investigation, particularly in cases classified as AGC-FN. In settings without access to HPV molecular testing, clinical, colposcopic, and histopathological evaluation remains essential.

Keywords: cervical cancer. cytology. screening. adenocarcinoma. HPV. colposcopy.

RESUMO

Introdução: Células glandulares atípicas (AGC) são raras, porém clinicamente relevantes em razão de sua associação com lesões cervicais e endometriais. Embora o papilomavírus humano seja o principal agente etiológico das lesões cervicais, nem todas as AGC estão relacionadas à infecção viral, como nas atipias de origem endometrial. Diante da heterogeneidade dos achados associados, sua caracterização é essencial para orientar o manejo clínico. **Objetivo:** Descrever a distribuição das subcategorias de AGC e avaliar os resultados da investigação diagnóstica subsequente, comparando os achados entre AGC (sem outras especificações) SOE e AGC (favorecendo neoplasia) FN em mulheres atendidas em um hospital universitário brasileiro. **Métodos:** Trata-se de estudo observacional, retrospectivo, analítico, com delineamento de coorte retrospectiva, baseado na análise documental de citologias com diagnóstico de AGC e sua investigação diagnóstica subsequente. As associações entre variáveis categóricas foram avaliadas pelo teste exato de Fisher, adotando-se um nível de significância de 5%. **Resultados:** Entre 22.246 citologias, 161 apresentaram AGC (0,72%). Após exclusões, 126 casos compuseram a amostra: 85,7% AGC-SOE e 14,3% AGC-FN. Neoplasia em qualquer sítio foi identificada em 22,2% das mulheres, sendo mais frequente em AGC-FN (55,6%) do que em AGC-SOE (16,7%) (p=0,001). Houve diferença estatisticamente significativa na distribuição dos achados cervicais entre os grupos (p=0,003), com maior proporção de lesões neoplásicas em AGC-FN. Para o endométrio, não houve diferença significativa (p=0,400). A citologia endocervical foi realizada em 68 mulheres, com associação significativa entre a categoria inicial de AGC e os achados subsequentes (p=0,003), embora 44,4% das pacientes com AGC-FN tenham apresentado resultado negativo. **Conclusão:** AGC constitui uma entidade clínica heterogênea, com maior frequência de achados neoplásicos na subcategoria AGC-FN em comparação ao AGC-SOE, especialmente no colo uterino. Esses achados reforçam a importância da investigação diagnóstica abrangente, particularmente nos casos classificados como AGC-FN. Em contextos sem acesso ao teste molecular para papilomavírus humano, a avaliação clínica, colposcópica e histopatológica permanece essencial.

Palavras-chave: câncer do colo do útero. citologia. rastreamento. adenocarcinoma. HPV. colposcopia.

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INTRODUCTION

Atypical glandular cells (AGC) is a rare finding in cytology and has gained relevance due to the relative increase in cervical adenocarcinoma, especially among young women[1,2]. This type of cancer already accounts for up to 25% of cases in North America and Europe, with 15 to 20% of these cases being HPV-negative[1,3,4]. In Brazil, cervical cancer is the third most common cancer among women, with an estimated 17,010 new cases per year for the 2023–2025 period[5]. Squamous cell carcinoma (SCC) is the most prevalent

histological type, followed by adenocarcinoma, which accounts for approximately 12.2% of cases in Brazil[6,7].

The primary cause of cervical cancer is persistent infection with oncogenic human papillomavirus (HPV), particularly types 16 and 18[8,9]. This viral infection, classified as a sexually transmitted infection (STI), can, over the years, lead to the malignant transformation of squamous and glandular epithelial cells located in the transformation zone of the cervix[10,11].

Although the colpocytological test still predominates in cervical cancer screening in Brazil, the country is undergoing a transition to screening with the molecular DNA-HPV test[8], with nationwide implementation expected by 2026[12]. This method offers greater sensitivity compared to conventional cytology and allows for screening intervals of up to five years for negative results. In this context, cytology plays a complementary role in screening women with non-16/18 oncogenic HPV through reflex cytology, since types 16/18 are referred directly for colposcopy[13]. Despite its historical and well-established role in the early detection of cervical dysplasia, cytology performs poorly in identifying glandular lesions, with reduced sensitivity for endocervical and endometrial abnormalities[14].

The most widely used cytopathological nomenclature classification system in the world is the Bethesda System (BS), last updated in 2014. In 2020, the Brazilian Society of Cytopathology released an update to the Brazilian Nomenclature for Cytopathological Reports of the Cervix and Anogenital Areas, fully adopting the BS 2014[15]. This cytological classification categorizes AGC as "not otherwise specified" (NOS) or favor neoplastic (FN), with mention of the site of origin of the atypia (endocervical, endometrial, or glandular)[15,16].

International studies indicate AGC prevalences ranging from 0.08 to 2.1%[17,18]. In Brazil, AGC accounted for 0.25% of all cytology tests and 7.3% of abnormal tests in 2024[2]. Despite their low prevalence, the clinical impact of an AGC diagnosis is significant, and their management is challenging, as they may correspond to benign conditions as well as precursor or invasive lesions of the cervix and endometrium or, more rarely, to extrauterine tumors[19–24]. Due to this potential for malignancy, the identification of AGC in cytopathological tests requires rigorous diagnostic investigation, with consensus on performing colposcopy with examination of the endocervical canal and, when necessary, the endometrial cavity (>35 years of age or with abnormal uterine bleeding) for appropriate management[8,20,21,25].

OBJECTIVE

To describe the distribution of AGC subcategories and evaluate the results of subsequent diagnostic investigation, comparing findings between AGC-NOS and AGC-FN in patients treated at a Brazilian university hospital.

METHODS

This is an observational, retrospective, analytical study with a retrospective cohort design, based on a review of cytology reports diagnosing AGC and their clinical outcomes.

This study was conducted in the city of Niterói (RJ), Brazil, from 2018 to 2023, in the Gynecology/Lower Genital Tract Pathology and Colposcopy (Patologia do Trato Genital Inferior e Colposcopia – PTGIC), part of the Fluminense Federal University (Universidade Federal de Fluminense – UFF).

The sample used was consecutive and non-probabilistic, including all eligible cases identified during the study period. No a priori sample size calculations were performed, as the sample size was determined by the sequential inclusion of registered cases. All analyzed variables had complete data, with no missing values. The inclusion criteria comprised all screening cytology tests with an AGC result performed between 2018 and 2023 at HUAP. Only pregnant women at the time of the index cytology and women who had previously undergone hysterectomy were excluded. Cytologies that were not screening-related, such as follow-up/control cytologies, were classified as ineligible; eligible records without any diagnostic outcome due to loss to follow-up or unavailable medical records were considered sample losses.

The data were organized in a spreadsheet in Microsoft Excel® (Office 365) and analyzed using Jamovi software, version 2.6.44, through descriptive statistics (absolute and relative frequencies, mean, standard deviation, and range) and in the R program (version 4.4.1) to perform Fisher's exact test, adopting a significance level of 5%.

The study used the results of cervical cytopathological examinations from participants diagnosed with AGC performed at HUAP, available in electronic spreadsheet records from the HUAP Pathology Service, the Cervical Cancer Information System (SISCOLO), the Cancer Information System (SISCAN), and records from the HUAP Gynecology/PTGIC Service logbook. A retrospective study was also conducted using data extracted from physical and electronic medical records to evaluate the results of diagnostic investigations following abnormal cytology, such as colposcopy results, endocervical cytology, pelvic or transvaginal ultrasound, hysteroscopy, and cervical and endometrial biopsies.

For the analysis of diagnostic investigation results, histopathological findings obtained through different diagnostic or therapeutic methods were considered relevant, depending on the anatomical site evaluated. For the cervix, colposcopy-guided biopsies, specimens from excisional procedures (such as conization and high-frequency surgery), and surgical specimens from hysterectomy were included. For the endometrium, samples obtained by diagnostic hysteroscopy with guided biopsy, uterine curettage, and specimens from hysterectomy were considered. All material was processed and analyzed by the HUAP Pathology Department, forming the basis for the final classification of the diagnostic investigation results.

For the purposes of analysis, the results of the diagnostic investigation by site (cervix and endometrium) were grouped into three mutually exclusive categories: normal, benign, and neoplastic. This categorization was based on the clinical relevance of the findings, grouping precancerous and cancerous lesions, in line with approaches described in the literature that consider the clinical significance of these lesions[19,26].

Both negative histopathology and normal colposcopic or hysteroscopic evaluation, with no indication for biopsy (no sample), were considered normal. The classification into benign and neoplastic was based on histopathological findings. Among the diagnoses observed in the sample, in the cervix, the following were identified as benign:

- endocervical polyp without atypia, endocervical tubal metaplasia, and low-grade squamous intraepithelial lesion (LSIL); and

- as neoplastic: high-grade squamous intraepithelial lesion (HSIL), endocervical adenocarcinoma *in situ* (AIS), and SCC.

In the endometrium, the following were observed as benign: polyps without atypia, endometritis, tubal metaplasia, and cystic atrophy; and as neoplastic: polyps with atypia, hyperplasia with atypia, adenocarcinoma (endometrioid or serous), carcinosarcoma, and undifferentiated carcinoma. When findings were available for both sites, each was classified independently.

he clinical and sociodemographic variables analyzed were age (years), postmenopausal status (yes/no), parity (nulliparous; 1–2; ≥3 children), race/ethnicity (white; non-white), immunosuppression (yes/no), and smoking status (yes/no), based on data available in the medical records. The analysis of these variables was descriptive, with absolute and relative frequencies and, for continuous variables, mean ± standard deviation (and range, when applicable).

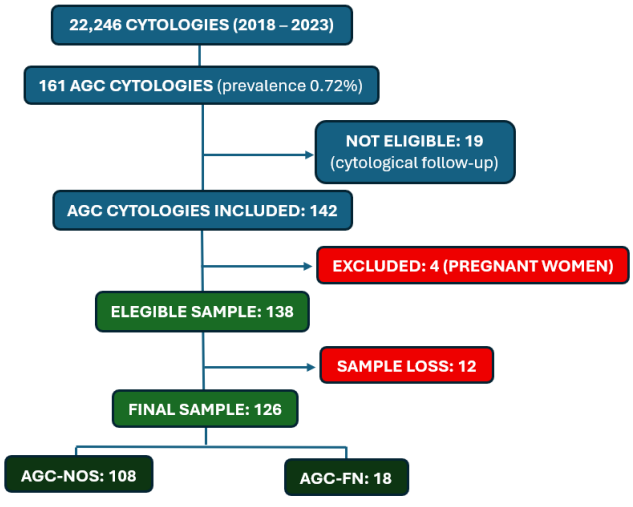
The manuscript followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies[27].

Ethical aspects

The study complies with the Brazilian National Health Council Resolution No. 466/2012 and was approved by the Research Ethics Committee of the Fluminense Federal University School of Medicine, under CAAE 74629423.0.0000.5243, on January 25, 2024.

RESULTS

Between 2018 and 2023, HUAP performed 22,246 cervical cytology tests, of which 161 showed AGC, corresponding to a prevalence of 0.72% (**Figure 1**). Of the 161 cases analyzed, 19 were excluded because they were follow-up tests and did not meet the inclusion criteria. Of the remaining 142 cytologies, 4 involving pregnant women were excluded, resulting in 138 eligible cytologies. In 12 cases, the absence of physical medical records made it impossible to access clinical information, resulting in sample losses. Thus, the final sample consisted of 126 AGC cytology samples from primary screening, classified according to the BS 2014 as AGC-NOS (n=108; 85.7%) and AGC-FN (n=18; 14.3%).



AGC: atypical glandular cells; NOS: not otherwise specified; FN: favor neoplastic.
Source: The authors (2025).

Figure 1. Flow diagram of study sample selection.

The clinical and sociodemographic characteristics are shown in **Table 1**: mean age of 52.2±9.9 years (31–86); postmenopausal status in 60 (47.6%); nulliparous in 16 (12.7%), 1–2 children in 63 (50.0%), and ≥3 children in 47 (37.3%); non-white race/ethnicity in 101 (80.2%).

The distribution of cervical and endometrial findings according to the AGC subcategory is shown in **Table 2**. Regarding cervical findings, there is a statistically significant difference in the distribution between AGC-NOS and AGC-FN (p=0.003). Among the AGC-FN cases (n=18), 10 (55.6%) were normal, 2 (11.1%) were benign, and 6 (33.3%) were neoplastic; among AGC-NOS cases (n=108), 83 (76.9%) were normal, 19 (17.6%) were benign, and 6 (5.6%) were neoplastic. Across all cases, cervical findings were 93/126 (73.8%) normal, 21/126 (16.7%) benign, and 12/126 (9.5%) neoplastic.

In the endometrium (**Table 2**), no statistically significant difference was observed in the distribution of findings between the AGC-NOS and AGC-FN groups (p=0.400). Among the cases classified as AGC-FN (n=18), 10 (55.6%) were normal, 4 (22.2%) were benign, and 4 (22.2%) were neoplastic; whereas among the AGC-NOS (n=108), 65 (60.2%) were normal, 31 (28.7%) were benign, and 12 (11.1%) were neoplastic. Overall, endometrial findings included 75/126 (59.5%) cases classified as normal, 35/126 (27.8%) benign, and 16/126 (12.7%) neoplastic cases.

When considering the patient as a unit (neoplasia at any site), 28/126 (22.2%) had at least one neoplastic finding (**Table 2**). This proportion was significantly higher in the AGC-FN group (10/18; 55.6%) than in the AGC-NOS group (18/108; 16.7%) (p=0.001).

Table 1. Clinical and sociodemographic characteristics of the sample (n=126) of women with cervical cytology screening compatible with atypical glandular cells.

Variable	Result (%)
Age (years)	52.2±9.9 (31–86)
Postmenopausal	60 (47.6)
Parity: nulliparous	16 (12.7)
Parity: 1–2 children	63 (50.0)
Parity: ≥3 children	47 (37.3)
Race/skin color: non-white	101 (80.2)
Race/skin color: white	25 (19.8)
Smoking: yes	26 (20.6)
Smoking: no	100 (79.4)
Immunosuppression: yes	13 (10.3)
Immunosuppression: no	113 (89.7)

Age is presented as mean ± standard deviation; all other variables as n (%). Parity categorized as: nulliparous; 1–2 children; ≥3 children. Race/skin color according to medical records.
Source: The authors (2025).

In both sites, the sum of non-neoplastic findings (normal + benign) was as follows: in the cervix, AGC-NOS 102/108 (94.5%) and AGC-FN 12/18 (66.7%); in the endometrium, AGC-NOS 96/108 (88.9%) and AGC-FN 14/18 (77.8%). When considering the patient as a unit (any site), 98/126 (77.8%) had no neoplasia, with AGC-NOS accounting for 90/108 (83.3%) and AGC-FN for 8/18 (44.4%).

Of the 126 participants, only 68 underwent endocervical brushing to evaluate the endocervical canal during colposcopy. Women classified as AGC-FN had a higher proportion of significant abnormalities in endocervical cytology, including 33.3% with AGC-FN, as well as 11.1% with atypical squamous cells of undetermined significance (ASC-US) and 11.1% with HSIL. Nevertheless, 44.4% of these patients had a normal result in the endocervical sample. On the other hand, patients initially diagnosed with AGC-NOS predominantly had endocervical cytology negative for intraepithelial lesion or malignancy (NILM) (74.6%), with 16.9% maintaining the AGC-NOS diagnosis in the endocervical smear, in addition to a low frequency of other results, including AIS and AGC-FN (**Table 3**).

DISCUSSION

The prevalence of AGC among screening cytology samples collected during the study period was 0.72%. This figure falls within the range described in international studies, which report prevalences between 0.08 and 2.1%[8,9], and is higher than those estimated in large institutional series, such as those by Kim et al.[17] (0.17%) and Goetz et al.[14] (0.15%), both with prevalences below 1.00%. In the Brazilian context, AGC accounted for 0.25% of all cytological examinations in 2024, a figure also close to the magnitude observed in the present sample. This difference may be attributed to HUAP's profile as a tertiary hospital, which treats more complex cases, in addition to the presence of professionals specialized in cytopathology and experienced gynecologists. The high proportion of postmenopausal and immunosuppressed patients, and those with comorbidities such as obesity and chronic anovulation may also have contributed to the higher detection rate of glandular atypia.

The findings demonstrated that 22.2% of women had neoplasia at any site, with a higher frequency in the AGC-FN subcategory (55.6%) compared to AGC-NOS (16.7%), a statistically significant difference

Table 2. Distribution of cervical and endometrial findings according to atypical glandular cells subcategories (Bethesda System, 2014).

Evaluation	AGC-NOS (n=108)	AGC-FN (n=18)	Total (n=126)	p-value*
Cervical				
Normal[a]	83 (76.9%)	10 (55.6%)	93 (73.8%)	
Benign	19 (17.6%)	2 (11.1%)	21 (16.7%)	0.003
Neoplastic	6 (5.6%)	6 (33.3%)	12 (9.5%)	
Endometrial				
Normal[a]	65 (60.2%)	10 (55.6%)	75 (59.5%)	
Benign[b]	31 (28.7%)	4 (22.2%)	35 (27.8%)	0.400
Neoplastic[c]	12 (11.1%)	4 (22.2%)	16 (12.7%)	
Any site (cervix or endometrium)				
Neoplastic	18 (16.7%)	10 (55.6%)	28 (22.2%)	0.001
Non-neoplastic	90 (83.3%)	8 (44.4%)	98 (77.8%)	

[a]Normal includes negative histology or normal colposcopic/hysteroscopic evaluation with no indication for biopsy. [b]Benign; [c]Neoplastic: according to the definitions provided in Materials and Methods. *p-values were obtained using Fisher's exact test. AGC: atypical glandular cells; NOS: not otherwise specified; FN: favor neoplastic.
Source: The authors (2025).

Table 3. Distribution of endocervical cytology performed during colposcopy, according to the initial atypical glandular cells category.

AGC	n(%)	Endocervical evaluation by brush cytology (n=68)								p-value*
		AIS n (%)	AGC-FN n (%)	AGC-NOS n (%)	ASC-H n (%)	ASC-US n (%)	HSIL n (%)	LSIL n (%)	NILM n (%)	
NOS	59 (86.8)	1 (1.7)	1 (1.7)	10 (16.9)	1 (1.7)	1 (1.7)	0	1 (1.7)	44 (74.6)	0.003
FN	9 (13.2)	0	3 (33.3)	0	0	1 (11.1)	1 (11.1)	0	4 (44.4)	

n=68: patients in the sample who underwent endocervical cytology during colposcopy for endocervical canal evaluation.
AGC: atypical glandular cells; NOS: not otherwise specified; FN: favor neoplastic; AIS: adenocarcinoma *in situ;* ASC-US: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; NILM: negative for intraepithelial lesion or malignancy.
*The p-value was obtained using Fisher's exact test.
Source: The authors (2025).

(p=0.001). This data reinforce the importance of initial stratification and targeted diagnostic investigation. A statistically significant difference was also observed in the distribution of cervical findings between AGC-NOS and AGC-FN (p=0.003), with a higher proportion of neoplastic lesions in the AGC-FN group, reinforcing the clinical relevance of this subcategory in identifying women with a higher frequency of significant cervical abnormalities. On the other hand, no statistically significant difference was observed in the distribution of endometrial findings between the groups (p=0.400), suggesting distinct behavior depending on the anatomical site evaluated. In a retrospective Italian study, Cianfrini et al. (2024)[18] analyzed 89 cases of AGC and observed that the malignancy rate was 35.4% in the AGC-NOS group and 70.7% in the AGC-FN group, a statistically significant difference (p=0.00089).

In the present study, the distribution of neoplastic lesions by site — 9.5% cervical neoplasia and 12.7% endometrial neoplasia — supports the dual investigation approach (cervical and endometrial) recommended by Brazilian and international guidelines, especially in postmenopausal women[20,21,25]. In a large study, Tao et al. (2025) [2] observed 58.9% of significant lesions and a malignancy rate of 46.3%, with a prevalence of endometrial carcinoma (24.4%) and cervical adenocarcinoma (10%). This distribution, with a higher incidence of endometrial involvement, reflects the trend observed in other international series and is consistent with the site-specific rate of 12.7% observed in the present study for endometrial malignancy, reinforcing the importance of endometrial investigation, particularly in postmenopausal women.

In the institutional cohort by Goetz et al. (2024)[14], the overall risk of high-grade lesions (cervical or endometrial) reached 21%, very close to the 22.2% found in this study when considering HSIL/AIS/invasion at any site. Furthermore, a positive DNA-HPV test increased the likelihood of cervical HSIL$^+$ cervical lesions by approximately 26-fold (odds ratio [OR] = 26.4) and HPV16 by 84-fold (OR = 84), highlighting the value of the DNA-HPV test for risk stratification in AGC — a point particularly relevant in this setting, which did not have systematic molecular testing for HPV during the study period.

In Kim et al. (2017)[17], among 508 cases with histology, 33.9% presented clinically significant lesions. In that study, most of the significant lesions were of endometrial origin (21.5% *versus* 10% cervical), with the frequency of endometrial findings being nearly double that found in the present study (12.7%).

Regarding subcategorization by site, the literature supports the view that reporting the cytological origin of the glandular change improves the estimation of the likely site of the lesion: Kawano et al. (2020)[26] demonstrated the clinical utility of subcategorization (endometrial or endocervical) in guiding the initial investigation[26]. On the other hand, cytology reports from the Brazilian Unified Health System did not include topographical qualifications, which reduced the accuracy of the predictions and hindered analyses regarding the location of atypia in the cytology.

The systematic absence of molecular testing for high-risk HPV in the cohort constitutes a major limitation. The literature robustly demonstrates that HPV status is one of the main risk stratifiers in women with AGC. Population-based studies, such as that by Norman et al. (2022) [3], show that women with AGC and HPV 16/18-positive status have a cumulative risk of CIN3$^+$ of 80% over two years, while those with other oncogenic HPV types have a risk of 58%. Even among HPV-negative women, the risk of significant lesions is not negligible, ranging from 10 to 15% across different series, including cervical adenocarcinomas of non-HPV-related types, such as clear cell and gastric-type adenocarcinomas[4,28]. Therefore, although HPV testing is a powerful tool for prioritizing cases, a negative result should not lead to a watch-and-wait approach in cases of AGC, but rather to a comprehensive investigation, including colposcopy, endocervical canal examination, endometrial evaluation, and histopathological assessment[4,20].

The data of the present study on endocervical cytology performed during colposcopy support this view. Even in the high-risk group (AGC-FN), 44.4% of endocervical samples were negative for malignancy, highlighting the limitation of this method alone in ruling out significant glandular lesions. This result supports the recommendations of more recent guidelines that advocate diagnostic excision of the endocervical canal (type 3) in cases of AGC-FN[20,21,25].

Strengths and Limitations

Among the strengths of this study are the consecutive inclusion of all eligible cases during the analyzed period and the pathological processing performed in a single laboratory, ensuring greater diagnostic standardization. The comprehensive inclusion of AGC categories and the structured correlation between cytology, colposcopy, and histology reinforce the consistency of the findings. Furthermore, endocervical sampling, even though applied to only a portion of the sample (68/126), provided important insights for characterizing glandular findings, broadening the understanding of cytological behavior in these subgroups.

Limitations include:

1. a single-center, retrospective design, and non-probabilistic sampling;
2. the systematic absence of molecular testing for high-risk HPV, limiting stratification and comparability with series that include this data;
3. the lack of subcategorization by site in cytology reports; and
4. the small number of AGC-FN cases (n=18), compromising the precision and stability of the estimates.

Implications for clinical practice and public health

In a country of continental dimensions with disparities in access to diagnostic technologies, the findings contribute to the understanding of AGC management in settings that do not yet have routine HPV testing. Thorough clinical evaluation, colposcopy with endocervical canal inspection, and targeted endometrial investigation (in women aged >35 years or with risk factors for endometrial cancer) remain the cornerstones of diagnosis. Concurrently, the nationwide implementation of HPV testing should be accelerated, as its integration would allow for more precise risk stratification, optimizing resources and improving outcomes.

Future perspectives

Prospective, multicenter studies incorporating HPV genotyping are urgently needed to better characterize the profile of AGC in the Brazilian population. Additionally, standardizing cytology reports to include topographic subcategorization (endocervical *vs.* endometrial) would improve

the accuracy of the initial investigation. Continuing education for healthcare professionals on the significance of AGC in the context of cervical cancer screening is essential, as these cytological changes are associated with a heterogeneous spectrum of conditions, including cervical and endometrial lesions, often requiring targeted further investigation.

CONCLUSION

AGC constitutes a heterogeneous group, with a predominance of the AGC-NOS subcategory over AGC-FN. A higher frequency of neoplastic findings was observed in the AGC-FN subcategory compared to AGC-NOS, especially in the cervix. This pattern reinforces the need for comprehensive diagnostic investigation, including cervical and endometrial evaluation, particularly in cases classified as AGC-FN. The lack of information regarding the likely site of origin of the cytological atypia may compromise initial stratification and limit comparability between services.

In settings with limited access to molecular HPV testing, clinical, colposcopic, and histopathological evaluation remains essential. Prospective, multicenter studies are needed to improve the understanding of glandular outcomes and management strategies.

Approval by the Research Ethics Committee

Approved by the Research Ethics Committee of the Fluminense Federal University School of Medicine (CEP/FM-UFF), under CAAE 74629423.0.0000.5243.

Authors' Contributions

KMD: Conceptualization, Investigation, Methodology, Supervision, Data curation, Writing – original draft. ICCVG: Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing. FRR: Conceptualization, Methodology, Supervision, Writing – review & editing. JRM: Methodology, Formal Analysis, Supervision, Writing – review & editing. SCAVF: Conceptualization, Methodology, Writing – review and editing. CAOM: Conceptualization, Methodology, Writing – review & editing. CBPG: Investigation, Writing – review & editing. ARC: Investigation, Data curation, Writing – review & editing. BMSC: Investigation, Data curation, Writing – review & editing. BDGC: Investigation, Data curation, Writing – review & editing. TDL: Investigation. RMZ: Conceptualization, Methodology, Writing – review & editing.

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Conflicts of interest

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The authors used artificial intelligence tools exclusively to assist with grammatical review of the manuscript. The writing, intellectual development, data interpretation, critical analysis, and final version of the article were performed by the authors.

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