# Bacterial vaginosis, cervical Human Papillomavirus infection and cervical cytological abnormalities in adult women in Central Brazil: a cross-sectional study

## *Vaginose bacteriana, infecção cervical pelo Papilomavírus humano e anormalidades citológicas cervicais em mulheres adultas no Brasil Central: um estudo transversal*

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**ABSTRACT**

**Introduction**: Bacterial vaginosis is the most common cause of vaginal discharge and occurs when there is an imbalance in the vaginal microbiota, predominantly composed of *Lactobacillus spp.* Human Papillomavirus is the most common sexually transmitted virus in the world. Persistent infection with high-risk Human Papillomavirus genotypes is the main cause of the development of cervical intraepithelial neoplasia and cervical cancer. **Objective:** To investigate the association between bacterial vaginosis and cervical Human Papillomavirus infection and between bacterial vaginosis and cervical cytological abnormalities in adult women. **Methods:** Cross-sectional study carried out in a gynecology outpatient clinic of the public health network. A total of 202 women were included in the study and underwent gynecological examination with cervical specimen collection. Cervical cytopathological examinations and bacterioscopy by the Nugent method were performed to identify bacterial vaginosis, and PCR and reverse hybridization were carried out for Human Papillomavirus detection and genotyping. Bivariate analysis was performed to investigate the association between bacterial vaginosis and cervical Human Papillomavirus infection, and between bacterial vaginosis and cervical cytological abnormalities. The odds ratio was calculated, with the respective 95% confidence intervals (95%CI) and 5% significance level (p≤0.05). **Results:** The prevalence of bacterial vaginosis was 33.2% (67/202), the prevalence of cervical Human Papillomavirus infection was 38.6% (78/202) and the prevalence of cervical cytological abnormalities was 6.0% (12/202). Bivariate analysis showed no significant association between bacterial vaginosis and cervical Human Papillomavirus infection (OR 0.69; 95% CI 0.37–1.27; p=0.23), or between bacterial vaginosis and cervical cytological abnormalities (OR 0.65; 95%CI 0.17–2.50; p=0.54). **Conclusion:** In this study, bacterial vaginosis did not represent a risk factor for cervical Human Papillomavirus infection or for the presence of cervical cytological abnormalities in the investigated adult women.

**Keywords:** Bacterial vaginosis. Human papillomavirus. Abnormalities. Women.

**RESUMO**

**Introdução:** A vaginose bacteriana é a causa mais comum de corrimento vaginal e ocorre quando há um desequilíbrio da microbiota vaginal, composta predominantemente de *Lactobacillus spp*. O papilomavírus humano é o vírus sexualmente transmissível mais comum no mundo. A infecção persistente com genótipos do papilomavírus humano de alto risco é a principal causa do desenvolvimento de neoplasias intraepiteliais cervicais e câncer de colo do útero. **Objetivo:** Investigar a associação entre vaginose bacteriana e infecção cervical pelo papilomavírus humano e entre vaginose bacteriana e anormalidades citológicas cervicais em mulheres adultas. **Métodos:** Estudo de corte transversal realizado em um ambulatório de ginecologia da rede pública de saúde. O total de 202 mulheres foi incluído no estudo e submetido ao exame ginecológico com coleta de espécime cervical. Foram realizados os exames citopatológicos cervicais, a bacterioscopia pelo método de Nugent para a identificação da vaginose bacteriana e reação em cadeia da polimerase e hibridização reversa para a detecção e genotipagem do papilomavírus humano. Análise bivariada foi realizada para investigar a associação entre vaginose bacteriana e infecção cervical pelo papilomavírus humano e entre vaginose bacteriana e anormalidades citológicas cervicais. Foi calculado o *odds ratio*, com os respectivos intervalos de confiança de 95% (IC95%) e nível de significância de 5% (p≤0,05). **Resultados:** A prevalência da vaginose bacteriana foi de 33,2% (67/202), a da infecção cervical pelo papilomavírus humano foi de 38,6% (78/202) e a de anormalidades citológicas cervicais foi de 6,0% (12/202). A análise bivariada não demonstrou associação significativa entre vaginose bacteriana e infecção cervical pelo papilomavírus humano (OR 0,69; IC95% 0,37–1,27; p=0,23), nem entre vaginose bacteriana e anormalidades citológicas cervicais (OR 0,65; IC95% 0,17–2,50; p=0,54). **Conclusão:** Neste estudo a vaginose bacteriana não representou um fator de risco para a infecção cervical pelo papilomavírus humano e nem para presença de anormalidades citológicas cervicais nas mulheres adultas investigadas.

**Palavras-chave:** Vaginose bacteriana. Papilomavírus humano. Anormalidades. Mulheres.

## INTRODUCTION

Bacterial vaginosis is the most common cause of vaginal discharge, affecting about 20 to 30% of women worldwide, with a higher frequency in women of childbearing age and sexually active[1]. Although it is not considered a sexually transmitted infection (STI), bacterial vaginosis shares risk factors with these infections, such as early onset of sexual activity, multiple sexual partners, history of other STIs and inconsistent condom use[1,2]. Thus, its prevalence can reach 50 to 60% in populations that exhibit risky sexual behavior[1].

Bacterial vaginosis occurs when there is a change in the vaginal microbiota, due to the decrease in *Lactobacillus spp.,* and a predominance of anaerobic microorganisms[3]. *Lactobacillus spp.,* through

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the production of hydrogen peroxide (H2O2) and lactic acid, maintain the acidic vaginal pH, thus preventing the excessive proliferation of Gardnerella vaginalis and other anaerobic bacteria that cause bacterial vaginosis[3]. Studies suggest that bacterial vaginosis is a cofactor for the acquisition and persistence of cervical infection by HPV[4-6] and, as a result, also a risk factor for the cytological abnormalities induced by this viral infection[5-7].

The mechanism by which bacterial vaginosis influences the acquisition of cervical infection by HPV remains unknown, however, studies show that a healthy vaginal microbiota dominated by *Lactobacillus spp.* plays an important role in preventing vaginal infections, inflammatory processes, as well as cervical HPV infection[8,9].

Studies in different countries with adult women show an association between bacterial vaginosis and cervical infection by HPV[10-15], even though in Brazil there are few studies addressing these conditions, making it necessary to carry out the present research.

## OBJECTIVE

To investigate the association between bacterial vaginosis and cervical HPV infection and between bacterial vaginosis and cervical cytological abnormalities in adult women.

## METHODS

A cross-sectional study carried out at the preventive gynecology outpatient clinic of the Paulo de Siqueira Garcia Emergency Care Unit (*Unidade de Pronto Atendimento* – UPA) – Chácara do Governador, located in the southern region of Goiânia, Goiás. Data collection was carried out from March to June 2018. The study was part of a larger project aimed at investigating the prevalence, associated factors and performance of diagnostic tests for bacterial vaginosis and genital infections in a preventive gynecology outpatient clinic. To calculate the sample size, the formula referenced by Andrade and Zicker[16] was used, taking into account the infection by Neisseria gonorrhoeae, described as the one with the lowest prevalence, with an approximate rate of 2%, alpha error of 5% and beta of 20%[17], which resulted in a total of 200 participants. This study follows the recommendations of the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) Initiative[18].

The inclusion criteria were women regulated for gynecological consultation at the aforementioned UPA, non-pregnant, not known to be immunosuppressed and who had not used antibiotics in the last 15 days before consultation. Women over 18 years of age who agreed to participate in the study and signed the Free and Informed Consent Term (TCLE, in Portuguese) were included, and agreed to answer the questionnaire and collect the necessary specimens during the gynecological examination for microscopic analysis and molecular testing.

Participants were interviewed by previously trained researchers who applied a semi-structured questionnaire regarding their sociodemographic data and behavioral habits. After the interview, the participants underwent gynecological examination, with the collection of cervical specimen for cytopathological examination, bacterioscopy and HPV detection. To prepare the cytological smear, secretions were collected from the ectocervix and endocervix with an Ayre spatula and plastic bristle brushes. The material was immediately transferred to a slide and fixed in 90% alcohol solution. The samples were sent to the Rômulo Rocha Clinical Analysis Laboratory of the Federal University of Goiás School of Pharmacy (FF-UFG, in Portuguese). All smears were subjected to strict quality control adopted by the aforementioned laboratory, carried out through the rapid review of all negative cases for cervical cytological abnormalities. The results of sample suitability and degree of cervical abnormalities were interpreted according to the Bethesda System[19].

All the results obtained were sent to the gynecology outpatient clinic of the Paulo de Siqueira Garcia Emergency Care Unit (UPA, in Portuguese) – Chácara do Governador, and the nurses of the relevant units of the Family Health Strategy (ESF, in Portuguese) were responsible for delivering and advising the participants.

The diagnosis of bacterial vaginosis was performed according to the Nugent score[20], which consist of counting, in a smear stained by the Gram method, bacterial morphotypes of *Lactobacillus spp., Gardnerella vaginalis* and *Mobiluncus spp.,* observing the scores: 0–3 (normal); 4–6 (intermediate flora); 7–10 (bacterial vaginosis).

Sample collection for HPV molecular analysis was performed with an appropriate cytobrush-type brush, immediately packed in a UCM buffer solution (*Universal Collection Medium QIAGEN Sample & Ensaio Technologies® – UCM*). The samples were sent to the Genetics and Biodiversity Laboratory of the Pontifical Catholic University of Goiás (PUC-GO), and frozen at -20°C until the analysis was performed.

DNA extraction was performed using the PureLink-Invitrogen kit according to the manufacturer's specifications. HPV detection and genotyping were performed using the commercial INNO-LiPA HPV Genotyping Extra© Kit (FujirebioEurope, Ghent, Belgium) according to the manufacturer's instructions. The primer set used in the INNO-LiPA HPV Genotyping Extra II Amp amplifies a 65 bp (base pair) fragment, specific for the L1 region of the HPV genome, from at least 54 different genotypes.

Data were analyzed using the SPSS statistical package (26.0). A descriptive analysis of sociodemographic characteristics and behavioral habits was performed, with their respective absolute and relative distributions. The association of bacterial vaginosis with cervical HPV infection and cervical cytological abnormalities went through a bivariate analysis. The sample was stratified into age groups of up to 30 years and older than 30 years, in order to investigate the association between bacterial vaginosis and cervical HPV infection, and between bacterial vaginosis and cervical cytological abnormalities. Odds ratios (OR), the respective confidence intervals, were calculated, with a significance level of 5% ($p \leq 0.05$).

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# RESULTS

A total of 202 women aged between 18 and 72 years participated in the study. The mean age was 43.2, with a standard deviation of ±13.7. **Table 1** describes the sociodemographic characteristics and behavioral habits of the participants included in the study. Among these, 159 (78.7%) were 30 years old or older, 119 (58.9%) were self-employed, employed and/or received social security benefits, 163 (80.7%) completed elementary or high school, 157 (77.7%) started sexual activity after 15 years of age, 116 (57.4%) reported up to three sexual partners, 162 (80.2%) reported using condoms, 23 (11.4%) reported being smokers, 67 (33.2%) were alcoholics, and 139 (68.8%) were married or living in a common-law marriage.

The prevalence of bacterial vaginosis was 33.2% (67/202), while cervical infection by HPV was 38.6% (78/202), cervical infection by high-risk HPV genotypes was 27.7% (56/202), and cervical cytological abnormalities was 6.0% (12/202), as shown in **Table 2**. Among the positive cases for cervical HPV infection, eight cases were not genotyped due to the sensitivity of the test used and, thus, they were not included as high-risk HPV.

**Table 3** shows that bacterial vaginosis was not associated with cervical HPV infection or cervical cytological abnormalities in the 202 participants.

Cervical HPV infection is more prevalent in women under 30 years of age, so the sample studied was stratified according to the age group of the participants, that is, of ages up to 30 years and ages over 30 years, and possible associations were investigated. **Tables 4** and **5** show that there was no association between bacterial vaginosis and cervical HPV infection, or between bacterial vaginosis and cervical cytological abnormalities, even after stratifying the sample by age.

**Table 1. Sociodemographic characterization and behavioral habits of the 202 participants assisted at the gynecological outpatient clinic in Goiânia, Goiás, 2018.**

| | n | % |
|---|---|---|
| Age | | |
| < 30 years | 43 | 21.3 |
| ≥ 30 years | 159 | 78.7 |
| Functional status | | |
| Employed, self-employed or pension beneficiary | 119 | 58.9 |
| Unemployed | 83 | 41.1 |
| Education | | |
| Higher education | 39 | 19.3 |
| Up to high school | 163 | 80.7 |
| Age of sexual debut | | |
| Up to 15 years old | 45 | 22.3 |
| Over 15 years old | 157 | 77.7 |
| Number of sexual partners | | |
| Above 3 | 86 | 42.6 |
| Up to 3 | 116 | 57.4 |
| Condom use | | |
| Yes | 162 | 80.2 |
| No | 40 | 19.8 |
| Smoking | | |
| Yes | 23 | 11.4 |
| No | 179 | 88.6 |
| Alcoholic | | |
| Yes | 67 | 33.2 |
| No | 135 | 66.8 |
| Marital status | | |
| Single or widow | 63 | 31.2 |
| Married or in a common-law marriage | 139 | 68.8 |

n: absolute frequency; %: relative frequency.

# DISCUSSION

In the present study, most of the women investigated were 30 years of age or older, and the prevalence of bacterial vaginosis and cervical HPV infection was high, while the prevalence of cervical cytological abnormalities remained within the expected range. Despite this, no significant association was found between bacterial vaginosis and cervical HPV infection, or between bacterial vaginosis and cervical cytological abnormalities, even after stratification of women by age.

The women included in this study were stratified into age groups of up to 30 years and older than 30 years. The prevalence of cervical infection by HPV and high-risk HPV genotypes was higher in women under 30 years of age, similar to what has been described in the literature[13]. These results reinforce the evidence that women are infected with HPV soon after starting sexual activity, have a peak

**Table 2. Prevalence of bacterial vaginosis, cervical Human Papillomavirus infection, high-risk Human Papillomavirus and cervical cytological abnormalities in 202 participants attended at the gynecological outpatient clinic in Goiânia, Goiás, 2018.**

| | n | % |
|---|---|---|
| Bacterial vaginosis | | |
| Positive | 67 | 33.2 |
| Negative | 135 | 66.8 |
| Cervical HPV infection | | |
| Positive | 78 | 38.6 |
| Negative | 124 | 61.4 |
| High-risk HPV infection | | |
| Positive | 56 | 27.7 |
| Negative | 146 | 72.3 |
| Cervical cytological abnormalities | | |
| Positive | 12 | 6.0 |
| Negative | 190 | 94.0 |

n: absolute frequency; %: relative frequency.

**Tabela 3. Bacterial vaginosis, cervical HPV infection and cervical cytological abnormalities in 202 participants assisted at the gynecological outpatient clinic in Goiânia, Goiás, 2018.**

| | Bacterial vaginosis | | OR (95%CI) | p* |
|---|---|---|---|---|
| | Positive | Negative | | |
| Cervical HPV infection | | | | |
| Positive | 22 (32.8) | 56 (41.5) | 0.69 (0.37–1.27) | 0.23 |
| Negative | 45 (67.2) | 79 (58.5) | | |
| High-risk HPV infection | | | | |
| Positive | 15 (22.4) | 41 (30.4) | 0.66 (0.33–1.31) | 0.23 |
| Negative | 52 (77.6) | 94 (69.6) | | |
| Cervical cytological abnormalities | | | | |
| Positive | 3 (4.5) | 9 (6.7) | 0.65 (0.17–2.50) | 0.54 |
| Negative | 64 (95.5) | 126 (93.3) | | |

*$\chi^2$; OR: odds ratio.

**Tabela 4. Bacterial vaginosis, cervical HPV infection and cervical cytological abnormalities in women up to 30 years of age (n=43) assisted at the gynecological outpatient clinic in Goiânia, Goiás, 2018.**

| | Bacterial vaginosis | | OR (95%CI) | p* |
|---|---|---|---|---|
| | Positive | Negative | | |
| Cervical HPV infection | | | | |
| Positive | 7 (46.7) | 14 (50.0) | 0.87 (0.24–3.07) | 0.83 |
| Negative | 8 (53.3) | 14 (50.0) | | |
| High-risk HPV infection | | | | |
| Positive | 4 (26.7) | 11 (39.3) | 0.56 (0.14–2.21) | 0.40 |
| Negative | 11 (73.3) | 17 (60.7) | | |
| Cervical cytological abnormalities | | | | |
| Positive | 1 (6.7) | 0 (0.0) | 0.33 (0.21–0.51) | 0.17 |
| Negative | 14 (93.3) | 28 (100.0) | | |

*$\chi^2$; OR: odds ratio.

**Tabela 5. Bacterial vaginosis, cervical HPV infection and cervical cytological abnormalities in women over 30 years of age (n=159) assisted at the gynecological outpatient clinic in Goiânia, Goiás, 2018.**

| | Ba cterial vaginosis | | OR (95%CI) | p* |
|---|---|---|---|---|
| | Positive | Negative | | |
| Cervical HPV infection | | | | |
| Positive | 15 (28.8) | 42 (39.3) | 0.62 (0.31–1.28) | 0.19 |
| Negative | 37 (71.2) | 65 (60.7) | | |
| High-risk HPV infection | | | | |
| Positive | 11 (21.2) | 30 (28.0) | 0.69 (0.31–1.11) | 0.35 |
| Negative | 41 (78.8) | 77 (72.0) | | |
| Cervical cytological abnormalities | | | | |
| Positive | 2 (3.8) | 9 (8.4) | 0.43 (0.09–2.09) | 0.28 |
| Negative | 50 (96.2) | 98 (91.6) | | |

*$\chi^2$; OR: odds ratio.

prevalence in the age group of 25 years, and a sharp drop in detection rates after the age of 30 years[21]. On the other hand, the prevalence of high-grade cervical cytological abnormalities, usually induced by persistent high-risk HPV infection, was higher in women over 30 years of age, which is also in line with the literature[13].

A prospective cohort study showed that, in the age group of 40 to 50 years, from a group of women who were HPV positive and without the presence of cervical cytological abnormalities, 25% of them developed cervical cytological abnormalities after five years, and 35% after ten years. In the age group from 22 to 32 years, 18% developed cervical cytological abnormalities after five years, and 25% after ten years[22]. These results confirm the transitional characteristic of cervical HPV infection in younger women and its greater persistence in women with more than 40 years old[22].

The prevalence of bacterial vaginosis was similar between the groups, even with a lower number of women under 30 years of age. The high prevalence of bacterial vaginosis identified in this study (33.2%) is compared to other studies that report rates of 31.4% to 41%[11,12]. Varied prevalences of bacterial vaginosis are found worldwide, and it is a frequent condition in young and sexually active women[1].

Based on the results of the present study, significant associations between bacterial vaginosis and cervical HPV infection, and between bacterial vaginosis and cervical cytological abnormalities, were not detected, corroborating studies that also investigated adult women in different age groups[23-25]. Frega et al[26] proposed a theory about the oncogenic effect of nitrosamines associated with bacterial vaginosis, and discussed the possibility that they may act synergistically with another agent, such as HPV. However, there is evidence that the amounts of nitrosamines, considered carcinogenic, produced by women with bacterial vaginosis did not differ significantly from women without bacterial vaginosis. On the other hand, according to Nam et al.[23] abnormal amines are closely related to the presence of bacterial vaginosis, but they can be eliminated through treatment with metronidazole. Corroborating this evidence, a study carried out by Boyle et al.[27] showed that women with bacterial vaginosis did not present cervical cytological abnormalities, known to be induced by HPV, more frequently than women without bacterial vaginosis.

Thus, the results obtained by the present study indicate that the bacteria associated with bacterial vaginosis may be part of the normal biome, which suggests a possible reconsideration of the pathogenic role of these microorganisms. However, it is unanimous that the vaginal microbiota, composed of Lactobacillus spp., plays an important role in the prevention of infections, especially cervical infection by HPV[8,9]. Studies show that women with vaginal microbiota dominated only by *Lactobacillus crispatus* have a low prevalence of cervical HPV infection, suggesting that *Lactobacillus* provide protection against cervical HPV infection, while a greater diversity of bacteria can lead to a high prevalence of this condition[28-30].

In contrast, significant associations between bacterial vaginosis and cervical HPV infection[10-15] and between bacterial vaginosis and cervical cytological abnormalities[12-13] have already been described by several research groups. These studies used the polymerase chain reaction (PCR) as a method for the detection of HPV DNA and the Nugent score for the diagnosis of bacterial vaginosis, similar to the diagnostic methods used in the present study, but they did not stratify women into age groups, which could have better demonstrated the relationship between these conditions at different ages. The methods employed allow a more accurate diagnosis, with greater sensitivity and specificity[20,31].

In the present study, the prevalence of bacterial vaginosis and cervical HPV infection was high. Our results reinforce that a broad vaccine coverage against cervical HPV infection[32], associated with the diagnosis and treatment of bacterial vaginosis when recommended[33], will certainly contribute to reducing the incidence of these diseases. Women diagnosed with high-risk HPV and with cervical cytological abnormalities in this study should be followed up and referred for cytopathology and colposcopy exams[34], thus allowing the screening of high-grade cervical lesions and interventions, before they progress to the cervical cancer[34].

### Strengths

The highlight of the present study is the inclusion criteria, as we included only adult and non-pregnant women known to be not immunosuppressed, who had not used antibiotics in the last 15 days before consultation. The detection of HPV DNA was performed by PCR and the diagnosis of vaginosis bacterial was given using the Nugent score. However, our results emphasize the need to carry out broader studies that allow a better investigation of these diseases, since they were evidenced in the group of women studied.

### Limitations

Some limitations of this study must be considered. The recruited sample was relatively small and the stratification of women into age groups further reduced the sample size and, consequently, the statistical power of the analyses. Another limitation includes the possibility of recall bias or omission of information from participants regarding risk sexual behaviors.

## CONCLUSION

The results of this study allow us to conclude that the prevalence of bacterial vaginosis and cervical infection by HPV was high, while cervical cytological abnormalities remained as expected, but there was no association between bacterial vaginosis and cervical infection by HPV, or between bacterial vaginosis and the cervical cytological abnormalities.

### Approval by the Human Research Ethics Committee

This research was approved by the Research Ethics Committee of the Cancer Fighting Association in Goiás (CEP/ACCG) under decision number: 2.322.218.

### Participation of each author

BCTM: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. KCC: Data curation. JPL: Data curation. JEPR: Data curation. CLS: Data curation. SHRS: Writing – original draft, Writing – review & editing. VAS: Data curation, Formal

Analysis, Writing – original draft, Writing – review & editing. RRFA: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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## Conflicts of interest

The authors declare no conflicts of interest.

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