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IMPACT OF TRICHOMONAS VAGINALIS AND HPV CO-INFECTION ON THE RISK OF CERVICAL INTRAEPITHELIAL NEOPLASIA: A NARRATIVE REVIEW OF THE LITERATURE

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Abstract: Objective: To analyze the association between co-infection with *Trichomonas vaginalis (TV)* and the increased risk of cervical intraepithelial neoplasia (CIN) in women infected with human papillomavirus (HPV), through a narrative review of the literature. **Method**: This is a literature review study carried out on the PubMed database, using the search terms "Trichomonas vaginalis", "risk", "HPV" and their combinations. Twelve articles were selected for detailed analysis. **Review**: The findings suggest that co-infection with TV and HPV, especially the HPV-16 subtype, is associated with an increased risk of CIN. In a study of 5,683 patients, an increased risk of CIN was identified in VT and HPV-16 co-infections, while another smaller study did not confirm this relationship (Hu et al., 2021). VT infection promotes changes in the vaginal microbiota, facilitating the persistence of HPV and making it more difficult to eliminate, which can aggravate the cervical lesions observed in cytological exams. **Final considerations:** Co-infection with *Trichomonas vaginalis* and HPV represents a significant risk factor for the development of CIN, since the chronic inflammation and epithelial damage caused by VT, combined with the persistence of HPV, weaken the immune system, favoring the development of precancerous lesions. These findings reinforce the need for rigorous monitoring and effective preventive approaches for women at risk of co-infection.

Keywords: Coinfection, Trichomonas vaginalis, Human papillomavirus, Cervical intraepithelial neoplasia, Oncogenic risk.

INTRODUCTION

Sexually transmitted infections (STIs) represent a serious public health problem worldwide, directly impacting reproductive health and overloading health systems. Among the most prevalent STIs are Trichomonas vaginalis (TV) and the human papillomavirus (HPV), the latter being the main etiological agent of cervical cancer, responsible for around 530,000 new cases of cervical neoplasms every year worldwide (Rizzo *et al*., 2024). HPV is classified as an oncogenic virus, with high-risk types (HR-HPV), such as HPV-16 and HPV-18, being directly associated with the development of cervical cancer, as well as other anogenital and oropharyngeal neoplasms (Suehiro *et al*., 2021).

Trichomonas vaginalis infection, in turn, is highly prevalent among sexually active women, with rates ranging from 29.2% to 30.8% in different studies (Lv *et al.*, 2019). Epidemiological data indicate that co-infection by VT and HPV can have a major impact on cervical health, since VT-induced inflammation in the cervicovaginal epithelium creates a favorable environment for HPV persistence and the progression of pre-neoplastic lesions. In a study conducted by Lv *et al*. (2019), it was shown that women with VT are 6.5 times more likely to contract high-risk HPV when compared to uninfected women.

Although HPV infection is often asymptomatic and, in many cases, the immune system eliminates the virus spontaneously, co-infections with pathogens such as VT can impair the local immune response, favoring viral persistence and the development of serious cervical lesions, such as cervical intraepithelial neoplasia (CIN). Studies suggest that VT can facilitate HPV access to the deeper layers of the cervicovaginal epithelium, as well as triggering inflammatory processes that compromise epithelial integrity and increase susceptibility to genetic mutations and DNA damage (Azadehrah *et al*., 2024).

According to Qulu *et al*. (2023), in a study of 243 sexually active women, 34% had HPV infection, with STIs being associated with viral persistence and complications such as cervical cancer. Suehiro *et al.* (2021) corroborate these findings, reporting a prevalence of 33.8% of HPV, with HPV-16 as the predominant genotype. In addition, co-infections with other STI agents were detected in 14.1% of HPV-positive women, suggesting a synergism between these infections in the worsening of cervical lesions.

Primary prevention against HPV is mainly based on vaccination, which is available through the Unified Health System (SUS), with bivalent, quadrivalent and 9-valent formulations. All of them protect against types 16 and 18, which are the most associated with cervical cancer. However, challenges such as low adherence to vaccination, age restrictions and lack of prevention against other STIs, such as trichomoniasis, limit the effectiveness of control strategies and contribute to the persistence of high rates of infection and cervical neoplasms globally (Jayapalan & Bindu, 2020).

Therefore, given the evidence presented, the significant relationship between co-infection by Trichomonas vaginalis and HPV may increase the risk of cervical intraepithelial neoplasia (CIN) and cervical cancer, especially in cases of viral persistence. Although the interaction between the two pathogens has yet to be fully elucidated, studies suggest that inflammation and epithelial damage induced by VT play a relevant role in facilitating HPV infection and progression.

Given this scenario, this study aims to investigate and analyze the relationship between co-infection by Trichomonas vaginalis and human papillomavirus (HPV) in the context of the risk of developing cervical intraepithelial neoplasia (CIN). The epidemiology, pathophysiological mechanisms involved and the implications of this co-infection for diagnosis, treatment and prognosis will be addressed, providing a broader understanding of this interaction and contributing to better prevention and clinical management strategies.

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METHODS

This study is a literature review drawn up according to the criteria of the PVO strategy (Research Population or Problem, Variables and Outcome), which guided the construction of the following research question: *"How does co-infection with Trichomonas vaginalis and human papillomavirus (HPV) influence the risk of developing cervical intraepithelial neoplasia (CIN), and what are the epidemiological, pathophysiological, diagnostic and therapeutic implications of this association?"*.

The searches were carried out on the PubMed-MEDLINE (Medical Literature Analysis and Retrieval System Online) database, one of the main sources of scientific publications in the biomedical field. To formulate the search strategy, controlled terms (MeSH Terms) and free terms were used, combined using the Boolean operators "AND" and "OR", guaranteeing a broad and specific search. The strategy was constructed as follows: ("trichomonas vaginalis"[MeSH Terms] OR ("trichomonas"[All Fields] AND "vaginalis"[All Fields]) OR "trichomonas vaginalis"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields] OR "risk of"[All Fields]) AND ("hpv"[MeSH Terms] OR "hpv"[All Fields]).

The initial search resulted in 114 articles, which were carefully screened to ensure the quality and relevance of the studies included. The inclusion criteria adopted were: articles in English and Portuguese, published between 2014 and 2024, and which directly addressed the proposed themes, such as epidemiology, pathophysiology, diagnosis and treatment of co-infection by Trichomonas vaginalis and HPV in the context of the development of cervical intraepithelial neoplasia (CIN). Studies of different methodologies were included, such as reviews, meta-analyses, observational and experimental studies.

Exclusion criteria were adopted to eliminate articles that did not meet the objectives of the study. Duplicate articles, publications available only in abstract format, and studies that did not directly address the relationship between co-infection by Trichomonas vaginalis and HPV in the development of CIN were excluded.

After applying the inclusion and exclusion criteria, the final selection resulted in 72 articles. In a second stage of analysis, the selected articles were reviewed for adequacy of content and methodological quality, resulting in a total of 12 articles included in the final collection of this study. These articles were fundamental to the construction of the discussions and conclusions presented, offering an up-to-date overview of the relationship between co-infection with Trichomonas vaginalis, HPV and the risk of developing cervical intraepithelial neoplasia.

REVIEW

Among STIs, HPV and TV are the most prevalent globally (Belfort *et al*., 2021). HPV infection is a necessary condition for the development of cervical lesions; however, not all infected women develop cervical cancer. This process depends on factors such as the specific type of HPV, viral load, persistence of the infection and incorporation of the viral genetic code into the host DNA (Mei *et al*., 2023). In many cases, the immune system eliminates the virus without the occurrence of a cervical lesion, suggesting the involvement of cofactors, such as co-infection with TV, in the persistence and progression of HPV.

In one study, women infected with HPV-16 and co-infected with VT had a higher incidence of cervical intraepithelial neoplasia (CIN), while those infected with HPV-18, even with co-infection with VT, did not have an increased risk. A study of 5,683 patients showed an increased risk of developing CIN in co-infections with VT and HPV-16, while a smaller

study by Hamar *et al.* (2023) did not find the same correlation, possibly due to sample limitation. In a study of 500 patients, 20.2% had alterations in the Pap test, and 30.1% of these alterations were associated with the presence of Trichomonas vaginalis (Amorim *et al.*, 2017).

The development of cervical lesions seems to be related to the length of exposure to the infectious agent. According to Amorim *et al.* (2017), women aged between 32 and 42 had a higher frequency of cervical lesions, while those without lesions were mostly younger than 31. This suggests that exposure time plays a crucial role in pathogenesis. In addition, hormonal factors and menstrual bleeding also increase susceptibility to T. vaginalis infection, which can consequently increase the risk of HPV and even HIV infection, causing significant impacts on reproductive health (Taku *et al.*, 2021).

Taku *et al.* (2021) also point out that women with HIV infection often have cervicovaginal inflammation and harbor various microbial agents in their vaginal flora, making STIs independent risk factors for cervical cancer. In line with this, Azadehrah *et al.* (2024) reported a high prevalence of T. vaginalis in women with abnormal Pap test results, highlighting the significant relationship between this infection and cervical alterations. In this context, 30.1% of the patients infected with TV had altered results in the preventive examination.

The risk factors for co-infection with HPV and VT include low schooling, use of intrauterine contraceptive methods, multiple sexual partners and marital infidelity. On the other hand, the number of pregnancies greater than one, post-menopause, previous HPV infection and poor socioeconomic conditions are more related to HPV alone than to co-infection (Hu *et al.*, 2021). On the other hand, condom use has been shown to be a significant protective factor, reducing the chance of TV infection (Suehiro *et al.*, 2021).

Some studies suggest that co-infection between VT and HPV occurs due to common factors, such as risky sexual behavior, but do not confirm a direct causal relationship. Vallely *et al.* (2023) state that, despite the correlation observed between the infections, the cross-sectional methodology of the studies limits the analysis and longitudinal follow-up is necessary for more robust conclusions.

On the other hand, Hamar *et al.* (2023) suggest that T. vaginalis and HPV often coexist due to similar risk factors, such as young age, multiple sexual partners and non-use of condoms. Although co-infection can occur simultaneously, it is not yet possible to determine whether TV infection directly affects the acquisition or persistence of HPV. Mei *et al.* (2023) add that VT infection may be a risk factor for the persistence or progression of low-grade cervical lesions, promoting progression to cervical cancer by facilitating HPV infection and progression.

Regarding pathophysiology, Yang *et al.* (2020) observed that co-infection with T. vaginalis increased both the risk of CIN 1 in women with high-risk HPV and the risk of CIN 2 and 3 in patients infected with HPV-16. This association is related to the chronic inflammation induced by T. vaginalis, which promotes the persistence of HPV by generating an imbalance in the vaginal flora. This imbalance reduces the levels of lactobacilli, causes alkalinization of the vaginal pH and induces inflammation, facilitating viral invasion and HPV persistence, preventing its elimination by the host's immune system.

Finally, Belfort *et al.* (2021) reinforce that the use of condoms is an effective measure to prevent TV infection and, consequently, reduce the risk of HPV infection, thus reducing the chances of developing cervical cancer. This highlights the importance of preventive measures such as sex education, the use of barrier methods and HPV immunization as fundamental strategies to mitigate the risks associated with these infections.

Azadehrah *et al*. (2024) observed that HPV infection leads to the release of lytic enzymes, which are responsible for reducing the mucosal protective layer of the vagina and causing microlesions in the epithelium. These alterations facilitate the attachment of HPV to the epithelium and the integration of its genetic material into the host cell's DNA, thus initiating the process of carcinogenesis. These observations reinforce the importance of understanding the mechanisms by which concomitant infections can alter the vaginal microenvironment, favoring viral persistence.

Fernandes *et al*. (2023) also showed that co-infections with Candida spp. and Trichomonas vaginalis were prevalent in women with pre-malignant and malignant cervical lesions, suggesting that these microorganisms act as cofactors in the progression of high-risk HPV-associated lesions. Persistent inflammation and changes in the vaginal microbiological balance have been identified as critical factors in this process. These findings reinforce the importance of an integrated clinical approach, especially in vulnerable populations such as sex workers.

The relationship between TV and HPV co-infection was also addressed by Taku *et al*. (2021), who emphasize that co-infection with other STIs can make treatment more difficult and increase the risk of developing cervical neoplasia. Women co-infected with Ureaplasma spp. or HSV-2 were more likely to have HPV persistence and progression of precancerous lesions. These factors reiterate the importance of evaluating coinfections such as VT, since the concomitant presence of these infections generates microenvironments favorable to HPV progression and the development of cervical lesions.

Population studies have also confirmed this correlation. Yang *et al.* (2020) showed that co-infection with Trichomonas vaginalis and HPV-16 significantly increased the risk of developing high-grade lesions (CIN 2-3). This effect was attributed to the chronic inflammation caused by VT, which promotes viral persistence and prevents the spontaneous elimination of HPV by the immune system. According to Belfort *et al.* (2021), women previously infected with Trichomonas vaginalis had a higher risk of high-risk HPV infection, reinforcing the hypothesis that VT creates an environment conducive to viral infection and lesion progression.

Furthermore, Hamar *et al.* (2023) reported that women infected with Trichomonas vaginalis were 1.79 times more likely to be diagnosed with concomitant HPV. This relationship suggests that TV may act as a facilitator in the development of cervical lesions in sexually active women, increasing the risk of progression to cervical cancer. However, Hu *et al*. (2021) point out that this association is more significant for the HPV-16 and HPV-18 genotypes, which are considered high risk, while co-infection with other types of HPV showed a high but not significant risk.

Therefore, the studies analyzed suggest that co-infection with Trichomonas vaginalis and high-risk HPV promotes an inflammatory microenvironment and alters the balance of the vaginal microbiota, favoring the persistence of HPV and increasing the risk of cervical neoplasia. The use of condoms, as observed by Belfort *et al*. (2021), remains an essential protective factor, significantly reducing the chances of TV and HPV infection and, consequently, the risk of developing cervical cancer. These findings highlight the importance of early screening, integrated diagnosis and the implementation of preventive measures in high-risk populations.

FINAL CONSIDERATIONS

Co-infection with Trichomonas vaginalis and human papillomavirus increases the risk of developing CIN due to persistent inflammation, epithelial damage and imbalance of the vaginal flora, which compromise the immune response. Studies suggest a higher incidence of CIN in women infected with HPV-16 and co-infected with TV. Among 500 patients who underwent Pap smears, 30.1% showed alterations associated with Trichomonas vaginalis. Factors such as risky sexual behavior are linked to co-infection, but the lack of longitudinal follow-up prevents definitive conclusions about its relationship with progression to CIN. Cohort studies with longitudinal follow-up are recommended in order to assess the impact of risk factors and concomitant infections on the development of CIN. This will contribute to more effective preventive strategies, appropriate clinical interventions and specific recommendations for higher risk groups.

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