Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2025**; 52(10): 42078
https://doi.org/10.31083/CEOG42078

Editorial

Vaginal Intraepithelial Neoplasia and Efficacy of Its Treatments: A Simulation

Ugo Indraccolo[1,*]

[1]Maternal-Infantile Department, Hospital of Gubbio and Gualdo Tadino (ASL 1 Umbria), 06024 Gubbio, Italy
*Correspondence: ugo.indraccolo@libero.it (Ugo Indraccolo)
Academic Editors: Andrea Giannini and Michael H. Dahan
Submitted: 22 May 2025 Accepted: 23 June 2025 Published: 23 October 2025

Vaginal intraepithelial neoplasia (VaIN) is a rare disease, and its infrequent occurrence still presents challenges in understanding its natural progression and determining appropriate treatments [1]. A recent meta-analysis has provided insights into the natural history of VaIN, particularly in untreated cases, suggesting that treatments may not significantly impact the recovery from both high-grade and low-grade VaINs [2]. However, these findings have been met with skepticism from peer reviewers who have raised concerns about potential biases in treated patients that could affect the validity of the results and lead to misinterpretation of current treatment guidelines recommending intervention [3–5], especially for high-grade VaINs.

While acknowledging the issue of biased results, it is important to highlight a recent study by Monti *et al.* [6] which found a 17% recurrence rate of high-grade VaINs following various treatments during a 5-year follow-up period. This study included a subset of immunosuppressed women (13.4%). Assuming all these women experienced VaIN recurrence, the estimated recurrence rate for treated high-grade VaINs in non-immunosuppressed patients was approximately 14.7%, aligning closely with the findings of the aforementioned meta-analysis despite concerns about its biases [2]. Additionally, Sopracordevole *et al.* [7] reported a 5.8% risk of progression to vaginal cancer in treated high-grade VaIN cases, a figure that closely mirrors the estimated 5.2% progression rate in untreated cases hypothesized in our meta-analysis [2]. Therefore, as we cannot fully trust the accuracy of our biased results, we are ethically obligated to advise our peers and scholars to cautiously consider the true effectiveness of VaIN treatments, which, to the best of our knowledge, have not been proven in randomized trials.

To evaluate the potential effectiveness of treatments, we conducted a gross simulation to estimate the incidence of vaginal cancer by combining Italian data on untreated high-grade VaINs. We utilized historical data on human papillomavirus (HPV) prevalence in Italy prior to the widespread use of HPV vaccines, which was reported to be 8% in the general population [8]. The probability of developing a high-grade VaIN in Italy was calculated by multiplying the VaIN incidence rate (0.004, sourced from Cardosi *et al.* [9]) by the proportion of high-grade VaIN cases (0.368, from Indraccolo and Baldoni [10]) and dividing it by the prevalence of HPV infection in Italy (0.08, from Giorgi Rossi *et al.* [8]), resulting in 0.0184. It is known (from our meta-analysis [2]) that untreated high-grade VaINs have a persistence probability of 0.142. Therefore, the expected rate of vaginal cancer in Italy from untreated high-grade VaINs was calculated as $0.0184 \times 0.142 \times 0.052$, where 0.052 represents the estimated rate of cancer development among persistent, untreated, high-grade VaINs [2]. The result is 0.000136.

In contrast, the actual estimated rate of gynecologic cancers in Italy is 17,300 cases [11] out of a female population of 30,134,298 (2023 female population in Italy [12]) multiplied by 0.02 (proportion of vaginal cancer among gynecologic tumors [13]), resulting in 0.000011. This data likely includes a significant number of women who have been screened and treated for VaIN without undergoing HPV vaccination. Therefore, screening and treating high-grade VaINs could potentially reduce the risk of vaginal cancer by tenfold if the estimates and data presented are accurate.

However, we cannot be certain about these estimates. Therefore, we can only conclude that screening and treating high-grade VaINs would reduce the risk of vaginal cancer onset in unvaccinated patients.

Usually, we are able to screen for common diseases, and VaIN is uncommon, making its detection challenging. Therefore, VaINs are typically an incidental finding during cervical intraepithelial neoplasia (CIN) screening, and the number of VaINs missed during colposcopic examination is unknown. In the case of an ideal 70% cervical cancer screening coverage in Italy, we would miss at least 30% of unscreened VaINs, potentially increasing the number of patients who could develop vaginal cancer due to lack of treatment. This suggests that treatments would be more effective than previously simulated in preventing vaginal invasive neoplasia. However, is this assumption reliable? Are there VaINs that regress spontaneously that we are unable to detect? Are all detected VaINs overtreated? Based on data from our simulation, it appears that the risk of developing vaginal cancer within 5 years would be 0.4% or less in treated patients, similar to untreated low-grade VaINs [2]. This risk estimate is significantly lower than the 5.8% risk of progression from high-grade VaINs to vaginal cancer re-

ported by Sopracordevole *et al.* [7], still raising concern about the real natural history of treated VaINs.

In conclusion, there are numerous unanswered questions regarding VaIN management that remain unclear. Screening and treating VaINs could have a significant impact on the incidence of vaginal cancer, as widely acknowledged. However, it is crucial to determine the frequency and duration of screening, the optimal follow-up period post-treatment for high-grade VaIN, the most effective treatment options (including combinations of treatments), and the identification of patients at higher risk of poor recovery from VaINs. Additionally, there is a lack of evidence regarding the management and outcomes of non-primary VaINs. We encourage our readers to contribute scientific evidence to help address these critical issues.

From our own research, we have registered a meta-analysis looking for the true estimate of risk of developing a vaginal cancer in VaINs patients.

Author Contributions

UI provided the reported information, planning and performing this probabilistic simulation by using data from the literature and from Italian institutional sites. All work was conceived and completed by UI.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest. Ugo Indraccolo is serving as one of the Editorial Board members of this journal. We declare that Ugo Indraccolo had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Andrea Giannini and Michael H. Dahan.

References

[1] Holschneider CH, Berek JS. Vaginal intraepithelial neoplasia. Available at: https://www.uptodate.com/contents/vaginal-intraepithelial-neoplasia (Accessed: 21 May 2025).

[2] Indraccolo U, Borghi C, Mattei Gentili M, Scutiero G, Caselli E, Favilli A. Natural history of primary vaginal intraepithelial neoplasia with and without treatments: A systematic review with meta-analysis. Clinical and Experimental Obstetrics & Gynecology. 2025; 52: 36377. https://doi.org/10.31083/CEOG36377.

[3] Preti M, Joura E, Vieira-Baptista P, Van Beurden M, Bevilacqua F, Bleeker MC, *et al*. The European Society of Gynaecological Oncology (ESGO), the International Society for the Study of Vulvovaginal Disease (ISSVD), the European College for the Study of Vulval Disease (ECSVD) and the European Federation for Colposcopy (EFC) consensus statements on pre-invasive vulvar lesions. International Journal of Gynecological Cancer. 2022; 32: 830–845. https://doi.org/10.1136/ijgc-2021-003262.

[4] Rountis A, Pergialiotis V, Tsetsa P, Rodolakis A, Haidopoulos D. Management options for vaginal intraepithelial neoplasia. International Journal of Clinical Practice. 2020; 74: e13598. https://doi.org/10.1111/ijcp.13598.

[5] Asociacíon Española de Patología Cervical y Colposcopia - AEPCC Guías 2015. 2015. Available at: https://www.aepcc.org/wp-content/uploads/2016/03/AEPCC_revista05-ISBN.pdf (Accessed: 24 July 2024). (In Spanish)

[6] Monti E, Libutti G, Di Loreto E, Boero V, Barbara G, Iorio M, *et al*. High-grade vaginal intraepithelial neoplasia and recurrence risk: analysis of an Italian regional referral center series. Archives of Gynecology and Obstetrics. 2023; 308: 201–206. https://doi.org/10.1007/s00404-022-06886-6.

[7] Sopracordevole F, Barbero M, Clemente N, Fallani MG, Cattani P, Agarossi A, *et al*. High-grade vaginal intraepithelial neoplasia and risk of progression to vaginal cancer: a multicentre study of the Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV). European Review for Medical and Pharmacological Sciences. 2016; 20: 818–824.

[8] Giorgi Rossi P, Chini F, Borgia P, Guasticchi G, Carozzi FM, Confortini M, *et al*. Human Papilloma Virus (HPV), cervical cancer incidence and screening uptake: differences among Northern, Central and Southern Italy. Epidemiology & Prevention. 2012; 36: 108–119. (In Italian)

[9] Cardosi RJ, Bomalaski JJ, Hoffman MS. Diagnosis and management of vulvar and vaginal intraepithelial neoplasia. Obstetrics and Gynecology Clinics of North America. 2001; 28: 685–702. https://doi.org/10.1016/s0889-8545(05)70229-1.

[10] Indraccolo U, Baldoni A. A simplified classification for describing colposcopic vaginal patterns. Journal of Lower Genital Tract Disease. 2012; 16: 75–79. https://doi.org/10.1097/LGT.0b013e318237ec82.

[11] Agenbio. Tumori ginecologici: ogni anno in Italia oltre 17mila nuovi casi. 2022. Available at: https://www.fnob.it/2022/09/20/tumori-ginecologici-ogni-anno-in-italia-oltre-17mila-nuovi-casi/ (Accessed: 21 May 2025). (In Italian)

[12] ISTAT. Censimenti permanenti popolazione e abitazioni. Popolazione residente e dinamica della popolazione. Anno 2023. Available at: https://www.istat.it/wp-content/uploads/2024/12/CENSIMENTO-E-DINAMICA-DELLA-POPOLAZIONE-2023.pdf (Accessed: 21 May 2025). (In Italian)

[13] Nout RA, Calaminus G, Planchamp F, Chargari C, Lax S, Martelli H, *et al*. ESTRO/ESGO/SIOPe Guidelines for the management of patients with vaginal cancer. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2023; 33: 1185–1202. https://doi.org/10.1136/ijgc-2023-004695.