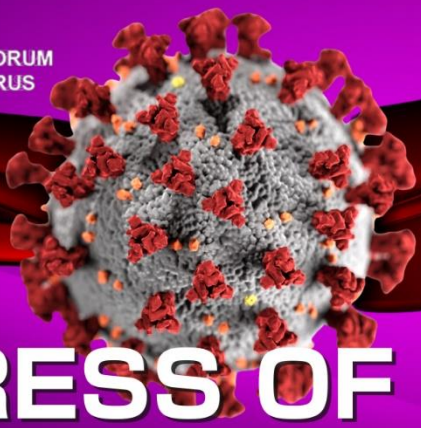
SEEFHPV

SOUTHEAST EUROPEAN FORUM
FOR HUMAN PAPILLOMAVIRUS



2ND CONGRESS OF SEEFHPV

HPV Infection and Associated Diseases

Hotel Holiday Inn, Skopje
N. Macedonia

30 January – 1 February 2026
Friday Sunday

BOOK OF ABSTRACTS

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In collaboration with:

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2nd Congress of Southeast European Forum for HPV
30.01-01.02.2026 North Macedonia
SUPPLEMENT TO THE MACEDONIAN MEDICAL REVIEW
Mac.Med.Review YEAR 2026 : 80 (SUPL, 114),1-180,2026
ISBN – 978-9989-37-053-3
UDK : 61+061.231=866=20
CODEN:MK MPA 3
ISSN0025-1097

SEEFHPV SOUTHEAST EUROPEAN FORUM FOR HUMAN PAPILLOMAVIRUS

WELCOME NOTE

Dear esteemed Colleagues and friends,
It is my great pleasure to welcome you to the 2nd Congress of the Southeast European Forum for HPV (SEEFHPV 2026).
This congress brings together experts from across Southeast Europe and beyond, united by a shared commitment to advancing knowledge, prevention, and management of HPV-related diseases. Through scientific exchange and interdisciplinary collaboration, we aim to strengthen regional strategies in HPV vaccination, screening, early detection, and patient care.
The scientific program of this congress reflects current challenges and future perspectives in the field of HPV, offering high-quality lectures, discussions, and opportunities for professional exchange. I am confident that the presented abstracts and sessions will contribute meaningfully to both clinical practice and public health policies.
I would like to sincerely thank all authors, speakers, and moderators for their valuable contributions, as well as our partners and sponsors for their continued support. Special appreciation goes to the Organizing and Scientific Committees for their dedication in making this congress possible.

I wish all participants a successful and inspiring congress.
Prof.Goran Dimitrov MD PhD
President - Southeast European Forum for Human Papilloma Virus – SEEFHPV

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Contents

BOOK OF ABSTRACTS

ALTERNATIVE HPV ONCOGENIC MECHANISMS BEYOND E6/E7

Rubens Jovanovic MD PhD
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Skopje

Abstract

Recent studies have revealed multiple novel mechanisms by which high-risk HPV strains contribute to oncogenic transformation—beyond the classic genome integration and E6/E7 expression pathways:

Several alternative and/or concurrent mechanisms have been implicated in the oncogenic transformation of infected cells:

- Host APOBEC-Mediated Genome Editing: elevated activity of APOBEC cytidine deaminases, which introduce mutations into viral and host DNA during persistent HPV infection, has been implicated in accelerating tumorigenesis.
- HPV-Derived microRNAs (miRNAs): HPV itself may produce viral miRNAs that modulate host gene expression—recently detected in HPV-positive tumors—adding a layer of post-transcriptional regulation that supports malignancy.
- Oxidative Stress and Reactive Oxygen Species (ROS): Chronic HPV infection can trigger oxidative stress, causing DNA damage (e.g., double-stranded DNA breaks), enhancing genomic instability, and promoting integration or E2/E4/E5 expression.
- Alternative Oncogenic Viral Genes: E2/E4/E5: Some HPV-positive cancers remain episomal, expressing E2, E4, and E5 instead of integrating E6/E7. These proteins activate EGFR/FGFR–PI3K – Akt-mTOR signaling and drive cellular proliferation, survival and resistance to apoptosis, thus favoring oncogenic transformation.

- DNA Damage Response Manipulation by HPV Proteins: HPV oncoproteins (not only E6/E7 but also E1/E2) interfere with host DNA repair pathways, altering homologous recombination and cell cycle checkpoints—favoring malignant progression.
- Epigenetic Reprogramming: DNA methylation, histone modifications, and dysregulated host microRNAs/long non-coding RNAs are emerging as co-factors induced by HPV infection that rewire host gene expression toward carcinogenesis.
- Microbiome and Co-Infections Influence: The interplay between HPV and other pathogens (e.g., HIV, EBV, HSV) or altered mucosal microbiomes can modulate inflammatory and immune responses, which promotes oncogenic progression.

In conclusion, these additional or alternative oncogenic mechanisms represent an alternative
oncogenic route in HPV-driven cancers that do not rely solely on E6/E7. It explains why some HPV- positive tumors exhibit strong growth factor signaling even without viral genome integration.

STATE OF THE ART INSIGHTS INTO HPV–VAGINAL MICROBIOTA INTERACTIONS IN CERVICAL CANCER DEVELOPMENT

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Cervical cancer remains one of the most significant HPV-related malignancies worldwide, yet persistent infection with high-risk human papillomavirus (HPV) alone is insufficient to explain disease progression. Increasing evidence highlights the crucial role of the vaginal microbiota as a co-determinant of HPV acquisition, persistence, and cervical carcinogenesis. This state-of-the-art review synthesizes recent findings on the multidimensional interplay between HPV and vaginal microbial communities, with a focus on the contrasting roles of Lactobacillus-dominant versus dysbiotic microbiota states. Lactobacillus species, particularly L. crispatus, promote antiviral defense through lactic acid production, maintenance of low vaginal pH, reinforcement of epithelial barrier integrity, and modulation of innate and adaptive immune responses, thereby supporting rapid HPV clearance. In contrast, dysbiotic microbiota enriched with anaerobes such as Gardnerella, Prevotella, Atopobium and Sneathia contribute to elevated pH, inflammatory cytokine release, oxidative stress, and mucosal barrier disruption—conditions strongly associated with persistent HPV infection and progression toward cervical intraepithelial neoplasia (CIN).
Emerging research increasingly supports the concept of a bidirectional relationship, wherein HPV infection itself induces local immune suppression and epithelial remodeling, further promoting microbial imbalance and chronic inflammation.

This reciprocal interaction forms a self-perpetuating cycle that enhances viral persistence and carcinogenic potential. Additionally, advanced molecular profiling and metagenomic approaches have revealed distinct microbial signatures linked to different stages of cervical disease, opening new possibilities for microbiome-based biomarkers in risk stratification and early detection. Integrating these insights suggests that therapeutic strategies aimed at restoring Lactobacillus-dominant microbiota, such as probiotics, microbiome-targeted therapies, or novel immunomodulatory approaches—may represent promising avenues for preventing HPV persistence and reducing the burden of cervical cancer development.

HIGH RISK HPV-INDUCED SQUAMOUS INTRAEPITHELIAL LESIONS: PATHOGENESIS AND THERAPEUTIC WINDOWS TO PREVENT INVASIVE CANCER

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Cervical cancer is highly preventable but is still the fourth most common cancer in women worldwide. Despite the availability of powerful tools for early detection of HPV-related SIL (Pap test, HPV testing, colposcopy), cervical cancer still causes over 600,000 new cases and 340,000 deaths annually. Most of this burden arises in regions without organized screening and vaccination programs.

Effective prevention depends on recognizing the critical milestones in HPV pathogenesis that define therapeutic opportunities.

Period of Invisibility

When HPV virions first enter the vagina, no visible changes occur and routine detection is impossible. Vaginal mucus acts as a dynamic defense system, creating a hostile environment for HPV, while the compact epithelium prevents viral

penetration into the deeper layers. During this phase, HPV may be naturally eliminated. However, if microabrasions are present, virions can penetrate through all layers of the epithelium, reaching the basal cells in depth. Supporting mucosal health, balanced microbiome, stable pH, and epithelial healing represents an early preventive strategy.

Basal Cell Infection – First Noticeable Moment

When HPV reaches the basal layer, it binds to the primary receptor - heparan sulfate proteoglycans (HSPG), undergoes conformational changes in the capsid proteins (L1, L2) and as such is transported to secondary receptors (α6-integrin) on the surface of basal cells and enters the cell via endocytosis. Viral DNA reaches the nucleus, disrupts cell cycle regulators (p53, Rb). Cytopathogenic effects such as „koilocytosis“ appear, and HPV testing becomes possible at this stage.

Early Gene Expression – Second Critical Moment

Episomal viral DNA expresses E6/E7, producing LSIL. Cytology may also show ASC-US, reflecting overlap in timing. Because viral replication remains controlled, epithelial maturation continues, and p16/Ki-67 double staining is negative.

This stage represents reversible changes, often managed with follow-up, however destructive techniques (cryotherapy, thermal ablation, laser) are effective, especially when paired with reepithelialization and immune support.

Integration – Point of No Return

The decisive event occurs when HPV DNA integrates into the host genome, disrupting the viral E2 gene and driving uncontrolled E6/E7 expression. This leads to loss of DNA repair and apoptosis control (p53), deregulated cell cycle progression (Rb),severe nuclear atypia and impaired maturation. These irreversible changes manifest as HSIL,

progressing toward invasive cancer. At this stage, p16/Ki-67 double staining becomes positive, even before visible HSIL, marking the transition from transient infection to precancerous transformation. At this stage excisional methods (LLETZ, laser conisation, cold knife conisation) are strongly recommended for both diagnosis and treatment.

Conclusion

Understanding the sequential milestones of HR HPV pathogenesis — from invisible entry to irreversible integration — provides a framework for targeted interventions. Strengthening mucosal defenses, recognizing early cytological changes, and applying excisional therapy at the decisive stage are key strategies for reducing cervical cancer mortality.

FROM PERSISTENT HPV INFECTION TO ONCOGENESIS : MECHANISMS AND CLINICAL IMPLICATIONS

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Abstract

Human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases and the main etiological agent responsible for multiple cancers, including cervical carcinoma. HPV is a double-stranded circular DNA virus that shows tropism for epithelial cells. Due to rapid immune clearance, most HPV infections do not cause symptoms and resolve spontaneously within 1 or 2 years. However, persistent high-risk HPV infection is associated with an increased risk of high-grade cervical intraepithelial neoplasia (CIN) and cancer. Moreover, high-risk HPV types are also responsible for anogenital and/or oropharyngeal cancers in both women and men. Viral E proteins are the major contributors to disease progression. E1, E2, and E4 are mainly associated with viral integration, replication, and transcription, whereas E6 and E7 act as oncoproteins associated with cancer progression. E5 regulates cell proliferation and apoptosis and facilitates the activity of E6 and E7. Despite the prophylactic HPV vaccine and other preventive and therapeutic strategies, including HPV screening, surgery, radiotherapy, and chemotherapy, the burden of HPV-associated carcinomas remains heavy worldwide. In addition, individuals with HPV-related diseases remain at risk for subsequent HPV infection and related disease after treatment of specific lesions. This risk may involve new HPV

infections caused by a different HPV type or re-infections with the same HPV type, whether from a new exposure to an infected partner or through autoinoculation from an adjacent or distant actively infected site. Accumulating data increasingly suggest that HPV infection may also be associated with infertility in both males and females, affecting human reproduction and reducing success rates in assisted reproductive technologies. In particular, the prevalence of HPV in the seminal fluid from infertile men is 3 to 4 times higher than in fertile controls, impairing sperm quality. In addition to its known efficacy, the HPV prophylactic vaccine has also shown benefits in preventing subsequent HPV-related disease when administered before or soon after treatment of lesions, and it has been associated with improved HPV clearance and healing in infertile HPV-positive men seeking infertility management.
Keywords: HPV, persistent infection, oncogenesis, vaccination

SCREENING, EARLY DETECTION AND EMERGING DIAGNOSTIC STRATEGIES FOR CERVICAL CANCER IN:INSIGHTS FROM NATIONAL RETROSPECTIVE STUDIES

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Introduction: Cervical cancer is the second most common type of cancer among women of reproductive age in Albania based on World Health Organization reports, with the highest burden observed in low- and middle-income countries. In Albania, cervical cancer represents the second most frequent malignancy among women of reproductive age. Persistent infection with high-risk human papillomavirus (HPV) types is identified in more than 99% of cervical cancer cases, making the disease largely preventable through effective vaccination, screening, early diagnosis, and timely treatment. This presentation reviews the epidemiology, risk factors, screening strategies, diagnostic methods for cervical cancer in Albania. Special emphasis is placed on the limitations of conventional Pap testing, including false-negative results related to pre-analytical and analytical factors, and on the advantages of liquid-based cytology, HPV DNA testing, and dual immunocytochemical staining (p16/Ki-67) for improved detection of high- grade lesions.

Methods: A retrospective study conducted at a tertiary oncology center in Tirana analyzed 640 women diagnosed with cervical cancer between 2015 and 2022. And also a retrospective study was conducted with 147 outpatient women between 2021 and 2024. Cervical smears were collected using Liquid Cytology (ThinPrep®), and the results were classified according to the Munich III system. HPV analyses were performed using the Polymerase chain reaction (PCR) method (cobas® HPV) to detect HPV High-Risk (HR) strains.

Results: The results demonstrate that the highest incidence occurs in women aged 40–60 years, with a mean age at diagnosis of 49 years. Early sexual debut, multiparity, smoking, and rural residence were associated with advanced-stage diagnosis. Although urban residence was more common among diagnosed cases, women from rural areas were more likely to present with advanced disease. Squamous cell carcinoma was the predominant histological subtype.Additionally, preliminary data from the first implementation of HPV and ThinPrep co-testing in Albania (2021–2024) highlight the feasibility and potential impact of modern screeningstrategies aligned with international guidelines (WHO, ACOG, NHS).

Conculsion: There is a statistically significant correlation between HPV HR strains and abnormal pap smear results. Therefore, it would be advisable to implement HPV-based primary screening for early cervical cancer detection, taking into consideration the lack of HPV vaccination and the lifestyle of the at-risk Albanian women population.

HPV TESTING AS A PRIMARY SCREENING TOOL FOR CERVICAL CANCER SCREENING

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Cervical cancer develops as a consequence of persistent infection with oncogenic human papillomavirus (HPV) types, most notably HPV 16 and 18, which together account for approximately 70% of cases worldwide. This well-established etiological link has led to a paradigm shift from cytology-based screening toward HPV testing as the primary modality for cervical cancer screening. The aim of this review is to evaluate the clinical performance of HPV testing as a primary screening tool, with emphasis on sensitivity, specificity, triage strategies, and clinical outcomes. Evidence from large randomized controlled trials and long-term follow-up studies demonstrates that primary HPV testing has significantly higher sensitivity than conventional cytology for the detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+), with relative increases in sensitivity ranging from 25% to 40%. Importantly, HPV-negative women have a substantially lower risk of developing CIN3+ or invasive cervical cancer over extended follow-up periods, supporting the safety of longer screening intervals of 5 years or more. Although HPV testing has lower specificity compared with cytology, especially in younger women with transient infections, this limitation is effectively addressed through structured triage algorithms. Clinically validated triage strategies include reflex cytology, partial HPV genotyping for HPV 16/18, and the use of

molecular biomarkers such as p16/Ki-67 dual staining. These approaches improve specificity, reduce unnecessary colposcopy referrals, and allow for risk-based management. From a clinical perspective, HPV testing facilitates earlier identification of women at increased risk before cytological abnormalities develop, enabling more timely surveillance and intervention.

The role of HPV primary screening is further strengthened in populations with high HPV vaccination coverage, where declining prevalence of high-grade lesions reduces the positive predictive value of cytology. In this context, HPV testing maintains robust performance and adaptability. Current clinical guidelines from the World Health Organization, European Union, and several national screening programs recommend HPV testing as the preferred primary screening method for women aged ≥30 years, with ongoing reassessment of screening algorithms in vaccinated cohorts. Implementation of HPV-based screening requires standardized laboratory methods, quality assurance, clear clinical pathways, and effective communication with patients regarding test results and follow-up. In conclusion, HPV testing as a primary screening tool offers superior clinical effectiveness, improved risk stratification, and enhanced long-term protection against cervical cancer, representing the cornerstone of modern cervical cancer prevention strategies.

THE METHODS OF TRIAGE OF HRHPV OTHER THAN 16 AND 18 IN HPV PRIMARY SCREENING

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Persistent infection with high-risk human papillomavirus (HRHPV) types is the principal risk factor of cervical cancer. Among these, HPV types 16 and 18 are responsible for approximately 70% of cases, and their detection in primary HPV screening typically warrants immediate colposcopy. However, effective triage strategies for women positive for other HRHPV types (non-16/18) remain essential to balance cancer prevention with the avoidance of unnecessary procedures. This review summarizes current and emerging methods for triaging HRHPV-positive, non-16/18 cases in primary screening programs.

Cytology (PAP smear) remains the most commonly used triage method, leveraging morphological assessment to identify cellular abnormalities indicative of precancerous lesions. Although widely available and cost-effective, cytology has limited sensitivity and reproducibility. Among them**, p16/Ki-67 dual immunostaining** has demonstrated superior sensitivity for detection clinically significant cervical intraepithelial neoplasia (CIN 2+), offering a promising balance between accuracy and feasibility. **DNA methylation**

testing of host and viral genes has also emerged as a valuable molecular triage tool, with increasing evidence supporting its ability to predict disease progression more objectively than cytology.

HPV genotyping beyond 16 and 18 – for example, identification of types 31, 33, 45, 52, and 58 – provides risk stratification that can refine triage decisions, particularly in populations where these types are prevalent. **mRNA testing for E6/E7 oncogenes expression** offers additional specificity by distinguishing transient from transforming infections. Recent advances also explore **machine learning-assisted cytology** and **artificial intelligence-driven image analysis** as adjunctive or standalone triage options, showing potential for automated, standardized assessment.

In conclusion, the triage of HRHPV types other than 16 and 18 represents a critical component of HPV-based cervical cancer screening strategies. While cytology remains a mainstay in many settings, biomarker and molecular approaches – particularly p16/Ki-67 and methylation assays – show greater promise for improving accuracy and efficiency. The integration of these methods, guided by resource availability and population risk profiles, is essential to optimize screening outcomes and reduce burden of cervical cancer worldwide.

CLINICALLY VALIDATED HPV TESTS FOR PRIMARY CERVICAL CANCER SCREENING:VALIDATION STANDARDS AND OPTIMAL SELECTION FOR ORGANIZED SCREENING PROGRAMS

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Persistent infection with high-risk human papillomavirus (hrHPV) is a necessary cause of cervical cancer, and the shift toward primary hrHPV testing has improved the detection of clinically significant cervical lesions. However, more than 250 commercial HPV assays exist, many lacking sufficient clinical data. Ensuring that only clinically validated tests are used is essential for maintaining accuracy, minimizing unnecessary follow-up and optimizing the effectiveness of population-based screening programs.

International validation frameworks, including World Health Organization recommendations and the VALGENT methodology, define performance criteria for hrHPV assays used in primary screening. These include high sensitivity and adequate specificity for CIN2+ detection, analytical reproducibility and proven clinical non-inferiority to established comparator assays. Additional characteristics, such as process automation, laboratory throughput, genotype reporting and compatibility with self-sampling, support efficient and scalable implementation. A limited number of hrHPV tests currently meet robust validation standards. The adoption of validated assays in organized screening programs enables extended screening intervals, risk-based patient management and improved utilization of healthcare resources.

Aligning cervical cancer prevention strategies with validated hrHPV testing and international standards is crucial for safeguarding screening quality. In regions such as Southeast Europe, the selection of reliable hrHPV assays supports sustainable program development and contributes to progress toward the global goal of cervical cancer elimination.

Keywords: High-risk HPV, clinical validation, test selection, organized screening, cervical
cancer prevention

REACTIVE OXYGEN SPECIES (ROS) AND HPV – THE MAIN ARCHITECTS OF CERVICAL EPITHELIAL CARCINOGENESIS

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Abstract: Cervical cancer is a complex, multistep process involving various molecular, viral, cellular, and environmental events that transform normal cervical epithelium into malignant growth. The contribution of the Human Papilloma Virus (HPV) to cancer is significant but not exclusive, as carcinogenesis involves complex mechanisms, notably oxidative stress (OS).
HPV infection and oxidative stress act synergistically in the functional damage of cervical cells by destabilising the p53

homeostatic system and over expression of two viral proteins, E6 and E7. For the discovery of HPV, Harald zur Hausen received the Nobel Prize in Physiology and Medicine in 2008. After 25 years of intensive HPV research, Harald zur Hausen came to the realization that only a small percentage of viral infections lead to invasive growth, which indicates that the expression of viral oncogenes E6/E7 alone is not sufficient for the development of cervical cancer. The main topic of this article is to explain the possible contribution of reactive oxygen species (ROS) to the development of cervical neoplasia, regardless of its endogenous or exogenous origin. Superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2), are the most important members of reactive oxygen species (ROS). Hydrogen peroxide (non-radical) is easily transformed into an ultrafast (10^{-9} s speed of action) hydroxyl radical (•OH) via the Fenton reaction. The rapid decomposition of hydrogen peroxide by the Fenton reaction, the formation of toxic hydroxyl radicals, and the possibility of damaging the genome suppressor TP 53, the p53 protein better known as the guardian of the genome and anticancer enzymes (COX-1 and ATP kinases) within the cervical epithelium, is not a rhetorical question, regardless of the fact that HPV has exactly the same intracellular targets. Oxidative stress (OS), a concept of Mother Nature that is approximately 2.7 billion years old, is not easily understood due to the unpredictable pathway of ROS, whose status in cellular metabolism can be described as a "double-edged sword." In recent decades, increasing knowledge has revealed the dual role of ROS in cellular physiology, showing that they serve as a major source of cellular damage and, under controlled conditions, are a master regulator of cellular homeostasis. In addition, to fully understand all the physiological and destructive activities of molecular oxygen (O_2), it is necessary to know its electronic configuration. The molecular orbital (MO) theory of O_2, based on the quantum mechanical model, is the only way to understand an important

metabolic concept, better known as oxidative stress. Routine determination of biomarkers of oxidative stress from cervical epithelial tissue, independent of the presence of HPV infection, raises hope. We can live in hope that new scientific knowledge and expertise, without outside influence, will free us from numerous diagnostic and therapeutic frustrations when it comes to cervical cancer.
Keywords: Reactive oxygen species, HPV, Cervical carcinoma

SHIFTING FROM COST TO VALUE IN HEALTHCARE: THE ECONOMIC CASE FOR HPV

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Healthcare systems in Central and Eastern Europe, including North Macedonia, face increasing pressure from population aging, limited public health expenditure, and persistent gaps in health outcomes. Over the past 5–6 years, public health spending per capita in North Macedonia has remained significantly below CEE and EU4 averages, contributing to lower life expectancy, higher treatable mortality, and a higher burden of disease measured in disability-adjusted life years (DALYs).

This presentation applies a value-based healthcare (VBHC) and health technology assessment (HTA) perspective to explore how shifting from cost containment to value creation can improve outcomes under constrained budgets. Comparative evidence highlights how delayed investment leads to avoidable disease burden and long-term economic losses. Human papillomavirus (HPV) is presented as a compelling case for value-based public health investment. Evidence on the return on investment (ROI) of HPV vaccination and screening is reviewed, alongside the clinical, economic, and societal costs of inaction. The presentation concludes with policy recommendations focused on strengthening prevention and early detection, adopting innovation-friendly HTA frameworks, and aligning healthcare financing with outcome-oriented objectives

HPV PREVENTION POLICY ATLAS

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Background
The European Parliamentary Forum on Sexual and Reproductive Rights (EPF) and the European Cancer Organisation (ECO) produced the 2025 HPV Prevention Policy Atlas— evaluating HPV vaccination, cervical cancer screening, and online information policies across 48 European countries, linked to WHO 90-70-90 targets and Europe's Beating Cancer Plan. The Atlas is developed by a multi-stakeholder expert group of cervical cancer and oncology specialists. Southeast European Context Almost all Southeast European countries have adopted gender-neutral HPV vaccination but face challenges in vaccination coverage rates and transitioning to HPV-based screening with self-sampling. The region remains in the mid-tier performance band (60–80%). Since the 2023 Atlas edition, Europe has demonstrated substantial progress: 42 countries now offer gender-neutral vaccination, 28 countries have mature population-based screening programmes, and 31 countries have established HPV vaccine registries.
Recommendations for Parliamentarians
1. Include HPV vaccination in routine state vaccination schedules; establish genderneutral
Programmes and extend catch-up age groups

2. Offer free HPV vaccination and mature population-based screening programmes
3. Transition to HPV-based testing with self-sampling options
4. Ensure publicly available vaccine coverage and screening participation data
5. Provide reliable, evidence-based government information on HPV prevention

Conclusion

HPV related cancer is preventable when we have the technical, medical, and policy tools to eliminate it. The 2025 HPV Prevention Policy Atlas shows significant progress across Europe, yet an East-West divide persists. Southeast European countries can accelerate progress toward WHO 2030 targets through parliamentary leadership and implementation of key policy recommendations, ensuring no person dies from HPV related cancer.

THE BURDEN OF CERVICAL CANCER TODAY VERSUS CURRENT STATUS OF SCREENING AND HPV VACCINATION

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Introduction
The international community aims making cervical cancer a rare disease (<4/100,000 cases/year) by the end of the century by vaccinating 90% of girls by age 15, screening 70% of eligible women aged 35-45 and treating 90% of (pre-)cancers by the end the current decade..
Methods
We assessed the 2022 burden of cervical cancer using IARC's GLOBOCAN database comprising 185 countries, updated screening policies from a survey onducted in 2024-25 involving 213 countries/territories, and the 2023 HPV vaccination status in 195 WHO member states.
Findings In 2022, approximately 661,000 women were diagnosed with cervical cancer, with 384,000 deaths with correspoinding age-standardized rates of 14 and 7/100,000 for incidence and mortality, respectively. Rates varied significantly by region, with the highest rates in Eastern-Africa (40 per 100,000) and the lowest in Western-Asia (4/100,000) and was very significantly correlated with income. Globally, cervical

cancer is the fourth most common female cancer and the leading cause of cancer- related mortality in 37 countries. Informants from 213 countries/territories reported that 45 have organized screening protocols, 87 have opportunistic screening, 76 have a mix, and five note little to no screening. HPV-based screening is fully implemented nationally in 20 countries, with more countries being at various stages of rollout or planning. Self-sampling for HPV testing is available or planned in several countries, and apply very diverse triage algorithms for HPV-positive women. Since 2023, 145 WHO Member States (74%) have introduced HPV vaccination programs with 56 and 83 countries applying a one-dose or a two-dose schedule, respectively. On average, vaccine coverage among girls was 27% for the first dose. Only ten countries achieved over 90% coverage with the last dose. HPV vaccination coverage varied widely by geographical region and socio-economic level.

Interpretation

With new tools of one-dose HPV vaccination, point-of-care testing on self-samples with validated, user-friendly and low-cost HPV assays, reaching the 90-70-90% objectives could be feasible in conditions of peace and economic stability. However, the current world situation will make reaching these goals extremely challenging.

INDIVIDUALSED CARE FOR CERVICAL PRECANCER

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When treating, particularly young nulliparous women, with cervical precancerous lesions,a state of the art balance should be achieved: to eradicate lesion in a life time ,with a single passage of excision and at the same time to keep both the long term risks for either future obstetrical morbidity as well the risk of future invasive disease post-treatment, not 3-5 times greater, but as close as possible to the general population corresponding relevant ones. Therefore :

- All women with CIN3, regardless of age, must inevitably be treated, ***at the moment***.
- Low-grade CIN (CIN1) should be managed conservatively in young women, as this reflects a state of viral replication with no true carcinogenic potential in most patients.
- The high spontaneous regression rates of CIN2 of up to 60% (in women younger than 30) should be balanced against the long-term cumulative risk of invasion.
- Every effort should be made to balance clearance that will minimise need for further excision, while preserving healthy cervical tissue.
- Treatments should ***only*** be performed ***under colposcopic guidance*** to balance oncological and reproductive outcomes.
- This balance can only be achieved with continuous, high-quality training.

MORPHOLOGIC SPECTRUM OF HPV ASSOCIATED ANOGENITAL LESIONS

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Abstract
Human papillomavirus (HPV) infection is a major etiologic factor in the development of a wide spectrum of anogenital lesions affecting both males and females. These lesions range from benign epithelial proliferations to high-grade intraepithelial neoplasia and invasive squamous cell carcinoma, reflecting differences in viral type, host response, and site-specific factors. This review summarizes the morphologic spectrum of HPV-associated anogenital lesions, highlighting key histopathologic features and their diagnostic significance. Characteristic morphologic findings include koilocytosis, acanthosis, parakeratosis, dyskeratosis, basal cell atypia, and increased mitotic activity. Low-risk HPV types are most commonly associated with condyloma acuminatum and low-grade squamous intraepithelial lesions, whereas high-risk HPV types are strongly linked to high-grade lesions and invasive carcinomas. Immunohistochemical markers, particularly p16, play a valuable role in distinguishing high-grade lesions and resolving morphologic overlap. Variability in lesion appearance across anatomic sites, including the cervix, vulva, vagina, penis, anus, and perianal region can pose diagnostic challenges, underscoring the importance of integrated morphologic and ancillary assessment. A comprehensive understanding of the morphologic spectrum of anogenital HPV-associated lesions is essential for accurate diagnosis, appropriate risk stratification, and effective clinical

management, and supports ongoing efforts in HPV-related cancer prevention and early detection.

Keywords: Human papillomavirus; anogenital lesions; morphology; squamous intraepithelial lesions; p16 immunohistochemistry; HPV-associated carcinoma

CONE BIOPSY: CONE BIOPSY: HISTOPATHOLOGY REPORT

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Histopathology reporting plays a vital role in cervical screening programmes, while histopathology services make a crucial contribution to reduce the incidence of and mortality from cervical cancer. It is therefore necessary that the pathologists know and follow protocols for dissecting and processing cervical specimens, know how to report histological findings and make sure to follow the changes in terminology of cervical lesions. According to the guidelines for the management of abnormal cervical cancer screening tests and cancer precursors, a diagnostic excisional procedure is recommended in women with biopsy-confirmed high-grade intraepithelial lesions. The procedure should be diagnostic and therapeutic. There are tree most common excisional techniques: cold knife conization, Large Loop Excision of the Transformation Zone (LLETZ) and Loop Electro-Excision Procedure (LEEP). By using any of these techniques the pathologist obtains a nearly cone-shaped tissue sample from the cervix. A cone-shaped tissue sample should be measured in three dimensions anterior- posterior x transverse x length, and must be examined in their entirety. Since Sanerkin and Fraser published first description of dissection of cone biopsies (1975), several methods of dissection have been accepted. In our laboratory we perform parallel antero-posterior cutting from left to right. The slicing is serial, at 2-3 mm intervals, and each slice is placed individually in designated cassettes. Histological reports should provide a well-defined pathological diagnosis which

should be in concordance with the WHO histological classification of tumors of the uterine cervix. In addition to a precise description of the histological type of the lesion, the reports include information concerning the localization of the lesion within the excision
biopsy; uni/multifocality of the lesion; extent of the lesion and, in case of microinvasive and invasive cancer, measurement of vertical and horizontal diameters, stromal reaction and involvement of micro vessels. Features to be reported also include the relation of the lesions to all resection margins and a description and characterization of additional non-neoplastic lesions. A semidiagramatic representation of the results clearly shows almost all of these parameters and characteristics. Immunohistochemical markers may be helpful in distinguishing intraepithelial lesions from benign mimics, especially in cases with glandular intraepithelial neoplasia, for the detection of involvement of micro vessels in cases of microinvasive carcinoma and for determination of the type of invasive neoplasm when the type of neoplasm is rare or when the tumor is poorly differentiated.
Conclusion: The accuracy of the histopathological diagnosis of conization depends on the appropriate macroscopic description, technical processing and microscopic interpretation.

TWO PATHWAYS TO MALIGNANCY: HPV-ASSOCIATED AND HPV-INDEPENDENT CERVICAL ADENOCARCINOMA

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Cervical adenocarcinoma arises through two distinct molecular pathways: one driven by high-risk human papillomavirus (HPV) infection and the other independent of viral oncoproteins. HPV- associated cases, comprising the majority, rely on viral E6 and E7 proteins to inactivate p53 and Rb tumor suppressors, promoting uncontrolled cell proliferation. In contrast, HPV-independent adenocarcinomas feature somatic mutations in host genes, leading to activation of alternative oncogenic pathways like PI3K/AKT signaling via PIK3CA alterations or SWI/SNF complex disruptions through ARID1A mutations.

HPV-Associated Pathway HPV integration disrupts host genome stability and expresses E6/E7, which degrade p53 and Rb, respectively, enabling cell cycle progression and evasion of apoptosis. These tumors show high p16 expression as a surrogate marker and respond to standard therapies targeting proliferation, but they dominate screening-detectable cases. Histologically, they align with usual-type endocervical adenocarcinomas and carry lower tumor mutation burdens compared to HPV-independent counterparts.

HPV-Independent Pathway Lacking viral drivers, these rarer tumors (about 10-14% of adenocarcinomas) exhibit higher mutation rates, particularly in PIK3CA (up to 52%), PTEN, and AKT, hyperactivating the PI3K/AKT pathway as a key oncogenic mechanism. Subtypes include gastric-type, clear cell, mesonephric, and endometrioid adenocarcinomas, often presenting at advanced stages with poorer prognosis due to

aggressive behavior and escape from HPV-based screening. Additional pathways like WNT (CTNNB1 mutations) and TGF-β dysregulation contribute, suggesting targeted therapies such as PI3K inhibitors. HPV- independent cases occur in older patients, show lymph node involvement early, and demand precise ubtyping for prognosis and treatment, as current therapies are less effective without viral targets.

With rising HPV vaccination, their relative incidence may increase, underscoring the need for non-HPV screening strategies and molecular profiling. Integrated genomic analyses reveal distinct subtypes—metabolic and immune—for personalized interventions.

Conclusion

Differential diagnosis between HPV-associated and HPV-independent cervical adenocarcinoma guides precise prognostication, treatment selection, and screening strategies due to their divergent behaviors and outcomes.

ADVANCING CERVICAL CANCER PREVENTION IN: THE IMPACT OF HPV GENOTYPING IN A NATIONAL PILOT SCREENING PROGRAM

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Human papilloma virus is the causative agent of one of the most common sexually transmitted diseases that affects both men and women. More than 150 types of HPV have been identified. The target HPV are the basal cells of the squamous layered epithelium, but also the metaplastic ones in the squamocolumnar junction of the cervix. Fortunately, most infections are asymptomatic and the reason for this is the phenomenon of spontaneous clearance of the virus, which largely depends on the state of the immune system of the infected person. Also, modern tests show that the development of infection towards malignancy depends a lot on the type of virus, and in recent years genotyping has been increasingly important. Unfortunately, in Serbia, screening for the early detection of cervical cancer is still carried out with a classic cytological examination - the PAPA test. In most developed countries, the screening system has changed over the last 30 years, and today we have countries where screening is performed as dual screening, but also countries where cytological screening is completely replaced by HPV testing. Certainly, the degree of implementation of primary prevention, that is, vaccination, contributed to changes in the field of screening. For this reason, in December 2024, the Ministry of

Health launched a pilot project in genotyping parallel with a cytological examination among 10,000 women in Serbia, of which 3,600 were performed in several Health Centers in Belgrade, and 6,400 were performed in the Health Center in Nis. Observing my city of Nis and the part of the project that I personally managed, voluntary women from the entire Nisava district between the ages of 30 and 65 could be tested within the project. After the first results of the processed data, it was concluded that the percentage of HR HPV positive corresponds to the European average (749 – 11.7%), but therefore a complete analysis (further performed colposcopy, histopathology) of a random sample of HPV HR + and cytologically positive (66 – 8.8%) showed the seriousness of deficiency of only isolated cytology in screening, especially in HPV 16+ women, but also the inevitability of defining algorithms and protocols that would be necessary to implement in Serbia with the introduction of dual screening.

THIN HSIL LESION OF THE UTERINE CERVIX POSSIBLE COLPOSCOPIC MANIFESTATION OF HPV INFECTION

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At the core of cervical carcinogenesis induced by HPV infection lies the viral entry through microdefects in the squamous epithelium or within the squamocolumnar junction (SCJ), reaching the basal cuboidal epithelial layer.This pathway leads to a progressive sequence of lesions from CIN I to CIN III (HSIL), involving the full thickness of the epithelium and resulting in characteristic colposcopic findings such as dense acetowhite epithelium, punctation, and mosaic patterns. Depending on the severity, these are defined as grade 2 colposcopic images (G2) and require histopathological evaluation. Cytologically, such lesions are frequently accompanied by koilocytotic changes.For these reasons, colposcopists focus their attention on visualization and exploration of the SCJ and the transformation zone, defined as the area between the original and newly formed SCJ developed through metaplastic processes. Since multipotent reserve cells play the key role in metaplasia and transformation zone formation, recent findings identifying two distinct types of reserve cells—located at the SCJ and in the subcolumnar epithelium (expressing CK7 and CK17, respectively)—have significantly modified the definition and concept of the

transformation zone. The latter reserve cell type, CK17-positive, is situated deeper within the endocervical canal, more than 3 cm proximal to the SCJ.Because such reserve cells are located beneath the basal layer of the columnar epithelium and far from the SCJ, they may represent a potential reservoir for HPV persistence and carcinogenesis, thus warranting a revision of the classical definition of the transformation zone.Carcinogenesis initiated by direct proliferation of infected reserve cells represents an alternative pathway of cervical oncogenesis, which does not necessarily progress through the precursor stages CIN I and II, but rather manifests directly as thin HSIL lesions.According to the WHO classification, thin HSIL lesions are defined as high-grade lesions less than 10 cell layers thick.These lesions typically produce subtle colposcopic findings of grade 1 severity (G1), located away from the SCJ within the columnar epithelium, often near the openings of endocervical crypts.Although histologically thin, immunohistochemical staining for p16 and E6/E7 markers, as well as molecular genetic analysis, confirms that these are indeed true HSIL lesions and recognized precursors of cervical carcinoma. Such findings have important clinical implications. During colposcopic evaluation of HPV-positive patients, special attention should also be directed to the columnar epithelium distant from the SCJ.Delicate G1-grade colposcopic changes observed as focal alterations within the columnar epithelium should be interpreted in correlation with HPV genotyping and immunohistochemical markers.Furthermore, the recognition that the distal reserve cells may be located up to 3 cm from the SCJ, within the subcolumnar epithelium extending toward the isthmic portion, bears clinical significance for post-excisional follow-up.Negative resection margins after LEEP or conization do not necessarily exclude the persistence of HPV reservoirs in deeper reserve cells, particularly those situated within the endocervical crypts.Therefore, the potential role of adjunctive protective

destruction (cauterization) of the non-excised cervical areas should be considered.In this regard, post-treatment HPV negativity may serve as a more reliable predictor of complete disease eradication than histologically negative excision margins alone.

COLPOSCOPY IN THE MENOPAUSE

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Menopause represents the final stage of the menopausal transition and it is defined as the permanent cessation of menstrual cycles due to loss of ovarian function. The average age at which the last menstrual period occurs in a woman's life is between 51 and 52 years. However, menopause may occur at any age as a consequence of loss of ovarian function. It is estimated that there are currently more than one billion women worldwide undergoing the menopausal transition or living in postmenopause, with a projected increase to 1.2 billion women by the year 2030. Changes in the genital tract caused by declining estrogen levels, previously referred to as vulvovaginal atrophy, are characterized by atrophy of the labia, dryness and thinning of the vaginal walls and cervical epithelium. Atrophy of the uterine body and cervix is present, along with loss of strength of the supporting tissues of the urinary bladder, rectum, and uterus. The introduction of the term genitourinary syndrome of menopause (GSM) highlights the importance of the local effects of hypoestrogenism on the quality of life of postmenopausal patients, resulting from genital symptoms such as dryness, burning, and irritation, as well as sexual dysfunction due to lack of lubrication and urinary symptoms including urgency, dysuria, and recurrent urinary tract infections. Due to epithelial atrophy and reduced cervical mucus production, there is increased vulnerability of the tissue and capillaries, which significantly complicates colposcopic and histological assessment and, in some situations, may make it completely impossible. Many postmenopausal women, as a result of atrophy and loss of

cervical stroma, have a type 3 transformation zone, which is the most common reason for inadequate visualization of the cervix during colposcopic examination. Shrinkage of the cervical stroma draws the squamocolumnar junction into the endocervical canal and narrows the external cervical os. Application of 3–5% acetic acid to the thinned surface epithelium is not always effective in revealing disease. Reduced glycogen content in squamous epithelial cells leads to uneven yellowish staining or complete lack of absorption, resulting in pale yellow staining. Short-term local application of estrogen for 7 to 10 days can help improve visualization and allow clearer assessment of the transformation zone. It should also be noted that involvement of the endocervical canal and/or vaginal walls is much more common in the postmenopausal population when cervical cancer is concerned. Therefore, special attention should be paid to the cervical canal sampling (endocervical cytology, curettage, and/or type 3 excision), as well as to a comprehensive examination of the vagina. Atrophic changes after menopause cause symptoms that may mimic malignant disease of the lower genital tract. Fortunately, the incidence of high risk HPV positivity and abnormal cytological findings is low in postmenopausal women with previously normal results. Nevertheless, in every woman with abnormal vaginal bleeding in postmenopause, the cervix must be examined.
Key words: colposcopy; menopause; hypoestrogenism; cervical cancer; postmenopausal bleeding.

GENITAL HPV LESIONS IN POSTMENOPAUSAL WOMEN

Ass Prof Iva Malahova Gjoreska

Abstract
Genital human papillomavirus (HPV) infections in postmenopausal women represent an increasingly recognized clinical entity with distinct epidemiological, biological and diagnostic characteristics. Age-related changes—including estrogen deficiency, epithelial atrophy, and immunosenescence—modify the natural history of HPV infection and contribute to higher rates of viral persistence and delayed clearance of high-risk (HR) HPV types. The transformation zone frequently retracts into the endocervical canal (type III TZ), complicating visualization and reducing the sensitivity of cytology and colposcopy. Consequently, HPV-based screening and triage strategies, including genotyping and biomarkers such as p16/Ki-67 dual staining, have demonstrated superior performance compared with cytology alone in this population. Postmenopausal women with persistent HR-HPV exhibit increased risk of CIN2+, supporting extended surveillance and individualized management. Treatment of HPV-related lesions can be more challenging due to epithelial thinning, impaired wound healing, and comorbidities, often necessitating pre-treatment vaginal estrogen to improve colposcopic assessment or procedural tolerance. Recognition of the unique pathophysiology of HPV infections in menopause is fundamental for optimizing screening, improving diagnostic accuracy, and reducing progression to invasive cervical cancer in older women.

MULTIZONAL ANOGENITAL DISEASE

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Human papillomavirus (HPV) has been described as the main etiological factor for the development of precancer and cancer the anogenital system. The focus of HPV prevention strategies has classically been on the uterine cervix. Some women present with disease at only
one anogenital site, but further develop disease in several anogenital zones. Such a condition is called Multizonal Anogenital Neoplasia (MZN). Multizonal Anogenital Neoplasia is defined by the presence of high-grade lesions (precancerous lesions) or cancer concurrently in two or more of the following sites or zones: perianal, anal canal, vulva, vagina or cervix. Multizonal neoplasia (consisting of both HSIL and/or carcinoma) is increasingly detected in women. In many case these neoplasia are asymptomatic, thus calling for the clinician to examine all anogenital sites. At present, referral for examination or screening all anogenital sites upon detection of neoplasia on one site, is not universal. In women with anogenital neoplasia, identification of risk factors for the involvement of more than one site is important to determine which patients might benefit the most from a full multizonal anogenital assessment.
The clear example are HPV infections involving the anal canal that have been neglected for decades. However increasing incidence anal HPV infection and related lesions was observed in some risk groups, including women who have an HPV infection involving the lower genital area, especially those with high-grade squamous intraepithelial lesions (HSILs).

Women with a history of genital neoplasia or cancer have a higher risk of anal neoplasia with the link between cervical and anal cancer well described. The risk of anal neoplasia increases with the number of anogenital sites involved, and there is evidence of preferential site involvement; the risk of anal canal neoplasia is greatest in patients with perianal disease, but is also elevated in those with vulval, vaginal and cervical neoplasia. The recent recognition that the treatment of anal precancers in HIV-positive MSM can reduce the incidence of anal cancer adds a new dimension to HPV-related cancer prevention. This high prevalence can be explained not only by sexual behavioral factors (i.e., anal intercourse), but also by the presence of similar epithelium in the anal canal and the uterine cervix which could favor the spread of the virus. Thus, several investigators have suggested that women with HPV- associated premalignant or malignant lesions in the genital or perineal area should undergo routine evaluation of the anal canal using high-resolution anoscopy (HRA) or anal cytology. However, these approaches are not currently included in any clinical guideline. Multizonal anogenital neoplasia (MZN) assessment might be essential to diagnose occult areas of HSIL or carcinoma, given the risk that such lesions are likely to be present at more than a single anogenital site. Such examinations can identify early cancers that have better patient outcomes and is likely to be cost-effective.

IS IT ENOUGH JUST FOLLOW UP OPTION AFTER PRECANCEROUS CERVICAL LESIONS TREATMENT ? DO WE HAVE AN OPPORTUNITY FOR BETTER PREVENTION IN THE PATIENTS?

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The introduction of HPV vaccines represents a revolutionary step in the prevention of CC. HPV vaccines are highly effective in preventing HPV infection and diseases related to HPV infection, but do not clear or reduce persistence of the virus in women with ongoing infections. Currently available prophylactic vaccines are: Gardasil® (licensed in 2006), a quadrivalent vaccine which targets HPV-6, HPV-11, HPV-16 and HPV-18, Cervarix® (licensed in 2007), a bivalent vaccine which targets HPV-16 and HPV-18, Gardasil 9® (licensed in 2014), a nonavalent which targets HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58. Recently, a bivalent vaccine, Cecolin® (licensed in China in 2020, and prequalified by WHO in 2021) was developed, and a recombinant bivalent HPV vaccine (licensed in China in 2022 and prequalified by WHO in 2022), both targeting HPV-16 and HPV-18.
The main mechanism of action of prophylactic vaccines is mediated by antibodies that neutralize viral particles, but they

cannot induce a cytotoxic immune response targeted against HPV-infected cells. Women who have been previously treated for high grade CIN, have a high risk of develop CC of other malignancies related to HPV infection. So, we need new strategies to reduce the risk and eliminate CC more rapidly.
First prospective study, SPERANZA, showed an 81% reduced risk of recurrent high grade CIN associated to HPV infection in vaccinated women, followed by VENUS observational study, which showed a 59% of reduction of persistent/recurrent high grade CIN2 in vaccinated women. In 2022 Kechagias et all. published that HPV vaccination might reduce the risk of recurrence of high grade CIN in women treated with local excision, in particular for disease related to HPV16 and HPV18 subtypes. Sand et al. published in 2020 a study, suggesting that vaccinating women in relation to conization could reduce the risk of subsequent development of high grade CIN. In 2023 Zou et al. published the research which showed that the three-dose HPV-4 vaccination was the most cost-effective vaccination strategy in women previously treated for CIN. The E. Joura study's analysed 295 9vHPV vaccine, 722 4vHPV vaccine, and 493 historic placebo recipients who underwent cervical surgery after a median of 1.7 years (range 0.1–4.4 years) after dose 1. Subsequent to surgery, HPV6/11/16/18–related SIL incidence was reduced by 95.4% (95% CI, 74.7–99.8%) with prior 9vHPV vaccine relative to historic placebo (1.3 vs 29.0/ 1,000 person-years, respectively); HPV31/33/45/52/58– related SIL incidence was reduced by 86.3% (95% CI, 47.5–97.8%) with 9vHPV vaccine compared with 4vHPV vaccine (2.7 vs 19.4/1,000 person-years, respectively). The incidence of high-grade SIL was numerically lower in the 9vHPV vaccine group relative to control, but this was not statistically significant (HPV6/11/16/18 related 69.6% reduction [95% CI, 2133.5% to 98.7%]; HPV31/ 33/45/52/58 related 82.7% [95% CI, 229.2% to 99.2%]). Authors concluded that participants who underwent

cervical excisional surgery, prior vaccination with 9vHPV vaccine (ie, 0.1–4.4 years before surgery) reduced the incidence of subsequent cervical and lower genital tract dysplasia.

In a systematic review of Pruski D et al authors showed the effectiveness of vaccination against HPV in HPV-positive adult women and those with histopathological confirmed SIL. Considering the timing of giving the authors concluded that the greatest effect is observed when the first dose is given before the excision procedure. Still authors point to that evidence is limited and highlight the need for standardized guidelines and prospective studies.

In Cochrane Database of Systematic Reviews by authors Kapp P et al who identified 13 studies (2 RCTs/randomized control trial, 11 NRSI/non-randomise control trial), with 21,453 women with conisation point to several facts. HPV vaccination compared to no HPV vaccination in women with conisation may reduce the risk of CIN 2+.There were similar results for CIN 2+ (related to HPV 16/18) .Effects on CIN 3+ varied between studies. One study suggested similar effects to CIN 2+ favouring HPV vaccination , while the remaining evidence was very uncertain evidence.

The evidence on CIN 3+ (related to HPV 16/18), incident invasive cervical cancer (irrespective of HPV type), and persistent HPV infections (irrespective of HPV type and related to HPV 16/18) was very uncertain. According to these findings authors concluded that additional RCTs with a placebo intervention in the control group to evaluate the efficacy and safety of HPV vaccination (particularly with the nonavalent vaccine) as an adjuvant to conisation would provide more robust evidence. Future RCTs should also aim to assess how effects of vaccination around the time of conisation vary according to whether a previous HPV vaccine for primary prevention was received, timing of HPV vaccination related to conisation, and different age groups.

In the meantime the VACCIN study did not show superiority of adjuvant HPV vaccination over placebo in women treated for CIN 2–3 and authors concluded that routine administration of adjuvant HPV vaccination did not contribute to the prevention of CIN recurrence in these women. Adjuvant HPV vaccination after treatment should be administered exclusively within trials to study subgroups that could potentially benefit.

We are expecting results from NOVEL, and HOPE9, clinical trials, about the effectiveness of the adjuvant HPV vaccination in women undergoing surgical excision of HPV associated cervical intraepithelial neoplasia.

Currently ongoing preclinical and clinical trials have the aim to develop an ideal therapeutic vaccine, which could induce a cytotoxic T-cell response, whose effector function is to eliminate infected or transformed cells. There are no licensed therapeutic vaccines yet, but VGX-3100 (DNA-based) is currently in phase 3 clinical trials, while bacterial vector therapeutic vaccines are in late clinical trial phases. VGX-3100 has the potential to be the first non-surgical treatment for precancerous cervical lesions, which could significantly change the treatment landscape. VGX-3100 is made of two synthetic DNA plasmids that carry instructions for the body's cells to make HPV-related antigens.This process stimulates the immune system to produce both humoral and cellular immune responses against HPV-16 and HPV-18 and destroy HPV-infected cells and precancerous lesions without the risks associated with surgery.

VAGINAL INTRAEPITHELIAL NEOPLASIA (VaIN) & VAGINAL CANCER : EPIDEMIOLOGY, DIAGNOSIS & TREATMENT

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Introduction

Vaginal intraepithelial neoplasia (VaIN) and primary vaginal cancer lie within the broader spectrum of lower genital tract disease. In day-to-day practice, VaIN is rarely an isolated finding and typically coexists with, follows, or precedes disease in other areas of the anogenital tract, such as the cervix, vulva, or anus. It is therefore important to evaluate VaIN within the context of “multizonal disease” from first presentation, as this approach influences how thoroughly clinicians examine the vagina and how follow-up is planned. (1,3) High-risk HPV infection is the principal aetiological factor; however, several factors determine whether infection clears or persists and influence progression to neoplasia. These include tobacco exposure, immunosuppression (including iatrogenic immunosuppression and HIV), chronic vaginal inflammation, and a prior history of high-grade cervical disease CIN2/3 or cervical cancer). Women who have undergone hysterectomy for CIN or cervical cancer also remain at risk for VaIN or invasive disease at the vaginal vault. In such cases, recurrence may be clinically subtle and is typically detected through regular vaginal vault surveillance, with vaginoscopy performed when surveillance tests are abnormal. (1,7) Primary prevention has advanced substantially in the last decade with prophylactic

HPV vaccination, which is expected to reduce the incidence of VaIN and HPV-related vaginal cancers as population coverage increases. Notably, the World Health Organization's cervical cancer elimination agenda also aims to reduce non-cervical HPV-associated cancers by achieving the 90–70–90 targets by 2030. (4–6)

VaIN Epidemiology, Diagnosis & Treatment

Epidemiology and natural history VaIN is uncommon compared with cervical or vulvar intraepithelial neoplasia and is typically asymptomatic. (1) It is graded using the two-tier system applied across HPV-associated lower genital tract disease into low-grade (LG) and high-grade (HG) VaIN. This categorisation also corresponds to clinical behaviour, as LG VaIN often represents transient HPV infection and may regress, whereas HG VaIN generally requires treatment owing to a higher risk of persistence, recurrence, and occasional progression to invasion. (1)

Progression rates are difficult to determine accurately because studies are small, retrospective, and heterogeneous, using different terminology and follow-up periods.

Nevertheless, a consistent clinical message emerges: HG VaIN is a premalignant lesion that should be managed with caution, particularly in high-risk groups such as women post-hysterectomy for CIN3/cancer, immunosuppressed patients, heavy smokers, and those with multizonal anogenital tract disease. (1)

Diagnosis of VaIN

As most patients do not present with symptoms, VaIN is often identified through:

• abnormal vaginal/cervical cytology,
• hrHPV positivity,
• surveillance after treatment for CIN/cervical cancer, or
• colposcopy for a different indication. (1)

To minimise the risk of missing vaginal disease, it is essential that a thorough assessment of the vagina (vaginoscopy) is

performed during colposcopy. Vaginal folds and the tendency of lesions to sit high in the vault (especially within the "dog-ears") post-hysterectomy can make disease easy to miss. The 2011 IFCPC terminology explicitly includes vaginal assessment and provides a shared language for describing findings. In practice, accurate assessment depends on a systematic approach including good lighting, appropriate speculum selection, careful manipulation to visualise the fornices/vaginal vault, acetic acid application, and the use of Lugol's iodine to facilitate visualisation of vaginal abnormalities. (3)

Another significant consideration is the importance of biopsies to ensure diagnosis. Cytology and HPV testing are screening tests which raise suspicion and can provide a statistical likelihood of a HG abnormality; however, colposcopy is the diagnostic test used to map the vagina and identify abnormal areas, whilst histology can reliably grade lesions and exclude invasion. For this reason, if cytology suggests high-grade disease and the cervix is absent or normal, the vagina must be carefully examined and any abnormal-looking areas sampled. In multizonal anogenital tract disease, multiple biopsies are advised to avoid missing disease.(1)

Treatment: selecting an approach that matches lesion grade and patient characteristics Management should be individualised according to grade (LG vs HG), lesion size/number (unifocal vs multifocal), location (vault/cuff vs lower vagina), patient characteristics (age, comorbidities, sexual function concerns), and certainty regarding the absence or presence of invasion. (1) LG VaIN Conservative management is often appropriate, as spontaneous regression is common. Follow-up strategies typically involve repeat cytology and/or HPV testing, with colposcopic reassessment if abnormalities persist or worsen. (1) HG VaIN Treatment is generally recommended. Options include:

Excision (local excision / partial vaginectomy in selected cases) Excision offers two advantages: it treats the lesion and provides a specimen to allow assessment of margins and exclude invasion. These are particularly important in cases with suspicious colposcopic features or in patients with high-risk factors. Excision is often preferred for vault lesions after hysterectomy due to the risk of dysplastic epithelium buried within the “dog-ears,” in which case ablative or topical treatment modalities may be less appropriate. (1) CO_2 laser ablation Laser is widely used and effective when invasion has been confidently excluded. It can be helpful for multifocal disease and for patients in whom tissue preservation is a priority. The trade-off is the absence of a full specimen, which is why careful patient selection is essential. (1) Topical therapy (imiquimod; 5-fluorouracil) Topical agents can be useful for multifocal or persistent disease, or for patients who wish to avoid—or are poor candidates for—surgery. Colposcopy-directed biopsies to exclude invasion should precede topical therapy. Among topical options, imiquimod is favoured in existing guidance based on its relative superiority in achieving HPV clearance and lower recurrence rates compared with alternatives. 5-fluorouracil and trichloroacetic acid are generally discouraged due to poor tolerability and/or inferior performance; however, they are still used in selected centres. (1) Follow-up after treatment VaIN recurrence rates are high, making follow-up an essential component of management. The ESGO/ISSVD/EFC/ECSVD consensus recommends early assessment (e.g., at 6 months) with cytology and HPV testing, followed by close surveillance in the first years and then annually. (1) In practical terms, the follow-up plan should be agreed before treatment,particularly for patients considered at risk of defaulting from scheduled review visits.

Vaginal Cancer Epidemiology, Diagnosis & Treatment Epidemiology and histological spectrum Primary vaginal cancer is rare. Population-level estimates vary by region and

registry methodology; however, vaginal cancer is consistently among the least common gynaecologic malignancies. GLOBOCAN provides standardised international snapshots of incidence and burden. (8)

Histological types are strongly related to aetiology and prognosis and include the following:

• Squamous cell carcinoma (SCC) is the most common subtype and is frequently HPV- associated.

• Adenocarcinoma may be HPV-associated in some cases, but a distinct subset—clear cell adenocarcinoma—is classically linked to in-utero diethylstilbestrol (DES) exposure rather than HPV. (2,11)

• Melanoma and some other rare tumours are generally not HPV-driven and behave differently, with limited evidence to guide management. (10)

It should be kept in mind that many malignant lesions identified in the vagina are not primary vaginal cancers, but rather represent extension from the cervix/vulva or metastatic disease from other sites. Therefore, the diagnosis of a primary vaginal cancer should be made with caution and ideally following multidisciplinary team review of histological, radiological, and clinical findings. In all cases, a cervical primary should be carefully excluded and appropriate staging ensured. (2)

Clinical presentation

Symptoms are often non-specific and may include:

• abnormal vaginal bleeding (post-coital or post-menopausal),

• watery or malodorous discharge,

• dyspareunia,

• pelvic pain, or

• a palpable lesion. (2)

Because symptoms overlap with benign conditions, delays in presentation are common,

particularly in older patients or those not routinely examined. Diagnosis and staging work-up Diagnosis is confirmed on histology from biopsy. Imaging is then used for staging and

treatment planning—typically pelvic MRI for local extent and CT/PET-CT when nodal or distant disease is a concern. The exact imaging modalities used may vary depending on centre and available resources; however, the principle remains the same: to define disease extent, determine whether management is curative or palliative, and guide selection of the most appropriate modality (i.e., surgery, radiotherapy/brachytherapy, or combination treatment). (2)
Treatment principles Given the rarity of disease, management is ideally centralised and should be discussed in a multidisciplinary team meeting. ESGO/ESTRO/SIOPe guidelines provide structured recommendations for adult disease and selected paediatric vaginal tumours. (2)
Broadly:
• Early-stage disease may be managed with surgery in selected patients, aiming for oncological control while preserving sexual function where feasible. (2)
• Radiotherapy (external beam radiotherapy with brachytherapy) is a cornerstone for more advanced disease and/or older patients, particularly when surgery would be morbid or when disease extent makes adequate surgical margins unlikely. (2)
• Chemoradiation is used for advanced-stage disease, nodal involvement, more aggressive histology, and palliative treatment intent. (2) For tumours of rare histological types (e.g., melanoma),evidence is limited and practice often
extrapolates from other mucosal melanoma sites, with immunotherapy playing a larger role in advanced disease. Within the limited evidence available, outcomes are generally poorer than for HPV-associated SCC. (10) Prognosis Outcomes depend strongly on stage and histology. Registry and national summaries consistently show better survival for localised disease than for regional or metastatic spread. For example, UK data report substantially higher 5-year survival in localised vaginal cancer compared with distant disease. (9)

Stage-stratified analyses of registry cohorts similarly demonstrate decreasing survival with advancing stage. (12)

Discussion

The common thread in both VaIN and vaginal cancer is that the vagina is a diagnostically challenging organ: lesions may be small, multifocal, hidden in folds, or masked by post- treatment scarring. In patients with abnormal cytology and no visible cervical lesion—especially post-hysterectomy—there is a recurring clinical risk of assuming a false- positive screening result rather than performing a meticulous vaginal assessment. (1,3) The concept of multizonal HPV-related disease becomes practically important in three ways:

1. An expert colposcopic vulvovaginal inspection should accompany cervical assessment in high-risk patients without obvious cervical disease. (1,3)
2. Patients should be counselled that treatment in one anatomical zone does not prevent disease from occurring in others. (1)
3. Recurrence is more likely to reflect susceptibility to persistent HPV infection biology rather than failed treatment; this perspective helps set realistic expectations and encourages adherence to follow-up. (1) VaIN treatment can appear deceptively straightforward ("excise or ablate"); however, quality-of-life outcomes present a significant challenge. Vaginal scarring/shortening, dyspareunia, and psychosexual impact may follow repeated procedures. Consensus guidance highlights these issues and supports clear counselling regarding options, side effects, and the need for long-term surveillance. (1)

For invasive cancer, the trade-off becomes sharper. Radical surgery may be curative in carefully selected early cases but can be functionally devastating; conversely, radiotherapy may preserve anatomy but carries risks of fibrosis, stenosis, and long-term pelvic toxicity.This is where multidisciplinary care adds value: patients benefit when gynaecologic oncologists,

radiation oncologists, radiologists, pathologists, and specialist nurses agree on a plan that is technically sound and aligned with patient priorities. (2) Prophylactic HPV vaccination has transformed the landscape of HPV-related disease. Vaccination is designed to reduce persistent infection with oncogenic genotypes, thereby reducing the downstream burden of HPV-associated disease, including VaIN and most vaginal SCC. The WHO elimination strategy provides global targets for vaccination, screening, and treatment that, although focused on cervical cancer, also support reduction of HPV-associated cancers across multiple anatomical sites. (4–6) That said, prevention will not eliminate all vaginal cancer. HPV-independent malignancies (including some adenocarcinomas and melanomas) will remain rare but clinically important, and DES-associated clear cell carcinoma continues to occur in ageing cohorts of exposed individuals. (10,11)

Conclusion

VaIN and vaginal cancer are uncommon but clinically significant conditions that demand careful examination, accurate histological diagnosis, and tailored management. HSIL VaIN requires treatment and structured follow-up, particularly in high-risk groups such as women post-hysterectomy for CIN3/cervical cancer and immunosuppressed patients. (1) For invasive disease, staging and treatment planning should be multidisciplinary and ideally centralised, with management guided by contemporary European recommendations. (2)

Finally, HPV vaccination and high-performance screening strategies represent the long-term route to reducing HPV-associated vaginal disease, aligning with global elimination efforts and offering the greatest population-level impact. (4–6)

Keywords

Vaginal intraepithelial neoplasia; VaIN; vaginal cancer; HPV-related disease; multizonal anogenital neoplasia

HPV INFECTION AND VULVAR DISEASE

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There were made changes in vulvar disease classification due to HPV status and immunohystochemistry. Regarding a different etiology and patogenesis World Health Organisation distinguish precancerous lesions as HPV-negative and HPV-associated vulvar epithelial neoplasias (VIN) (1). Low grade (VIN1) and high grade (VIN2 and 3) are types of HPV associated VIN and in the HPV independent group there are differentiated VIN with its horizontal spread (d-VIN), the differentiated exophytic VIN lesion (DEVIL) and vulvar acanthosis with altered differentiation (VAAD) (1). WHO recommend using HPV associated and HPV independent squamous cell carcinoma. For the purpose of diagnostic p16 was defined as adequate surrogate marker for HPV associated vulvar disease in addition of p53 if it is needed. It is important to notice that the ratio between HPV independent to HPV associated squamous cell carcinoma is between 0.60 and 0.83 (1).

Prognosis of VIN and squamous vulvar cancer is significantly different in HPV associated and HPV independent disease. Thuijs et al. showed a higher 10 years cancer risk in the HPV independent VIN compared to HPV associated VIN (H SIL) (8.0%) (2). In the HPV independent VIN p53 mutant the risk was 67.4% and 27.8% in HPV independent VIN p53 wild type (2).

There are a lot of evidence that HPV associated and HPV independent squamous cell vulvar carcinoma are different disease. Thus in the study of Eva L. Et al., they showed that HPV independent vulvar squamous cell carcinomas had significantly worse prognosis than HPV associated (HR 3.6

(95% confidence interval (CI): 1.6 to 8.2)) (3). This was independent of stage and age.

Further there is a difference in the recurrence rate regarding HPV status. As Boo et al. reported in their study, recurrence was confirmed in 7.2% in HPV associated group compared to 27.3% in HPV independent group ($p < .001$) (4). The question of pathological margins in this study turned out to have a different value in those groups. In HPV independent cancers margins <8 mm were significantly associated with increased local recurrence with univariable (HR 2.34, 95% CI 1.33-4.10, $p = .003$) and multi-variable analysis (adjusted HR 2.06, 95% CI 1.14 to 3.71, $p = .0017$) (4). Unlike in HPV associated group there was no significant association of margins and recurrence rate (HR 0.70, 95% CI 0.22 to 2.24, $p = .55$) (4).

There are evidences in molecular status as well that those groups are different disease. Analysing 161 tumor relevant genes Farkas et al. detected increased number of variants in HPV independent group (2.5) compared to HPV associated group (5). In the HPV independent group there were more variants of unknown significance and likely pathogenic than in HPV associated group (5).

Copy number variations (CNV) were more common in HPV associated tumors ($n = 13/16$, 81%) compared to HPV-negative tumors ($n = 9/14$, 64%).

Based on the facts in the text we could conclude that HPV associated and HPV independent vulvar disease are two diferent disease in their molecular pathway, natural history and prognosis. This deserves to have a different approach in diagnostic, treatment and follow up due to HPV status of vulvar disease.

ELECTROCONIZATION WITH A PISTOL SHAPED ELECTRO KNIFE – 15 YEARS OF EXPERIENCE. A RETROSPECTIVE STUDY

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Abstract
Introduction. Cervical intraepithelial neoplasia (CIN) is an established precursor to invasive cervical cancer. Women with untreated high-grade CIN are at high risk of developing cancer. The treatment provided greatly reduces the risk of disease. Classical surgical techniques used in the treatment of CIN are giving way to new technological methods.
Objective: To determine the clinical effectiveness of our LEEP conization method for the treatment of high-grade cervical CIN.
Material and methods. This study included for the period of 15 years (2008 -2023 years), 327 (100%) women (19-50 years) with histologically proven by abrasion or biopsy CIN II / III including Ca in situ (CIS) of the cervix. At hospitalization all included women underwent: gynecological examination, colposcopy, hr-HPV cervical screening test and the same without HPV tests after 60 days at follow up. All women underwent pistol LEEP electroconization. The clinical efficacy of the method is determined by the permanent histological result and the condition of the cervical margins. Positive for cervical hrHPV infection in our study are n- 303/92.7% of the women included, negative n-24/7.3%. From all 327 (100%) patients included and treated with our method of LEEP, n-310 / 94.8% have negative margins from histology and n-17 / 5.2%

positive. At the beginning colposcopy atypical findings, we found at n-289 / 88.4% women, at the end of the study period only at n-9 / 2.7%. Conclusions. The results of the 15-year statistically significant (p-0.001339; p< 0.05) clinical effectiveness of the LEEP conization method used by us – 94.8% cured and 5.2% untreated, prove that it can be used successfully in the treatment of high-grade dysplasia and carcinoma in situ of the cervix in daily and routine gynecological practice.

Key words: HPV; CIN; CIS; pistol electroconization; clinical efficacy

V-Y ADVANCEMENT FLAP RECONSTRUCTION AFTER VULVO-GLUTEAL BOWEN DISEASE RESECTION

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Bowen's disease is an HPV-associated in situ carcinoma and affects different areas of the skin-mucosal genital areas. When conservative treatment is inapplicable or unsuccessful, surgical resection is required, in which the removal of the lesions laterally within healthy limits is an absolute oncosurgical imperative. After resection, extensive wound surfaces remain, in which simple suturing and primary healing is impossible. Various restorative techniques have been developed over the years, the most successful being those with repositioning of mobilized and pediculated flaps, providing tension-free surgical sutures and good local blood supply and microcirculation.
The purpose of this presentation is to remind the benefits and good results of the application of this reconstructive technique with over 90 years of history.
We present a case of 38 years old nulliparous woman with a history of persistent HPV-16 infection, genital warts, and an established large vulvo-gluteal lesion on the right side more of than 6 years, histologically verified as Bowen's disease. The previously applied local treatment did not lead to improvement, and the patient did not present any medical documentation for it. Because of the condition and the diagnosis, the patient was offered to surgical treatment, for which she signed an informed consent. Under general

anesthesia, surgical resection of the lesion was performed within lateral macroscopic healthy limits. The resulting wound defect with an area of 7 sq.cm. was restored by a V-Y skin flap mobilized on a vascular pedicle.

Surgical technic is very simple: after the resection adjacent tissue flap shaped in a 'V' are mobilized, translocated and closed with single stitches as a 'Y' to reconstruct vulvar defect.

The postoperative period went without complications and the patient was disadmitted on day 3. Histology report confirm Bowen's disease with clear resection margins. Follow-up established normal primary healing of the surgical wound and within the next 2 years did not reveal recurrent or newly lesions on the vulva, the vagina and cervix. The patient general condition and HPV status after two years remains unknown.

Discussion. Bowen's disease is an HPV-associated lesion.[1] Large-area resections require augmentation technique to repair the defect and ensure primary healing. The V-Y advancement flap was originally described by Tranquilli-Leali in 1935 [2] and first reported in the United States by Atasoy et al in 1970 [3]. With this technique, a triangular flap is designed with the base at the edge of the amputation and the apex at the distal interphalangeal crease. It is currently used in various areas of the body in plastic reconstructive surgery and particular in the reconstructive phase of radical surgery for vulvar carcinoma [4,5,6], and vulvovaginoperineal region[7] , with tension-free margins and good prospects for primary healing. This technique and its modifications should be known well and applied by gynecologists in order to reduce postoperative morbidity and preserve genital anatomy and sexual functions.

SURGICAL TREATMENT OF EARLY-STAGE CERVICAL CANCER

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Abstract
The surgical management of early-stage cervical cancer is undergoing a fundamental paradigm shift. For decades, the standard of care has been radical hysterectomy, a procedure associated with significant short- and long-term morbidity, including autonomic nerve damage leading to urinary, bowel, and sexual dysfunction. However, accumulating evidence has identified a distinct subgroup of patients with low-risk disease—characterized by tumors ≤2 cm, limited stromal invasion, absence of lymphovascular space invasion (LVSI), and negative lymph nodes—in whom the risk of parametrial involvement is negligible (<1%).
This has prompted the investigation of de-escalation strategies, moving towards less radical surgeries. Landmark prospective and randomized trials, including ConCerv (2021), LESSER (2023), and the pivotal SHAPE trial (2024, provide high-level evidence that simple hysterectomy with pelvic lymph node assessment is non-inferior to radical hysterectomy in terms of oncologic safety, with 3-year recurrence rates below 3%. Crucially, this conservative approach significantly reduces surgical morbidity. The SHAPE trial demonstrated a dramatic reduction in urologic complications such as urinary retention (0.6% vs. 11%) and incontinence, alongside markedly improved patient-reported quality of life and sexual function.
Supported by this robust evidence, simple hysterectomy with lymph node evaluation is establishing a new standard of care

for carefully selected, low-risk patients. This evolution in surgical strategy demonstrates that de-escalation can achieve equivalent oncologic outcomes while significantly minimizing morbidity and optimizing the quality of life for survivors of early cervical cancer.

SENTINEL LYMPH NODE BIOPSY (SLNB) IN GYNECOLOGICAL ONCOLOGY

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Abstract
Background:
Sentinel lymph node (SLN) biopsy has emerged as a major advancement in the surgical management of gynecologic malignancies. By identifying the first draining lymph node from a primary tumor site, SLN mapping provides accurate nodal staging with significantly reduced morbidity compared to systematic lymphadenectomy.
Objective:
To summarize current evidence, clinical applications, and future perspectives of SLN biopsy in gynecologic oncology, with particular focus on cervical and endometrial cancers.
Methods:
A comprehensive review of pivotal prospective trials (GROINSS-V, SENTICOL I–II, FIRES, SENTIX) and current international guidelines (ESGO, NCCN, SGO) was conducted to evaluate detection rates, oncologic outcomes, and procedural standardization.
Results:
SLN biopsy is an established standard of care in early-stage vulvar and endometrial cancers and demonstrates high sensitivity and low false-negative rates in cervical cancer. Ultrastaging enhances micrometastasis detection and informs individualized adjuvant therapy. The procedure reduces operative time, blood loss, and postoperative complications without compromising oncologic safety.

Conclusions:
SLN biopsy represents a paradigm shift toward precision and minimally invasive surgery in gynecologic oncology. Ongoing integration of molecular diagnostics, advanced imaging, and artificial intelligence is expected to further refine mapping accuracy and prognostic value, shaping the future of personalized staging and treatment strategies for women with gynecologic cancers.
Key words: *cervical cancer, endometrial cancer, SLNB, vulvar cancer*

SUCCESS RATES AND DIAGNOSTIC BENEFITS OF LLETZ VS OTHER METHODS IN THE TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Introduction:
Human papillomavirus (HPV) is a sexually transmitted disease and presents a significant risk factor for the development of cervical intraepithelial neoplasia (CIN). HPV 16 is the most carcinogenic and accounts for 55 to 60% of cervical cancers while HPV 18 is the second most carcinogenic and accounts for 10 to 15% of cervical cancer (1) . CIN is a spectrum of precancerous conditions found on the cervical epithelium and consists of mild (CIN I), moderate (CIN II) and severe (CIN III) dysplastic changes. There are several techniques used to prevent progression of CINs to invasive cervical cancer and are divided into ablative (cryotherapy and laser ablation) and excisional methods (LLETZ/LEEP, cold knife conisation-CKC). Choice of treatment depends on the grade and extent of the disease. Large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excision procedure (LEEP) is the most widely used technique because of its diagnostic and treatment value (2).
Aim:
To compare the success rates and diagnostic advantages of LLETZ with other treatment modalities for CIN.
Findings:
The excisional techniques offer the advantage of obtaining a large specimen enabling precise diagnosis and evaluation of

complete lesion removal (3). Ablative methods showed higher recurrence rate and they do not provide tissue samples for pathohistological examination. By allowing excision of a larger, intact specimen, CKC offers superior diagnostic accuracy, although shows increased morbidity and greater effects on future pregnancy outcomes when compared to LLETZ. Among excisional methods, cure rates of CIN confirmed by biopsy reached 90–94% with cold-knife cone biopsy, 91–98% with LLETZ, and 93–96% with laser conization. Among ablative techniques, cure rates reached 85–94% with cryotherapy and 95–96% with laser ablation (4). According to meta-analysis published in Lancet in 2022, obstetrical outcomes show that all excisional procedures are associated with an increased risk of preterm birth, low birth weight, and premature rupture of membranes compared with no treatment (5).

Conclusion:

LLETZ has now become the standard of care for cervical premalignant lesions due to its balance of effectiveness, diagnostic capability, and safety while also suitable for patients with reproductive tendencies. Cold knife conization is reserved for complex or suspicious cases where maximal diagnostic accuracy is required. Ablative techniques may be appropriate for carefully selected low-risk patients but are limited by the absence of histological confirmation.

PRETERM BIRTH AFTER TREATMENT FOR CERVICAL PRE-CANCER. INDIVIDUALISED MANAGEMENT OF WOMEN DURING SUBSEQUENT PREGNANCIES

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Preterm birth remains a significant global health concern, accounting for substantial neonatal morbidity and mortality, with long-term implications for children and healthcare systems. Among various risk factors, prior treatment for cervical pre- cancer, primarily through procedures such as Cold Knife Conisation, Laser Conisation (LC), Loop Electrosurgical Excision Procedure (LEEP) or Large Loop Excision of the Transformation Zone (LLETZ), has been increasingly recognized for their potential impact on subsequent pregnancy outcomes. These interventions, while vital for preventing cervical cancer progression, might alter cervical structural integrity and physiological function. The biological mechanisms underlying the association between cervical treatment and increased preterm birth risk are complex and multifaceted, potentially involving cervical insufficiency, inflammatory responses, or changes in cervical collagen composition, which collectively comprise the cervix's ability to maintain pregnancy to term. Evidence from meta-analyses and observational studies indicates that women who have undergone cervical pre-cancer treatment face a higher likelihood of preterm delivery compared to untreated women, with the magnitude of risk potentially varying based on the

type, extent length or more precisely the overall percentage of the tissue excised. Despite these findings, there remains a critical need for individualized management strategies during subsequent pregnancies to mitigate preterm birth risk while ensuring effective cervical disease control. Estimation of the cervical volume and dimensions with 3D- TVS prior to the treatment, as well as accurate assessment of the volume and the dimensions of the excised cone before fixation by a volumetric tube and a ruler would easily make feasible the computation of the percentage of excision. Women with a high proportion of excision appear to be at higher risk for adverse obstetric outcomes and obstetric morbidity therefore they might be requiring closer monitoring. When a LLETZ procedure is planned for a woman wishing for future fertility, the risks and benefits of treatment must be carefully balanced. Assessing the volume fraction and the dimensions of the excised cone could identify individuals requiring closer monitoring during future pregnancies.

HPV ASSOCIATED DISEASES AND THEIR PREVENTION

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Human papillomaviruses (HPVs) represent one of the most prevalent sexually transmitted pathogens globally, with an estimated 630 million individuals currently infected. Epidemiological studies suggest that between 75% and 89% of all sexually active men and women will acquire HPV at some stage during their lifetime, underscoring the extraordinary burden of this infection on public health. To date, more than 440 HPV subtypes have been identified. These subtypes are broadly classified into low-risk types, such as HPV 6 and 11, which are primarily responsible for benign lesions including genital warts and recurrent respiratory papillomatosis, and high-risk (oncogenic) types, of which approximately 13–15 (notably HPV 16 and 18) are strongly associated with malignant transformation. Persistent infection with these oncogenic strains has been recognized as a necessary causal factor in the development of several malignancies, including cervical, vulvar, vaginal, anal, penile, and oropharyngeal cancers. Indeed, virtually all cases of cervical cancer are attributable to persistent high-risk HPV infection, with HPV 16 and 18 alone accounting for over 70% of cases worldwide.

From a biological perspective, HPV-induced carcinogenesis is mediated by the integration of viral DNA into the host genome, leading to the overexpression of viral oncoproteins E6 and E7. These proteins disrupt key tumor-suppressor pathways, including p53 and retinoblastoma (Rb), thereby promoting genomic instability, uncontrolled cellular proliferation, and malignant progression. While approximately 80% of HPV infections are transient and spontaneously cleared by the host

immune system within 1–2 years, persistent infection substantially increases oncogenic risk. Factors such as immune suppression, smoking, co-infections, and early onset of sexual activity may facilitate viral persistence and progression to high-grade intraepithelial lesions.

Prevention and control strategies for HPV-associated diseases include both secondary prevention (screening) and primary prevention (vaccination). The primary objective of screening programs—such as cytology-based Pap smears, HPV DNA testing, and co-testing—is the early detection and treatment of pre-cancerous lesions, thereby reducing the incidence of invasive cervical cancer. Advances in molecular diagnostics, including HPV genotyping and mRNA testing, have further enhanced the sensitivity and specificity of screening protocols.

In terms of primary prevention, prophylactic HPV vaccination is regarded as one of the most effective public health measures ever introduced in oncology. At present, three vaccines are licensed: the bivalent, quadrivalent, and nonavalent formulations. All vaccines target HPV 16 and 18, while the nonavalent vaccine additionally protects against five other high-risk types (31, 33, 45, 52, and 58), thereby broadening cancer prevention coverage. Clinical trials and real-world data consistently demonstrate that HPV vaccines are highly immunogenic, with more than 98% of recipients developing protective antibodies within one month after the completion of the vaccination schedule. Long-term follow-up studies indicate durable immunity of at least 10–12 years, with evidence suggesting even longer-lasting protection. Beyond cervical cancer prevention, widespread HPV vaccination programs have already led to a dramatic reduction in the prevalence of genital warts and high-grade cervical lesions in vaccinated populations. The implementation of gender-neutral vaccination strategies is expected to amplify herd immunity, significantly lowering the burden of HPV-related malignancies across all organ sites.

In conclusion, HPV remains a global health concern due to its extraordinary prevalence and causal association with a wide spectrum of malignancies. However, the combination of effective screening programs and comprehensive vaccination strategies offers a realistic pathway toward the eventual elimination of HPV-related cancers as a major public health threat.

EFFECTIVENESS AND SAFETY OF NINE VALENT HPV VACCINE AND ITS INTRODUCTION IN NATIONAL IMMUNIZATION PROGRAM OF NORTH MACEDONIA

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The 9-valent human papillomavirus (HPV) vaccine (9vHPV) was developed to expand protection against HPV-associated diseases by targeting HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Randomized, double-blind clinical trials have demonstrated high efficacy of 9vHPV in preventing HPV infection and high-grade cervical, vulvar, vaginal, and anal neoplasia attributable to vaccine-covered HPV types. Immunogenicity studies show non-inferior antibody titers for HPV types and robust immune responses for the five additional oncogenic types, which together account for approximately 90% of cervical cancer cases worldwide. Safety data from clinical development programs and extensive post-authorization surveillance from more than 10 years of use of this vaccine indicate a favorable safety profile, with most adverse events being mild and primarily as pain on injection-site. From 2024, the 9-valent HPV vaccine has been introduced in North Macedonia in National immunization program as gender-neutral immunization, both for girls and boys 12 to 19 years old. This represent an important public health measure to reduce the burden of HPV-related diseases across the population.

NEW ERA IN THE TREATMENT OF CERVICAL CANCER

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Cervical cancer remains a significant global health problem, but recent advances have ushered in a new era of disease management, where current standard care is complemented by precision and individualized care.
Advances in percutaneous radiotherapy, as well as image-guided and MRI-based adaptive brachytherapy, improve local control while minimizing damage to surrounding tissues. Personalized treatment approaches guided by molecular profiling, PD-L1 receptor status, and other biomarkers increasingly guide therapy, strictly targeting the detected problem. Immunotherapy, particularly immune checkpoint inhibitors targeting PD-1, have shown durable responses in recurrent, persistent and metastatic disease, while targeted therapies, including antiangiogenic agents and antibody-drug conjugates, have improved outcomes with reduced systemic toxicity.
The integration of immunotherapy, targeted therapy, precision radiotherapy and personalized care represents a change to the decades-old standard treatment, offering improved survival and highly personalized treatment.

Keywords: cervical cancer, immunotherapy, personalized treatment.

THERAPEUTIC HPV VACCINES AND IMMUNOTHERAPEUTIC COMBINATIONS IN THE TREATMENT OF HSIL AND INVASIVE HPV-ASSOCIATED CANCERS: CURRENT STATUS AND EMERGING CLINICAL DIRECTIONS

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Therapeutic HPV vaccines, primarily targeting the E6 and E7 oncoproteins, represent one of the most promising approaches for the treatment of premalignant lesions and invasive HPV-associated cancers. The development of DNA-, peptide-, and vector-based platforms has enabled robust antigen-specific T-cell responses; however, the clinical efficacy of vaccine monotherapy remains modest. Combination strategies with immunotherapy—particularly PD-1/PD-L1 inhibitors—are currently undergoing clinical validation.

The most robust evidence comes from VGX-3100 phase II/III trials, which demonstrated increased rates of histologic regression of CIN2/3 and clearance of HPV16/18 compared with placebo. SLP vaccines (HPV16-SLP) and GX-188E have shown significant immunologic and clinical responses, particularly in HPV16-positive lesions. In vulvar HSIL, the combination of TA-CIN and imiquimod has achieved complete regression rates of up to 60%, and the synthetic long-peptide approach has been supported by long-term follow-up data in VIN3. In anal and vulvar HSIL, the role of adjuvant 9-valent HPV vaccination is being actively investigated, although meta-

analyses have yielded heterogeneous results regarding recurrence prevention.

While therapeutic vaccine monotherapy produces limited clinical responses, combination regimens with immune checkpoint inhibitors are yielding encouraging results. ISA101/ISA101b combined with nivolumab or cemiplimab has demonstrated durable objective response rates of approximately 30–35% in HPV16-positive tumors, including recurrent or metastatic cervical cancer. The DNA vaccine MEDI0457 has shown immunogenicity and potential clinical activity in combination with durvalumab, as well as in the adjuvant setting following chemoradiotherapy. Preclinical development of mRNA-based therapeutic vaccines further expands the translational potential of this field.

Therapeutic HPV vaccines are now entering a phase of clinical maturation. The greatest advances are expected from combination strategies (vaccine plus PD-1/PD-L1 blockade), particularly in invasive HPV-associated malignancies and HSIL, where the need for non-invasive, tissue-sparing treatment approaches is greatest. Ongoing and upcoming phase II/III trials will define their role in future ESGO/ESMO treatment algorithms.

PROTOCOLS OF DIAGNOSE, TREATMENT, MONITORING AND OUTCOMES OF ADULT LARYNGEAL NEOPLASIA, ASSOCIATED WITH HUMAN PAPILLOMA VIRUS

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Abstract
Introduction: Laryngeal papillomas is induced by HPV infection. Even though millions of people have HPV, only a small number develop laryngeal papillomatosis. HPV infection in conjugation with risk factors (alcohol, cigarettes and alcohol) can lead to field cancerization that occurs over several years, transforming the basis for intraepithelial neoplasm and providing epithelial carcinomas with the risk of invasive disease.
Aim: To represent not only the methods of detecting laryngeal neoplasm that are associated with Human papilloma virus, but also describing by our experience the best protocol of this irritant disease.
Material and method: The first protocol is clinical symptomatology that persists for more than 3 weeks, a condition that does give us the right to perform endoscopic evaluation and biopsy of the laryngeal neoplasm. If it is only laryngeal papillomatosis without oncogenic transformation than radical removal of laryngeal papillomatosis does not exist, since the unwanted effects are greater than the desired positive outcome for the patient. Endoscopic complete removal with a cold knife of the lesion does not guarantee the return of the neoplasm itself. To distinguish and to make an more credible diagnose whenever or not there is a malignant progression it is inevitable to make a CT scan with contrast of the neck and

thorax. Contradictory when we have all the signs of malignancy of the papillomatous process in some patients after several biopsies we cannot prove malignancy

Conclusion: Due to date Laryngeal papillomatosis is irretrievable. Disease development as it is is inconsistent, wandering from mild to an severe conditions including airway obstruciton and malignant alteration. Though a number of therapies have been investigated, the recurrence after treatment is always a challenge.

HPV-ASSOCIATED CANCERS: CERVICAL CANCER VS OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Abstract

Cervical cancer and HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) are two malignancies linked by a common viral etiology but characterized by substantial differences in epidemiology, demographics, transmission pathways, screening opportunities, and public health control. High-risk HPV types, particularly HPV-16 and HPV-18, drive carcinogenesis in both diseases through persistent infection, resulting in inactivation of key tumor suppressor pathways and uncontrolled cellular proliferation.

Cervical cancer is almost universally caused by persistent infection with high-risk HPV and affects individuals with a cervix, predominantly women. It is most commonly diagnosed in younger to middle-aged adults, typically between the third and fifth decades of life. HPV transmission occurs primarily through genital sexual contact, and the disease follows a predictable progression from precancerous lesions to invasive carcinoma. This well-defined natural history has enabled the development of effective population-based screening and vaccination programs, resulting in substantial reductions in incidence and mortality in many regions.

In contrast, HPV-positive OPSCC represents a biologically distinct subset of head and neck cancers, predominantly associated with HPV-16 infection. It shows a marked male predominance and is usually diagnosed later in life, most commonly in the fifth to seventh decades. Transmission is

believed to occur mainly through oral sexual contact, leading to infection of the oropharyngeal mucosa. Unlike cervical cancer, HPV-positive OPSCC lacks an established screening strategy and frequently presents with symptomatic, locally advanced disease. Despite this, it demonstrates significantly better treatment response and survival compared with HPV-negative OPSCC.

Clinically, cervical cancer is often asymptomatic in early stages and detected through organized screening programs, whereas HPV-positive OPSCC typically presents with symptoms and is frequently diagnosed at a locally advanced stage. Prognosis in cervical cancer is strongly stage-dependent, while HPV-positive OPSCC demonstrates significantly better treatment response and overall survival compared with HPV-negative OPSCC, despite advanced presentation.

HPV vaccination has proven highly effective in preventing cervical HPV infection and precancerous lesions. Although definitive population-level evidence for OPSCC prevention is still emerging, reductions in oral HPV prevalence suggest substantial long-term preventive potential. These two malignancies illustrate both the successes and ongoing challenges of HPV-related cancer control and underscore the need for tailored clinical and public health strategies. While cervical cancer highlights the effectiveness of coordinated screening and vaccination, HPV-positive OPSCC emphasizes the critical importance of expanding vaccination coverage to both sexes and advancing research into early detection strategies.

ONCOLOGY TREATMENT OF HPV-ASSOCIATED OROPHARYNGEAL CANCER

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INTRODUCTION: Oropharyngeal cancer is a rare solid tumor that most commonly arises in the tonsil, followed by the base of the tongue, the soft palate, and the posterior pharyngeal wall. Human papillomavirus (HPV) - associated oropharyngeal cancer represents a distinct subset of oropharyngeal carcinoma, with an increasing incidence worldwide and a more favorable prognosis with longer survival and longer time to disease progression compared to HPV-negative disease. In the Republic of North Macedonia, a standardized clinical protocol mandating HPV testing at the time of oropharyngeal cancer diagnosis has not yet been implemented. Consequently, treatment strategies are not currently distinguish based on HPV status, and all patients included in this study received the same therapeutic approach regardless of HPV positivity.
OBJECTIVES: The aim of this study was to investigate incidence, stage and treatment of patients with HPV positive and HPV negative oropharyngeal squamous cancer in the last two years in University Clinic of Radiotherapy and Oncology – Skopje (UKRO).
MATERIALS & METHODS: This study included all patients with histologically confirmed oropharyngeal squamous cell carcinoma treated in the last 2 years at UKRO. Regardless of their HPV positivity and depending on the stage of the cancer, patients were appropriately treated with surgical treatment, volumetric modulated arc therapy, with or without concurrent chemotherapy, biological therapy, immunotherapy and chemotherapy.

RESULTS: Over a two-year period, 36 patients were newly diagnosed with oropharyngeal squamous cell carcinoma at UKRO. HPV status was not available for all of patients. Volumetric modulated arc therapy was first choice as adjuvant postoperative treatment or definitive treatment administered to patients with loco-regional disease metastatic disease, while patients with locoregionally advanced disease and metastatic disease patients were treated with immunotherapy (Pebrolizumab), biologic therapy (cetuximab) or chemotherapy (platinum and taxane).
CONCLUSION: HPV testing in squamous cell oropharyngeal carcinomas should be established as a mandatory standard in diagnostic work-up in the Republic of North Macedonia, given their increased sensitivity to radiotherapy and chemotherapy, which would allow avoidance or reduction of treatment-related adverse effects.
KEY WORDS: HPV, cancer, radiotherapy, immunotherapy

RECURRENT RESPIRATORY PAPILLOMATOSIS IN CHILDREN: CLINICAL CHALLENGES AND LONG-TERM MANAGEMENT

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Recurrent Respiratory Papillomatosis (RRP) is a rare chronic disease of childhood characterized by recurrent papillomatous growths in the respiratory tract, leading to significant morbidity. The objective of this study is to review the clinical challenges, diagnostic approach, and long-term management.
Materials and Methods: A narrative review of available literature was conducted, focusing on pediatric patients diagnosed with juvenile-onset RRP. Data were analyzed regarding etiology, clinical presentation, diagnostic methods, treatment modalities, and long-term outcomes. Emphasis was placed on surgical techniques, adjuvant therapies, and the role of HPV vaccination.
Discussion: RRP is most commonly caused by HPV types 6 and 11, with onset typically before five years of age. The disease course is unpredictable and often aggressive, requiring multiple surgical interventions to maintain airway patency and preserve voice quality. Recurrent procedures pose risks of airway scarring, voice impairment, and psychological burden. Adjuvant therapies, particularly intralesional bevacizumab, have shown promising results in reducing recurrence rates. HPV vaccination appears to decrease disease severity and prolong intervals between surgeries, highlighting its preventive and therapeutic importance.
Conclusion: Juvenile-onset RRP remains a significant clinical challenge due to its recurrent nature and impact on quality of

life. Optimal management requires early diagnosis, repeated but conservative surgical intervention, appropriate use of adjuvant therapies and a multidisciplinary approach. HPV vaccination plays a crucial role in long-term disease control and prevention.
Keywords: Recurrent respiratory papillomatosis, children, HPV, airway management, bevacizumab, HPV vaccination

EPIDEMIOLOGIC, CLINICAL, AND SOCIOLOGICAL ASPECTS OF ANOGENITAL WARTS AMONG ADULTS

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Anogenital warts are a common sexually transmitted disease caused predominantly by low- risk human papillomavirus (HPV) types 6 and 11. They occur most frequently in young, sexually active adults and are associated with multiple sexual partners, unprotected intercourse, smoking, and immunosuppression. Clinically, anogenital warts present as soft, papillomatous lesions affecting the anogenital skin and mucosa, often asymptomatic but prone to recurrence due to viral persistence. Beyond cutaneous involvement, the condition is associated with significant psychosocial burden, including stigma, anxiety, and impaired quality of life. Understanding the epidemiologic, clinical, and sociological aspects of anogenital warts is essential for optimal dermatologic management and prevention.

CONDYLOMATA ACUMINATA AND THE ROLE OF LASER THERAPY

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Background:
Condylomata acuminata, or anogenital warts, are among the most common sexually transmitted infections caused by low-risk human papillomavirus (HPV) types 6 and 11. These lesions frequently affect the genital and perianal regions in both males and females and can lead to discomfort, psychosocial distress, and significant therapeutic challenges due to recurrence and anatomical complexity.
Objective:
To evaluate the efficacy, precision, and safety profile of laser therapy as a treatment modality for condylomata acuminata.
Methods:
Laser therapies—including CO_2 lasers, Er:YAG lasers, and long-pulse Nd:YAG systems—provide controlled ablation or coagulation of HPV-infected tissue with minimal thermal damage. CO_2 and Er:YAG lasers allow for precise vaporization of exophytic lesions, while Nd:YAG lasers may be used for deeper vascular lesions. Laser treatment is compared with conventional options such as cryotherapy, chemical agents, immunomodulators, and surgical excision.
Results:
Laser therapy demonstrates high clearance rates, excellent hemostasis, and superior precision in anatomically sensitive areas, making it especially suitable for extensive, recurrent, or

intra-urethral and peri-anal lesions. Healing times are typically short, and cosmetic outcomes are favorable. Studies show reduced recurrence when laser treatment is combined with post-procedural topical immunomodulation (e.g., imiquimod). Adverse events are uncommon and generally limited to transient pain, erythema, or superficial ulceration.

Conclusion:

Laser therapy represents a highly effective and safe option for the management of condylomata acuminata, particularly in patients with multiple, recalcitrant, or anatomically complex lesions. Its precision, reduced bleeding, and rapid recovery make it a valuable component of modern HPV lesion management. Further research should focus on combination protocols with immunotherapies to optimize long-term remission and reduce recurrence rates.

TREATMENT OF CONDYLOMA ACUMINATUM USING LASER ABLATION WITH CO2

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Condyloma acuminatum, or genital warts, caused by the human papillomavirus (HPV), is a common sexually transmitted infection that can affect the genital, anal, and perineal regions. Treatment options include topical therapies, cryotherapy, electrosurgery, and surgical excision, with laser ablation emerging as a highly effective approach for managing extensive or refractory lesions. This abstract compares the use of two laser technologies—CO2 laser and Erbium YAG laser—for the treatment of condyloma acuminatum. The CO2 laser emits a 10,600 nm infrared beam, which is strongly absorbed by water in tissues, leading to rapid vaporization and ablation. It is particularly effective for larger, more extensive warts, offering precision and minimal bleeding, making it ideal for treatment in sensitive areas. However, its deeper tissue penetration can lead to longer recovery times and a higher risk of scarring compared to other methods. The Erbium YAG laser, with a 2940 nm wavelength, provides more superficial tissue penetration, resulting in less thermal damage to surrounding tissues. This laser is best suited for smaller, superficial lesions and mucosal areas, such as the cervix or urethra. The Erbium YAG laser offers faster healing times and a lower risk of scarring, but may be less effective for larger, more deeply embedded warts. Both lasers are precise, minimally invasive treatments that allow for targeted removal of warts, with fewer complications compared to traditional excisional methods.

While recurrence rates can be low, HPV persistence can lead to wart reappearance, necessitating follow-up treatment. Ultimately, the choice between CO2 and Erbium YAG lasers depends on lesion size, location, and depth, as well as patient-specific factors. In conclusion, laser ablation with CO2 and Erbium YAG lasers offers a safe and effective treatment option for condyloma acuminatum, with each modality having its distinct advantages based on the clinical presentation of the warts. The advantages of laser surgery for condyloma acuminatum are many: (1) rapid lesion destruction (recurrences are rare); (2) precise control of tissue destruction; (3) excellent hemostasis; and (4) minimal postoperative edema, pain, and scarring.

Key words: Co2 laser, Erbium yag laser, Condylomata acuminatum, genital warts

Condylomata Acuminata, Laser Therapy, and Associated HPV-Related Diseases

Background:

Condylomata acuminata (genital warts) are benign epithelial proliferations caused primarily by low-risk human papillomavirus (HPV) types 6 and 11. They frequently coexist with other HPV-associated diseases, including high-risk HPV–related intraepithelial neoplasia (VIN, PIN, AIN), bowenoid papulosis, and subclinical HPV infections and Hepatitis C, HIV and STD. Their recurrence, anatomical complexity, and variable clinical morphology present significant treatment challenges.

Objective:

To evaluate the effectiveness of laser therapy in the management of condylomata acuminata and to summarize its role in treating or identifying associated HPV-related diseases.

Methods:

CO_2 and Er:YAG lasers were reviewed as the primary ablative modalities for condyloma treatment, with additional consideration of Nd:YAG and PDL systems for vascular or

keratinized variants. The relationship between condylomata and associated HPV-induced diseases was examined, highlighting laser utility for both visible and subclinical lesions.

Results:

Laser therapy provides precise, controlled ablation of condylomata acuminata with excellent hemostasis and minimal thermal spread—advantages particularly important for peri-anal, intra-vaginal, intra-urethral, and cosmetically sensitive areas. Lasers also enable vaporization of flat, recalcitrant, or extensive lesions and allow detection of subclinical disease through fluorescence and intra-operative visualization. Furthermore, laser ablation is effective in the management of HPV-related conditions such as VIN, PIN, AIN, and bowenoid papulosis. Recurrence rates are reduced when laser treatment is combined with immunomodulatory therapies (e.g., imiquimod). Adverse effects are generally mild and transient.

Conclusion:

Laser therapy is an effective, safe, and tissue-sparing option for the treatment of condylomata acuminata and other HPV-associated diseases. Its precision, suitability for complex anatomical sites, and ability to address both clinically visible and subclinical lesions make it a valuable first-line or adjunctive modality in genital dermatology. Integration with immunotherapy may further improve long-term clearance and reduce recurrence.

HPV IN PREGNANCY: TWO GENOMES, ONE SHARED IMMUNITY

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Human papillomavirus (HPV) infection during pregnancy reveals a unique immunologic environment in which two distinct genomes—the maternal and the fetal—share a single immune system. Pregnancy induces a shift toward T-helper-2 and regulatory T-cell predominance to promote fetal tolerance, but this adaptive balance also weakens antiviral defense and facilitates viral persistence. Persistent high-risk HPV infection may be influenced by hormonal changes, microbiome composition, and maternal psychoneuroendocrine activity. Activation of the hypothalamic–pituitary–adrenal (HPA) axis under chronic stress elevates cortisol and proinflammatory cytokines (IL-6, TNF-α), suppressing cytotoxic immunity and delaying viral clearance.

Recent psychoneuroimmunologic data indicate that anxiety, burnout, and depression in pregnancy may increase susceptibility to persistent HPV infection, cervical intraepithelial neoplasia, and adverse obstetric outcomes such as preterm birth and preeclampsia. Dysbiosis of the cervicovaginal microbiome—with reduced Lactobacillus dominance—further impairs local mucosal defense. Detection

of HPV DNA in placental and amniotic samples suggests possible vertical transmission, though its clinical impact remains uncertain. Integrative approaches addressing immunologic, microbial, and psychosocial factors may improve viral clearance and pregnancy outcomes.

The concept of “two genomes, one shared immunity” highlights the complex interplay between virology, maternal immunity, and psychological wellbeing, underscoring the importance of holistic, evidence-based strategies for managing HPV infection in pregnancy and protecting the health of both mother and child.

THE ROLE OF HPV IN FEMALE INFERTILITY: CURRENT EVIDENCE AND CLINICAL IMPLICATIONS

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Background: Human papillomavirus (HPV) is the most prevalent sexually transmitted viral infection worldwide and is well known for its role in cervical cancer. Increasing evidence suggests that HPV infection may also influence female fertility, although results across studies remain inconsistent.
Objective: To summarize current evidence on the relationship between HPV infection and female infertility, with emphasis on prevalence, ovarian reserve, and reproductive outcomes.
Methods: A narrative review of observational studies, case–control analyses, and systematic reviews published up to 2025 was performed. Studies evaluating HPV prevalence in infertile women, ovarian reserve markers, and assisted reproductive outcomes were included.
Results: Across different infertility cohorts, HPV infection was detected in approximately 10–20% of women undergoing infertility evaluation. Among HPV-positive infertile women, 80–90% were infected with high-risk HPV genotypes. Several studies reported a higher frequency of HPV infection in infertile women compared with fertile controls, with high-risk HPV associated with a two- to threefold increased likelihood of infertility. Ovarian reserve assessment demonstrated significantly lower anti-Müllerian hormone levels in HPV-positive women, with mean values approximately 35–40% lower than in HPV-negative controls (around 3.1 ng/mL vs. 4.9 ng/mL). In assisted reproductive settings, HPV-positive women showed 10–20% lower implantation and clinical pregnancy

rates in some studies, although other cohorts reported no significant differences. Evidence linking HPV infection to recurrent pregnancy loss was limited, with HPV detected in approximately 10–15% of women with recurrent miscarriage.
Conclusions: Current evidence suggests that HPV infection, particularly high-risk genotypes, may be associated with female infertility and reduced ovarian reserve. Although causality cannot be definitively established, the observed prevalence rates, reduced ovarian reserve, and adverse reproductive outcomes indicate potential clinical relevance. Awareness of HPV status may be useful in selected infertility cases, especially in women with unexplained infertility or diminished ovarian reserve. Further prospective studies are required to clarify mechanisms and guide clinical management.
Keywords: Human papillomavirus; female infertility; ovarian reserve; anti-Müllerian hormone;
assisted reproductive technology

INFLUENCE OF HUMAN PAPILLOMA VIRUS ON MALE INFERTILITY, SEMEN QUALITY AND REPRODUCTIVE OUTCOMES

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Men with unexplained abnormal semen analysis results and those with normal test outcomes but unexplained infertility are becoming more common in clinical practice. Inflammatory processes and infections of the genital tract remain among the primary causes of male fertility problems (Akhigbe et al., 2022). Interest has increased in examining the effect of seminal human papillomavirus (HPV) infection on male infertility, semen quality, and reproductive outcomes. The lifetime likelihood of HPV infection in men reaches 90%, mainly due to the virus's high contagiousness and the often-asymptomatic nature of the infection (Bruni et al., 2023; Capra et al., 2022). The HPV ontogenetic cycle has two phenotypic phases: infectious virions and the subsequent transient pathway of producing infectious virions in non-dividing cells (virions present on or in these cells—including spermatozoa and exfoliated epithelial cells in the ejaculate); and virus present in dividing cells, which is non-infectious and part of the non-infective, transformation-related cancer pathway. Regarding infertility and subfertility, the transient virion-producing infections are particularly relevant (Depuydt et al., 2016a; Depuydt et al., 2019; Gheit, 2019). HPV affects spermatozoa by inhibiting Aquaporin 8, an important transmembrane channel responsible for transporting water, hydrogen peroxide, and small molecules that regulate the spermatozoon's volume

and oxidative stress (Pellavio et al., 2020). Infection with HPV does not eliminate the infected sperm's fertilizing ability. In vitro studies show that HPV DNA localizes at the equatorial region of the sperm head through interaction of the viral capsid protein L1 with the syndecan-1 receptor (Foresta et al., 2011).
Numerous studies have linked the presence of HPV in semen with idiopathic asthenozoospermia, lower sperm concentration, abnormal morphology, idiopathic infertility, the presence of anti-sperm antibodies in the ejaculate, higher sperm DNA fragmentation, reduced viability, and longer time to spontaneous pregnancy. HPV-positive semen is associated with a lower intrauterine insemination success rate, increased risk of spontaneous abortion, and repeated miscarriages. Additionally, a decreased blastulation rate has been reported when using HPV-positive sperm for intracytoplasmic sperm injection. (Depuydt et al., 2016a; Xiong et al., 2018; Wang et al., 2021; Weinberg et al., 2020; Moreno-Sepulveda & Rajmil, 2021; Siristatidis et al., 2018; Capra et al., 2022; Depuydt et al., 2016b; Garolla et al., 2016; Das et al., 2023). The role of HPV in medically assisted reproduction has been emphasized in a recent guideline (ESHRE Guideline Group on Viral infection/disease et al., 2021). However, current literature remains inconclusive, and data from clinical research and experimental studies are limited, warranting further investigations.
In conclusion, the presence of HPV in the ejaculate of men from infertile couples significantly impacts sperm function, as evidenced by changes in key microscopic parameters – sperm concentration, motility, and morphology. This supports considering HPV as a potential factor in male infertility. HPV screening could be added to the diagnostic process for infertile men and may serve as a new therapeutic target in the field of andrology.

KNOWLEDGE AND ATTITUDES TOWARD HUMAN PAPILLOMAVIRUS VACCINATION AMONG PEDIATRIC, FAMILY MEDICINE, AND OBSTETRICS AND GYNECOLOGY RESIDENTS IN TÜRKİYE

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Abstract

Background:

Human papillomavirus (HPV) vaccination is a critical preventive tool against HPV-related cancers. Healthcare providers play a central role in vaccine advocacy; however, differences in specialty training and health policy may influence provider knowledge and attitudes. Comparative data across residency programs in Türkiye remain limited.

Methods:

We conducted a national, cross-sectional survey between August 2024 and January 2025 among residents in Pediatrics, Family Medicine, and Obstetrics and Gynecology across tertiary healthcare centers in Türkiye. An anonymous online questionnaire assessed sociodemographic data, comprehensive

knowledge of HPV infection and vaccination, and attitudes toward vaccine counseling. Specialty-based comparisons were made using Pearson’s chi-square test.
Results:
A total of 453 residents participated (Pediatrics: 150; Family Medicine: 151; Obstetrics and Gynecology: 152); 60.3% were female and the median age was 29 years. While 99.3% had heard of HPV vaccination, only 74.2% reported detailed knowledge. Comprehensive knowledge of HPV-related diseases was found in 66.0% of participants and was significantly higher among Obstetrics and Gynecology residents (p < 0.001). Awareness of the 9-valent vaccine was reported by 77.7%. Knowledge gaps were observed especially regarding age indications and dosing. Although 97.1% recommended HPV vaccination, only 30.9% had been vaccinated, with uptake significantly higher among female residents (p < 0.001).
Conclusions:
Despite high awareness and positive attitudes, significant knowledge gaps about defining all HPV related diseases remain, especially among Pediatrics and Family Medicine residents. The gap between recommendation and self-vaccination highlights that education alone may be insufficient. Specialty-specific training and policies to improve vaccine access may help close these gaps in Türkiye, where HPV vaccination is not yet part of the national immunization program.
Keywords: Papillomavirus Vaccines, Health Knowledge, Medical Residency

PREVALENCE OF HIGH-RISK HPV TYPES IN PREMALIGNANT CERVICAL LESIONS IN TUZLA CANTON

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Background
High-risk human papillomavirus (HR-HPV) infection is the main etiological factor for cervical intraepithelial neoplasia (CIN) and cervical cancer. HPV-16 and HPV-18 are the most oncogenic types and are most frequently associated with disease progression.
Methods
Data from a cross-sectional study conducted at the University Clinical Center Tuzla between January 2019 and March 2020 were analyzed. A total of 880 women underwent HR-HPV testing and cytological evaluation. HR-HPV prevalence, age distribution, and associations with abnormal Pap smear findings were assessed.
Results
HR-HPV infection was detected in approximately 28% of the tested women. The highest prevalence was observed in women aged ≤40 years (33.5%). Among HR-HPV-positive women, around 40% had abnormal Pap smear results, with high-grade squamous intraepithelial lesions (HSIL) occurring more frequently in HR-HPV-positive women and those older than 30 years. Although detailed genotype distribution was not available locally, regional data indicate HPV-16 and HPV-18 as the most prevalent high-risk genotypes.
Conclusion
HR-HPV infection is highly prevalent among women in Tuzla Canton, particularly in younger age groups. Strengthening primary prevention through HPV vaccination and

implementing HPV DNA testing as a primary screening method are essential strategies for reducing the burden of premalignant cervical lesions and preventing progression to invasive cervical cancer.

Keywords: high-risk HPV, cervical intraepithelial neoplasia, premalignant lesions, HPV-16, HPV-18, Tuzla Canton

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HPV GENOTYPE–SPECIFIC RISK FOR CERVICAL PRE-CANCER AND CANCER OF UTERINE CERVIX

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Abstract: Cervical cancer is one of the most commonly diagnosed cancer in females worldwide. Oncogenic human papillomavirus (HPV) infection is a major risk factor for cervical cancer. The overall prevalence of high-risk human papillomavirus (HR-HPV) increases from 12% in normal cytology to 89% in cervical cancer. Globally, HPV 16/18 are the 2 most common genotypes in approximately 70% of invasive cervical cancer cases . The remaining 30% are caused by other HR-HPV types. HPV infections are common among young women and most spontaneously clear within 1–2 years. Persistent infection with HR-HPV is considered essential for the development of cervical cancer. However, the trend of persistent infection differed by HPV genotype and age. The most persistent types are 16, 31, 33, and 52 and the least persistent types are 35, 51, 66, and 68. The association between age and persistent infection is inconsistent. Previous studies suggested that women over 30 years of age have a higher rate of persistent HPV infection than women under 30 years of age.

SURGICAL MANAGEMENT OF HPV EXTERNAL GENITAL LESIONS: SIMPLE EXCISION TO ADVANCED RECONSTRUCTION

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HPV-related external genital lesions are highly prevalent and often recurrent, with a subset requiring surgery due to symptom burden, failure of topical therapy, or suspicion of malignancy
Surgery is primarily indicated for extensive or bulky condyloma acuminata causing pain, bleeding, pruritus, or functional impairment (voiding, intercourse, hygiene); lesions refractory to medical or ablative treatments, or those with atypia, rapid growth, or suspected high-grade intraepithelial neoplasia or invasive carcinoma; and giant condyloma (Buschke–Löwenstein) requiring complete excision and histologic assessment.
Limited disease is treated with simple tangential or elliptical excision, curettage, or electrosurgical/laser excision aiming for complete macroscopic clearance and preservation of normal tissue. Extensive or deep lesions require wide local excision with planned reconstruction using local flaps,and split-thickness skin grafts to restore contour and function of the vulva, penis, scrotum, or perineum.
Surgical excision provides the highest immediate clearance rates, often approaching 90–100% for visible lesions, but does not eradicate latent HPV, so recurrence remains common. Functional and aesthetic outcomes are generally favorable when reconstruction is planned with attention to urethral patency, sexual function, and anal continence, although giant or recurrent disease carries higher risks of wound complications and need for reoperation. A structured,

indication-based approach combining appropriate excisional extent with tailored reconstruction enables reliable clearance of HPV-related external genital lesions while preserving function and minimizing morbidity.

DIETARY AND IMMUNOMODULATORY SUPPORT IN GENITAL HUMAN PAPILLOMAVIRUS (HPV) INFECTION

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Persistent genital infection with human papillomavirus (HPV) is closely related to host immune competence, oxidative stress, and micronutrient status. Although no specific diet can eradicate HPV, growing evidence suggests that targeted dietary interventions and selected immunomodulators may support viral clearance and regression of HPV-associated lesions. The proposed dietary regimen emphasizes high-dose antioxidants (β-carotene, vitamins C and E), vitamin D3, folic acid, zinc, selenium, quercetin, and green tea extracts, all of which have documented roles in immune regulation, DNA synthesis and repair, and reduction of oxidative damage. Mandatory daily intake of fruits, vegetables, and raw carrots provides additional carotenoids, polyphenols, and fiber, while wheat germ oil contributes vitamin E and essential fatty acids.
Supplementation with Coriolus versicolor (PSK/PSP-containing mushroom biomass) is recommended for its immunomodulatory properties, particularly enhancement of cellular immunity and natural killer cell activity. Inosine acedoben dimepranol (inosine pranobex, IAD) is included as an adjunct immunostimulant with antiviral effects, administered in cyclical regimens for both partners to support systemic immune response and reduction of clinical manifestations.
Overall, this integrative dietary and supplement-based approach aims to optimize host immunity and antioxidant

defenses, potentially facilitating HPV clearance and reducing persistence. Such regimens should be considered as supportive measures alongside standard clinical surveillance and evidence-based management of HPV-related disease.

FIGHTING ANOGENITAL HPV INFECTION – A NUTRITIONIST'S PERSPECTIVE

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Abstract

Anogenital infection with human papillomavirus (HPV) represents one of the most prevalent sexually transmitted viral infections worldwide. While spontaneous viral clearance occurs in a significant proportion of individuals, persistent infection is influenced by multiple host-related factors. From a nutritionist's perspective, nutritional status, immune resilience, and oxidative balance represent important determinants in the host response to HPV infection. Nutrition does not aim to diagnose, prevent, or treat HPV infection, but rather to support physiological immune function and cellular integrity through adequate nutrient availability. Sufficient intake of micronutrients involved in immune regulation, antioxidant defense, and epithelial maintenance is of particular relevance. Antioxidants such as beta-carotene, vitamin C, and vitamin E contribute to the neutralization of oxidative stress associated with chronic viral exposure and inflammatory processes. Vitamin C plays a central role in immune cell function, collagen synthesis, and protection of epithelial barriers, while also acting synergistically with other antioxidants. Vitamin D is recognized for its immunomodulatory properties, influencing both innate and adaptive immune responses. Folic acid supports normal DNA synthesis and methylation, processes essential for epithelial cell turnover and genomic stability. Trace elements such as zinc and selenium are indispensable for antioxidant enzyme activity, immune cell signaling, and overall immune competence. A dietary pattern rich in fruits, vegetables, legumes, and whole grains provides natural sources

of carotenoids, flavonoids, fiber, and essential micronutrients, contributing to systemic immune balance. Specific foods, including carrots and wheat germ oil, may be highlighted due to their content of carotenoids, vitamin E, and essential fatty acids. From a nutritional standpoint, selected nutraceutical components with documented immunonutritional properties, such as medicinal mushroom biomass (e.g., Coriolus versicolor), may be considered within the broader context of nutritional support. In conclusion, the nutritionist's view addresses HPV infection through the lens of nutritional adequacy and immune support. Targeted dietary strategies and evidence-based supplementation aim to optimize host nutritional status and immune resilience, without replacing medical care or clinical management.

HPV-ASSOCIATED HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (VIN3, WARTY TYPE) OF THE VULVA IN A 39-YEAR-OLD PATIENT: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

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Abstract
Background:
HPV-related vulvar intraepithelial neoplasia (VIN) represents a clinically significant premalignant condition with rising incidence among women under 50 years old. High-grade squamous intraepithelial lesions (HSIL/VIN3), particularly the warty subtype, are strongly associated with high-risk HPV genotypes and carry a measurable risk for progression to invasive vulvar carcinoma.
Case Presentation: We present the case of a female patient born in 1985, admitted with a clinical diagnosis of Tu vulvae lat. dex. Colposcopic examination identified a suspicious vulvar lesion with areas of acetowhite epithelium and mosaic patterns. The patient underwent biopsy of the vulvar tumor, and histopathological analysis (HPA No. 1282282) revealed HPV-associated high-grade SIL (VIN3), warty type. No evidence of stromal invasion was detected. The patient reported no prior history of vulvar dysplasia but had a history suggestive of chronic HPV exposure. HPV genotyping is pending/was

performed (specify if needed), with high-risk HPV infection considered the likely driver of dysplastic changes.

Management:

Following current ESGO/ISSVD recommendations, excisional management was considered the preferred therapeutic approach to achieve complete removal of the lesion and allow margin assessment. Additional therapeutic options—including laser ablation or topical immunotherapy—were evaluated based on lesion size, anatomical location, and patient fertility/quality-of-life considerations. A multidisciplinary evaluation emphasized the importance of vigilant follow-up due to the significant risk of recurrence, particularly in HPV-driven VIN3.

Discussion:

This case highlights the diagnostic challenges of vulvar HSIL/VIN3 and the necessity of integrating colposcopy, targeted biopsy, and HPV molecular diagnostics for accurate characterization. The warty type is typically linked to HPV 16 infection and demonstrates higher recurrence rates after treatment. Early detection and optimized management are crucial for preventing progression to invasive vulvar carcinoma. The role of HPV vaccination—both prophylactic and potentially therapeutic—is especially relevant for reducing recurrence risk in similar patient populations.

Conclusion:

HPV-associated VIN3 remains a significant premalignant condition requiring precise diagnosis and individualized therapy. This case underscores the importance of HPV-driven disease recognition and reinforces the need for comprehensive follow-up strategies and HPV vaccination counseling as part of long-term management.

HUMAN PAPILLOMAVIRUS POSITIVITY AND CERVICAL INTRAEPITHELIAL

LESION IN CERVICAL BIOPSY AND ENDOCERVICAL CURETTAGE IN WOMEN

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There is no shared global consensus on the best screening method, interval, or starting age for cervical cancer screening in women younger than 30 years, mainly because HPV infections are frequent and often transient in this age group.
This retrospective study from a tertiary teaching and research hospital in Türkiye (January 2016–June 2024) investigated high-risk HPV prevalence in women aged ≥21 years and HSIL/CIN2+ detection by colposcopy-directed biopsy plus endocervical curettage (ECC) in women <30 years. The prevalence cohort included 57,381 women. Overall high-risk HPV positivity was 14.3%, but it decreased strongly with age: 36.8% in ages 21–24, 24.0% in ages 25–29, and 12.7% in women ≥30.
A total of 735 women younger than 30 years underwent colposcopy; 291 were managed with follow-up and 444 received biopsy/ECC. Follow-up without tissue sampling was more common in ages 21–24 than 25–29 (49% vs 35.8%). Among the 444 women who underwent biopsy/ECC, HSIL/CIN2+ was found in 37.8% and HSIL/CIN3+ in 14.6%, with similar high-grade rates between 21–24 and 25–29 year groups. Importantly, even with benign cytology, 30.1% had HSIL/CIN2+ on pathology. Pap testing alone showed very low sensitivity and poor agreement with histology (low Cohen κ), while co-testing dramatically reduced the number needed to screen (≈2–3 vs ≈40). Two cervical cancers were detected at ages 22 and 29.

Overall, the findings support starting screening at age 21 and favor HPV-based screening/co- testing in women under 30 to avoid missing clinically significant high-grade disease.

DISTRIBUTION AND FREQUENCY OF HUMAN PAPILLOMAVIRUS (HPV) GENOTYPES AMONG 400 PATIENTS TESTED IN POLOG REGION FROM 2024 ONWARD: A CLINICAL LABORATORY OVERVIEW

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Background: Human papillomavirus (HPV) genotype surveillance provides essential data for vaccination strategy evaluation and cervical cancer prevention. This study analyzes HPV genotype frequency and co-infection patterns from recent clinical testing in LAOR Laboratory.
Methods: Between 2024 and present, 400 patients were screened for HPV, where 66 testing were positive (positivity rate: 16.5%). Genotyping results were analyzed for frequency distribution, co-infection prevalence, and birth cohort patterns, where patient ages ranged from 21 to 68 years (birth years: 1956–2003).
Results: Among 66 HPV-positive patients, the most prevalent genotypes were HPV 31 and HPV 52 (each n=11, 9.5%), followed by HPV 16 (n=10, 8.6%). Half of the patients (50%) harbored multiple HPV genotypes, with one individual infected with six different types. High-risk HPV types (16, 18, 31, 33, 45, 52, 58, 59) accounted for over 55% of all type entries. Patients born in the 1990s were mostly infected (40.9%), followed by those born in the 1980s (36.4%).
Conclusion: This dataset demonstrates significant HPV diversity and a high rate of co-infections in the study population. The high co-infection rate (50%) indicates frequent multiple genotype exposure, which may influence disease

progression and clinical management. Furthermore, the significant detection across all adult age groups—from individuals born in the 1950s to the 2000s—supports the need for lifelong HPV screening and reconsideration of age-based vaccination cutoffs. The 16.5% positivity rate and widespread multi-genotype infections underscore the continued importance of comprehensive HPV screening across adult age groups.
Keywords: HPV genotyping, co-infection, epidemiology, high-risk HPV, screening.

MACHINE LEARNING AND AI IN COLPOSCOPY

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Background: Colposcopy remains a cornerstone in the evaluation of abnormal cervical screening results; however, its diagnostic accuracy is highly operator-dependent and subject to substantial inter- and intra-observer variability. In recent years, machine learning (ML) and artificial intelligence (AI), particularly deep learning–based image analysis, have emerged as promising tools to enhance colposcopic assessment and improve detection of cervical intraepithelial neoplasia (CIN) and cervical cancer.
Objective: To summarize current evidence on the application, performance, and clinical relevance of machine learning and artificial intelligence in colposcopy.
Methods: A narrative synthesis of high-quality, peer-reviewed studies was performed, including original research, validation studies, and systematic reviews evaluating AI-based systems applied to colposcopic images. The reviewed literature focused on convolutional neural networks, transformer-based architectures, and multimodal models integrating colposcopic images with clinical data. Key outcomes included diagnostic accuracy, sensitivity and specificity for CIN2+/HSIL detection, lesion localization, biopsy guidance, and comparison with expert colposcopists.
Results: Across multiple studies, AI-assisted colposcopy systems demonstrated high diagnostic performance for identifying cervical precancer and cancer, with reported sensitivities and specificities frequently comparable to or exceeding those of experienced clinicians. Deep learning models showed particular strength in lesion classification, segmentation, and transformation zone identification.

Multimodal approaches combining image data with clinical variables further improved predictive accuracy. Meta-analytic evidence confirms robust pooled diagnostic performance of AI systems across screening and colposcopic settings. Importantly, AI tools have shown potential to reduce observer variability and improve diagnostic consistency, especially among less-experienced colposcopists.
Conclusion: Machine learning and artificial intelligence represent transformative advancements in colposcopy, offering objective, reproducible, and clinically meaningful support for cervical disease detection. While current evidence supports strong diagnostic performance, further multicenter prospective validation, standardization across imaging devices, and integration into clinical workflows are required before widespread implementation. AI-assisted colposcopy holds significant promise to enhance cervical cancer prevention strategies and optimize patient care.
Keywords: Irtificial intelligence; Machine learning; Colposcopy; Cervical intraepithelial neoplasia; Cervical cancer

THE FUTURE OF HPV SELF-SAMPLING IN CERVICAL CANCER SCREENING

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Cervical cancer continues to be a significant global public health challenge, despite being largely preventable through effective primary prevention and early detection strategies. The World Health Organization (WHO) emphasizes that eliminating cervical cancer as a public health problem requires achieving and maintaining high coverage of HPV-based screening programs. WHO has set ambitious targets, including screening at least 70% of women with a high-performance HPV test by the ages of 35 and 45. However, conventional clinician-based screening programs face persistent barriers. These include limited access to healthcare facilities, low participation rates, socioeconomic disparities, cultural barriers, and discomfort associated with pelvic examinations, as well as inadequate coverage among under-screened or never-screened populations. These challenges contribute to delayed diagnosis and treatment, and underscore the urgent need for innovative strategies that expand screening access and uptake. HPV self-sampling has emerged as an innovative and evidence-based approach with the potential to overcome many of these barriers. Self-sampling allows individuals to collect vaginal samples themselves using validated collection devices, outside of clinical settings, which are subsequently tested for hrHPV using molecular assays. Evidence from large randomized trials and real-world implementation studies demonstrates that PCR-based testing of self-collected samples provides clinical sensitivity comparable to clinician-collected samples for

detecting CIN2+ lesions or worse. Importantly, self-sampling consistently improves screening uptake, particularly among women who are under-screened, socioeconomically disadvantaged, or reluctant to participate in conventional clinician-based programs. WHO guidelines now endorse HPV self-sampling as an acceptable alternative to clinician- based sampling within primary HPV screening programs. Implementation strategies include home-based self-sampling with mailed kits, community distribution, access through primary care or pharmacies, and digital platforms for result communication, recall, and follow-up. Proper integration ensures that self-sampling strengthens the continuum from screening to diagnosis and treatment of pre-invasive disease. This includes standardized triage for HPV- positive results, consideration of vaccination status, and reliable follow-up pathways incorporating reflex cytology, partial genotyping, biomarker testing, and colposcopic assessment to prevent loss to follow-up. Laboratory quality assurance, patient adherence, and overall system readiness are particularly important for countries establishing or reorganizing national screening programs, especially in low- and middle-income settings. In conclusion, HPV self-sampling represents a strategic innovation, not only improving screening coverage and reducing inequalities, but also accelerating progress toward the WHO cervical cancer elimination targets.

HPV SELF-SAMPLING AND AT-HOME TESTING

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Introduction:
HPV self-sampling and at-home testing are emerging as key innovations in modern cervical cancer screening programs. They are particularly valuable for hard-to-reach and underscreened populations, in which traditional screening pathways show limited coverage. The aim of this article is to present the latest evidence on the clinical performance, validation, and implementation of HPV self-sampling and at-home testing devices, with a focus on data published in 2024–2025.
Methods:
Recent systematic reviews, multicenter clinical trials, and validation studies comparing HPV self-sampling with clinician-collected samples for the detection of high-risk HPV (hrHPV) and CIN2+
lesions were analyzed.
Results:
Multiple new studies confirm that HPV self-sampling is as sensitive as clinician-collected cervical samples for detecting hrHPV infection and precancerous lesions. Large studies conducted in 2024 and 2025 demonstrated high concordance, reliability, and safety of home-based self-sampling devices. A major advancement is the introduction of the first FDA-approved at-home HPV testing device (e.g., Teal Wand), which has been incorporated into routine screening protocols in California since 2025. Its sensitivity for detecting precancerous

lesions is approximately 96%, comparable to clinician-collected samples.
Conclusion:
HPV self-sampling and at-home testing represent proven, effective, acceptable, and scalable strategies that substantially increase accessibility and screening coverage, particularly among women who do not regularly participate in cervical cancer screening programs. These technologies are expected to become an integral part of personalized and population-based screening in the coming years.
Human Papillomavirus Viruses; Mass Screening; Self-Testing; Uterine Cervical Neoplasms

EPIDEMIOLOGICAL SHIFTS IN HPV-ASSOCIATED CERVICAL DISEASE FOLLOWING QUADRIVALENT VACCINE INTRODUCTION IN NORTH MACEDONIA

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Background: Human papillomavirus (HPV) vaccination has become a cornerstone of cervical cancer prevention globally. Quadrivalent HPV vaccine (targeting types 6, 11, 16, and 18) introduction into national immunization programs has raised important questions regarding long-term population-level shifts in HPV-associated cervical disease burden, particularly the potential for disease replacement and clinical unmasking of non-vaccine-type infections.
Objective: To identify the HPV types detected in women vaccinated with the quadrivalent HPV vaccine and to evaluate the complex phenomenon of epidemiological disease shift, specifically the redirection of premalignant cervical lesions toward HPV types not covered by the vaccine.
Methods: A statistical analysis was conducted on 100 consecutively vaccinated women across different age groups that were HPV positive, with comparison to the distribution of HPV types in unvaccinated women during 2021-2025.
Data extraction focused on type-specific HPV occurrence, correlated with histological diagnosis and disease severity, including CIN1, CIN2+, and CIN3+ lesions.
Results: Among vaccinated women, vaccine-covered HPV types (HPV 16 and 18) were detected in significantly low

percentage (2 patients with type 16 and 1 patient with type 6), with a predominance of non-vaccine HPV types of lower oncogenic potential. The ratio of occurrence for 31 and 45 was statistically significantly less in the vaccinated group.
This finding is likely attributable to partial cross-protection conferred by the quadrivalent vaccine, as well as natural epidemiological variability. The interesting fact is that 2 patients with type 16 had no histopathologic evidence of CIN.
Conclusion: Published data, surveillance research and population studies showed non- vaccine types tend to be more frequently detected in vaccinated cohorts. The results of our study show that the introduction of 9 valent HPV vaccine could lead to further protection.

RECURRENT CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE III 15 YEARS AFTER CONIZATION

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Background

Cervical intraepithelial neoplasia (CIN) is a precancerous lesion of the uterine cervix strongly associated with persistent infection with high-risk human papillomavirus (HPV). High-grade CIN (CIN III, severe dysplasia or grade gravis) carries a significant risk of progression to invasive cervical cancer if left untreated. Cervical conization is an established and effective treatment, particularly when complete excision with negative margins is achieved. Despite adequate initial management, long-term recurrence remains possible, highlighting the importance of extended follow-up.

Aim

The aim of this report is to present a rare case of CIN III recurrence 15 years after successful cervical conization and to emphasize the need for lifelong surveillance in patients previously treated for high-grade cervical lesions.

Case Presentation

A female patient underwent cervical conization 15 years ago due to histologically confirmed CIN III (grade gravis). The excised specimen showed clear surgical margins, indicating complete removal of the lesion in healthy tissue. She was positive for HPV type 16. Following the procedure, the patient cured the HPV infection and was without abnormal cytological or colposcopic findings for 15 years. During

routine gynecological screening after 15 years, abnormal cervical cytology was detected. Further evaluation, including colposcopy and biopsy, confirmed recurrent CIN III. HPV testing was positive for a high-risk HPV type 45.
The patient was treated with a loop electrosurgical excision procedure (LEEP) in accordance with current clinical guidelines for high-grade CIN. Due to the history of recurrent high-grade disease, close post-treatment follow-up was advised, including regular cervical cytology, colposcopy, and HPV testing.
Conclusion
This case demonstrates that CIN III can recur even after a long disease-free interval following successful conization. Complete excision does not exclude long-term risk, particularly in the presence of high-risk HPV infection. Lifelong follow-up with combined cytological and HPV test of cure is essential in women previously treated for high-grade CIN to prevent invasive cervical cancer.
Key Words
Cervical intraepithelial neoplasia; CIN III; conization; LEEP; recurrence; human papillomavirus; long-term follow-up

CLINICAL PRESENTATION AND MANAGEMENT OF HIGH-GRADE IMMATURE OVARIAN TERATOMA

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Introduction: High-grade immature ovarian teratoma is a rare malignant germ cell tumor derived from all three germ layers, occurring more frequently in adolescents and young women. The diagnosis is usually based on the clinical presentation of abdominal pain and distension, supported by imaging modalities and confirmed by histopathological analysis. Treatment is determined by tumor grade and, in most cases, includes adnexectomy with adjuvant chemotherapy.
Case report: A 25-year-old female patient was admitted from the emergency department due to the presence of free fluid in the abdomen, dyspnea, and chest-radiating pain accompanied by vomiting. The patient had undergone an appendectomy two years earlier. The menstrual cycle was regular, and there was no history of pregnancy or abortion. Ultrasound examination revealed an enlarged uterus and a unilateral mass measuring 74 × 91 mm with mixed echogenicity located in the left adnexa, along with free fluid in the pelvis, perisplenic, splenorenal, hepatorenal, and paracolic spaces. The abdomen was tender on deep suprapubic palpation. A laparoscopic procedure was performed to remove the adnexal mass, and the tissue was sent for histopathological analysis, which confirmed a high-grade immature ovarian teratoma. Following the diagnosis, the patient underwent a restaging operation, including left-sided adnexectomy, infracolic omentectomy, and left lateral pelvic peritonectomy. Postoperatively, antibiotic therapy and thromboprophylaxis with heparin were administered. Based on

the disease stage and histopathological findings, chemotherapy according to the PEB protocol (etoposide, cisplatin, bleomycin) was recommended. On the fourth day of therapy, the patient experienced a neurological episode of vertical nystagmus and diplopia. Computed tomography (CT) of the brain and neurological examination revealed no abnormalities. After administration of diazepam, the symptoms resolved. At discharge, the patient was in stable condition, with continued oncological follow-up and ongoing chemotherapy.

Conclusion: High-grade immature ovarian teratoma is a rare but aggressive malignancy that occurs most often in young women. This case highlights the importance of timely diagnosis, appropriate surgical management, and adjuvant chemotherapy. A multidisciplinary approach is essential for achieving clinical stability and optimizing patient outcomes.

Keywords:

Adnexectomy, combined chemotherapy protocols, neoplasm staging, teratoma

HPV MULTIDISCIPLINARY EXTENDED UPDATE — ANATOMY MATTERS. RISK DECIDES

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Background

HPV infection is frequent, often silent, and may persist long enough to drive precancerous and cancerous disease across multiple anatomical sites, particularly the anogenital region and head & neck epithelium. Contemporary shifts in sexual behavior across the lifespan, combined with increasing rates of immunosuppression, complicate risk profiling and population categorization. In parallel, growing evidence suggests clinically relevant gender-related differences in HPV susceptibility, persistence, and HPV-related disease burden, reinforcing the need for prevention and clinical pathways that remain precise even when risk categories are not clear.

Aim

To present a multidisciplinary, anatomy- and risk-based framework for HPV education, vaccination, screening, testing, counseling, and follow-up across life stages, addressing HPV-related diseases with a contemporary clinical perspective.

Approach

The proposed model is structured around an anatomy-first workflow that links clinical indication to the most appropriate site-specific evaluation (cervix/vulva/vagina, penis, anus, oropharynx). It integrates prevention priorities (vaccination and education), evidence-based screening and testing strategies, and patient-centered result discussion with clear next-step management. The framework defines coordinated roles across primary care (vaccination, continuity, follow-up coordination), gynecology (cervical/vaginal/vulvar assessment, colposcopy, dysplasia management), urology/andrology (penile lesions and counseling), STI/sexual health services (risk assessment and prevention counseling), public health (screening access and program alignment), laboratory medicine (specimen selection, preanalytics, reporting language), and oncology prevention (HSIL management and surveillance). The goal is a practical pathway that improves adherence and reduces missed prevention opportunities through consistent multidisciplinary ownership.

Conclusion / Future Perspective HPV care is moving toward a contemporary model where anatomy guides the pathway and risk defines the action. A multidisciplinary, site-specific approach strengthens prevention impact, improves testing quality and interpretation, and supports reliable follow-up—advancing long- term cancer prevention and more targeted management of HPV-related diseases in real-world clinical practice.

Keywords

HPV; risk-based screening; anatomy-based prevention; HPV-related diseases; gender differences

HPV-ASSOCIATED HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (VIN3, WARTY TYPE) OF THE VULVA IN A 39-YEAR-OLD PATIENT: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

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Globally, cervical cancer is the fourth most common cancer in women, with an estimated 660,000 new cases in 2022. In the same year, about 94% of the 350,000 deaths from cervical cancer occurred in low- and middle-income countries. The highest incidence and mortality rates from cervical cancer are in sub-Saharan Africa, Central America, and Southeast Asia. Regional differences in the burden of cervical cancer are related to inequalities in access to vaccination, screening, and treatment services, risk factors, including HIV prevalence, and social and economic determinants such as sex, gender bias, and poverty. Women living with HIV are 6 times more likely to develop cervical cancer compared with the general population, and about 5% of all cervical cancer cases are attributed to HIV. Cervical cancer disproportionately affects younger women, and as a result, 20% of children lose their mothers to cervical cancer . The WHO Global Strategy defines elimination as reducing the number of new cases per year to 4 or fewer per 100,000 women and sets three targets to be achieved by 2030 to put all countries on the path to elimination in the coming decades: -90% of girls vaccinated with HPV vaccine by age 15 -70% of women screened with a

high-quality test between ages 35 and 45 -90% of women with cervical disease receiving treatment. Modeling estimates that a cumulative 74 million new cases of cervical cancer could be avoided and 62 million deaths could be avoided by 2120 by achieving this elimination target. In Europe, cervical cancer is ranked as the 9th most common cancer in women and the second leading cause of cancer death in women aged 15–44 years. Europe is characterized by significant differences in cervical cancer incidence and mortality. Keywords: cervical cancer, HPV, vaccine.

HPV GENOTYPING AND PERSONALIZED RISK-BASED MANAGEMENT IN ACCORDANCE WITH ESGO RECOMMENDATIONS

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Abstract

The introduction of primary HPV testing as the cornerstone of cervical cancer screening, in line with current European recommendations, has enabled the development of more precise risk stratification strategies through HPV genotyping. According to the latest recommendations of ESGO and partner European professional societies, genotype-specific analysis, with particular emphasis on HPV16 and HPV18, plays a pivotal role in the triage of HPV-positive women due to the well-documented higher risk of progression to CIN2+ lesions and invasive cervical cancer. Integration of HPV genotyping into screening and triage algorithms allows for personalized clinical decision-making, including earlier referral to colposcopy for women at highest risk, while safely extending follow-up intervals for those infected with lower-risk high-risk HPV types. This approach is consistent with ESGO recommendations, which emphasize the need to balance high screening sensitivity with the avoidance of unnecessary diagnostic and therapeutic interventions. HPV genotyping therefore represents a key component of modern, effective, and sustainable cervical cancer screening programs,

contributing to the overarching goal of cervical cancer elimination.

Key message:

HPV genotyping, in accordance with ESGO recommendations, enables precise risk stratification and supports rational, personalized management of HPV-positive women.

A DECADE OF DIGITAL INTEREST IN "HUMAN PAPILLOMAVIRUS" IN TURKIYE

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Introduction: Cervical cancer remains a major global health concern, with 660,000 new cases and 350,000 deaths in 2022 alone—94% of which occurred in low- and middle-income countries. Persistent infection with high-risk Human Papillomavirus (HPV), particularly types 16 and 18, accounts for over 95% of cases. In Türkiye, the incidence is 4.2 per 100,000, underscoring the importance of public awareness and preventive strategies.
Objective: This study aimed to track the evolution of HPV-related public interest across Türkiye using digital epidemiology tools, focusing on temporal shifts, geographical disparities, user trends, and implications for public health policies.
Methods: A retrospective, descriptive analysis was conducted using Google Trends data (01.2016–01.2026) for the keyword "HPV" across all 81 provinces of Türkiye. Search volumes were standardized as Relative Search Volume (RSV: 0–100).
Results: National HPV search interest rose by 362% over the decade, peaking in 2024. Provinces with the highest RSV were İzmir (100), İstanbul (97), and Ankara (88), while Şanlıurfa (33) recorded the lowest. Search terms like "Symptoms", "Medical Test", and "Treatment" reached

breakout status (>5,000% increase). Notably, searches for "HPV Vaccine" surged by 650%.
Discussion: Peaks in search volume align with key public health events, including ministerial announcements, WHO guidelines, and the launch of free municipal vaccination programs. Regions with higher health literacy and proactive vaccination policies showed stronger digital engagement.
Conclusion: This study demonstrates that digital behavior reflects health policy impact and public responsiveness. Google Trends data offer actionable insights for optimizing communication strategies and monitoring health awareness. Digital epidemiology stands out as a cost-effective, scalable tool for shaping preventive health initiatives.

THE ROLE OF PSYCHOLOGICAL FACTORS IN HPV INFECTION OUTCOMES

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Psychological stress is an important factor involved in disease manifestations of human papillomavirus (HPV) infection, and it can participate in HPV-associated carcinogenesis. The impact of stress depends on a person's genetic pool, experiences and behaviors and this issue remains a subject of researchers.
Due to the course of HPV manifestations, it has been observed that a higher number of life stressors in at least the previous 6 months, the absence of social support and the types of personal coping mechanisms employed, all influence on HPV progression. In women with cervical dysplasia, a connection between greater stress experiences and dysregulation of specific immune responses has been observed. Once HPV enters a cell via the α6 integrin there are three possible sequences: latent infection, subclinical infection, and clinically manifest disease. HPV proliferation in differentiated epithelial cells induces morphologically cytopathic changes (koilocytosis, epidermal thickening, hyperplasia, hyperkeratosis). Oncogenic transformation requires the integration of the virus genome into the host genome. In doing so, DNA in the E1 region of E2 breaks down, leading to transcription disorders of E6 and E7 genes followed by suppression of apoptosis and the stabile expression of E6 and E7 oncoproteins that protect transformed cells from apoptosis.
A successful immune response is characterized by a strong, local cell-mediated immune response. Several factors are important for the regression of HPV infection. Stress hormones may reactivate latent tumor viruses, stimulate viral oncogene expression, and inhibit antiviral host responses. In the regression of HPV infection, increased activity of Th1 cells was

observed. However, during psychosocial stress, a decrease in the Th1 type of immune response is seen, and there is a shift towards a Th2 response. Understanding perceived stress and biological changes in stress, as well as the evaluation of immune parameters, gives researchers a better picture of how stress influences HPV infections and how to improve disease management and outcomes.
Keywords: Psychological stress impact; HPV infection.

HPV AGAINST CORIOLUS-VERSICOLOR-BASED VAGINAL GEL – CASE STUDY

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Introduction There are more than 400 types of human papillomavirus (HPV) have been identified. Despite the creation of effective prophylactic vaccines against the most common genital HPVs, the viruses remain among the most prevalent pathogens found in humans. According to WHO data, they are the cause of 5% of all cancers. Even more frequent are persistent and recurrent benign lesions such as genital and common warts. Diagnosis of HPV infection can be challenging because the infection is often asymptomatic, especially in men. In women, HPV testing can be done through cervical screening programs, which involve the collection of cervical cells for analysis. Abnormal results may lead to further diagnostic procedures, such as colposcopy or biopsy, to detect precancerous or cancerous changes. Overall, HPV infection is a prevalent sexually transmitted infection with significant implications for public health. Vaccination, regular screening, and early treatment of precancerous lesions are key strategies to reduce the burden of HPV-related diseases and their associated complications. Education and awareness about HPV and its prevention are crucial in promoting optimal sexual health.

Methods: We reviewed the history of a patient diagnosed with HPV-associated cervical lesion. Clinical data was collected, including demographics, working status, sexual history, and smoking status. The patient was treated *Coriolus-Versicolor*-Based Vaginal gel. (Papilocare)

Results: 43 years old patient with LSIL lesion (proven with biopsy) with 7 hpv types (6 high risk types and one low risk) was treated with *Coriolus-Versicolor*-Based Vaginal gel for 6

months .After that, the control was made with Pap smear test, colposcopy and HPV tipisation. Pap test was clear and only one hpv type stayed (hpv 68).We continued with the treatment for 3 months more. The next control will be made after three months.

Conclusion: *Coriolus-Versicolor*-Based Vaginal gel shows promising potential as a supportive treatment in managing HPV infections. Its unique formulation, which includes antioxidant, anti-inflammatory and mucosal repairing agents, may help enhance the local immune response, promote epithelial healing and create an unfavorable environment for viral persistence. Preliminary findings suggest that *Coriolus-Versicolor*-Based Vaginal gel can contribute to the clearance of hpv and the regression of low grade cervical lesions when used as an adjunct to standard monitoring protocols.

Kew words: HPV, LSIL lesions, *Coriolus-Versicolor*-Based Vaginal gel

MULTIMODAL TREATMENT AND IMAGING FOLLOW-UP IN FIGO STAGE IIA CERVICAL SQUAMOUS CELL CARCINOMA: A CASE REPORT

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Background:
Invasive squamous cell carcinoma of the uterine cervix remains a major oncological challenge, particularly in locally advanced stages. Multimodal treatment combining chemoradiotherapy, brachytherapy, surgery, and imaging follow-up is often required to optimize outcomes.

Case Presentation:
We report the case of a female patient born in 1960 with histologically confirmed invasive squamous cell carcinoma of the uterine cervix, diagnosed on 11 July 2025 following cervical biopsy. Initial clinical and radiological evaluation classified the disease as FIGO stage IIA. The patient underwent concurrent chemoradiotherapy (CCRT) with planned high-dose-rate brachytherapy (HDR-BT); however, the brachytherapy course was incomplete. Given the incomplete local radiotherapy and multidisciplinary evaluation, further surgical management was indicated.

Methods:
The patient subsequently underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and

selective pelvic lymphadenectomy. Follow-up magnetic resonance imaging (MRI) of the pelvis and abdomen was performed on 11 November 2025 and compared with a previous MRI from 29 July 2025 to assess treatment response and detect residual or recurrent disease.

Results:
Follow-up MRI demonstrated complete resorption of the previously identified soft-tissue mass in the cervix, which had corresponded to the primary tumor on the earlier examination. These findings indicate a complete radiological response of the cervical lesion following multimodal treatment. Additionally, a stable endoluminal proliferative lesion in the uterine fundus, measuring approximately 7 mm, was noted, with no evidence of progression. No pathological lymphadenopathy or distant metastatic disease was detected.

Conclusion:
This case illustrates the value of a multimodal therapeutic approach in the management of FIGO stage IIA cervical squamous cell carcinoma, particularly when standard chemoradiotherapy and brachytherapy are incomplete. MRI follow-up played a crucial role in evaluating treatment response and guiding further clinical decision-making. Long-term surveillance remains essential to monitor for disease recurrence.

EPIDEMIOLOGY AND BURDEN OF CERVICAL CANCER WORLDWIDE

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Globally, cervical cancer is the fourth most common cancer in women, with an estimated 660,000 new cases in 2022. In the same year, about 94% of the 350,000 deaths from cervical cancer occurred in low- and middle-income countries. The highest incidence and mortality rates from cervical cancer are in sub-Saharan Africa, Central America, and Southeast Asia. Regional differences in the burden of cervical cancer are related to inequalities in access to vaccination, screening, and treatment services, risk factors, including HIV prevalence, and social and economic determinants such as sex, gender bias, and poverty. Women living with HIV are 6 times more likely to develop cervical cancer compared with the general population, and about 5% of all cervical cancer cases are attributed to HIV. Cervical cancer disproportionately affects younger women, and as a result, 20% of children lose their mothers to cervical cancer . The WHO Global Strategy defines elimination as reducing the number of new cases per year to 4 or fewer per 100,000 women and sets three targets to be achieved by 2030 to put all countries on the path to elimination in the coming decades: -90% of girls vaccinated with HPV vaccine by age 15 -70% of women screened with a high-quality test between ages 35 and 45 -90% of women with cervical disease receiving treatment. Modeling estimates that

a cumulative 74 million new cases of cervical cancer could be avoided and 62 million deaths could be avoided by 2120 by achieving this elimination target. In Europe, cervical cancer is ranked as the 9th most common cancer in women and the second leading cause of cancer death in women aged 15–44 years. Europe is characterized by significant differences in cervical cancer incidence and mortality. Keywords: cervical cancer, HPV, vaccine.

SUCCESS RATES AND DIAGNOSTIC BENEFITS OF LLETZ VS OTHER METHODS IN THE TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Introduction:
Human papillomavirus (HPV) is a sexually transmitted disease and presents a significant risk factor for the development of cervical intraepithelial neoplasia (CIN). HPV 16 is the most carcinogenic and accounts for 55 to 60% of cervical cancers while HPV 18 is the second most carcinogenic and accounts for 10 to 15% of cervical cancer (1) . CIN is a spectrum of precancerous conditions found on the cervical epithelium and consists of mild (CIN I), moderate (CIN II) and severe (CIN III) dysplastic changes. There are several techniques used to prevent progression of CINs to invasive cervical cancer and are divided into ablative (cryotherapy and laser ablation) and excisional methods (LLETZ/LEEP, cold knife conisation-CKC). Choice of treatment depends on the grade and extent of the disease. Large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excision procedure (LEEP) is the most widely used technique because of its diagnostic and treatment value (2).
Aim:
To compare the success rates and diagnostic advantages of LLETZ with other treatment modalities for CIN.
Findings:
The excisional techniques offer the advantage of obtaining a large specimen enabling precise diagnosis and evaluation of

complete lesion removal (3). Ablative methods showed higher recurrence rate and they do not provide tissue samples for pathohistological examination. By allowing excision of a larger, intact specimen, CKC offers superior diagnostic accuracy, although shows increased morbidity and greater effects on future pregnancy outcomes when compared to LLETZ. Among excisional methods, cure rates of CIN confirmed by biopsy reached 90–94% with cold-knife cone biopsy, 91–98% with LLETZ, and 93–96% with laser conization. Among ablative techniques, cure rates reached 85–94% with cryotherapy and 95–96% with laser ablation (4). According to meta-analysis published in Lancet in 2022, obstetrical outcomes show that all excisional procedures are associated with an increased risk of preterm birth, low birth weight, and premature rupture of membranes compared with no treatment (5).

Conclusion:

LLETZ has now become the standard of care for cervical premalignant lesions due to its balance of effectiveness, diagnostic capability, and safety while also suitable for patients with reproductive tendencies. Cold knife conization is reserved for complex or suspicious cases where maximal diagnostic accuracy is required. Ablative techniques may be appropriate for carefully selected low-risk patients but are limited by the absence of histological confirmation.

BIOMARKERS FOR DETECTION OF SQUAMOUS CELL ABNORMALITIES OF THE UTERINE CERVIX

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Introduction: The aim of the study was to prove that viral oncoproteins E6/E7 are superior biomarkers for the detection of high-risk HPV-associated cervical squamous cell abnormalities.

Material and Methods: A prospective cohort study was conducted on a series of 128 sexually active women, aged 21 to 59 years (49.50 ± 8.40) with cytological findings of squamous cell abnormalities of the cervix. All patients underwent: HPV-DNA testing, HPV E6/E7 mRNA testing, and colposcopic cervical biopsy with endocervical curettage for histopathological analysis.

Results: Data analysis showed an association between the presence of HPV-DNA infection and the occurrence of squamous cell abnormalities of the cervix (chi-square test=5.618, p=0.023, p<0.05). Data analysis showed an association between the presence of viral oncoproteins E6 and E7 and the occurrence of squamous cell abnormalities of the cervix (chi-square test=11.178, p=0.001, p<0.05). HPV-DNA testing, compared with HPV E6/E7 mRNA testing, was superior in detecting low-grade squamous intraepithelial lesions (63.41%; 26/41 vs. 9.76%; 4/41), while HPV E6/E7 mRNA testing was superior in detecting high-grade squamous intraepithelial lesions (92.60%; 50/54 vs. 83.33%; 45/54) and invasive squamous cervical cancer (95.83%; 23/24 vs. 87.50%; 21/24). The accuracy of HPV-DNA testing was 75.78%, while

the accuracy of HPV E6/E7 mRNA testing was 66.41%. HPV E6/E7 mRNA testing had higher specificity (88.89% vs. 55.56%) and higher positive predictive value in HSIL+squamous invasive carcinoma (93.59% vs. 84.61%) than HPV DNA testing.

Conclusion: There is an association between HPV-DNA infection, viral oncoproteins E6/E7 and cervical squamous cell abnormalities, and viral oncoproteins E6/E7 are superior biomarkers for the detection of high-risk HPV-associated cervical squamous cell abnormalities.

Keywords: biomarkers, squamous cell abnormalities, viral oncoproteins E6 and E7

CORRELATION BETWEEN PAP SMEARS AND HISTOPATHOLOGICAL DIAGNOSIS IN PREMALIGNANT LESIONS OF THE UTERINE CERVIX

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Introduction:
Cervical cancer is one of the leading causes of mortality among women. The Papanicolaou (PAP) smear is a simple, widely used cytological screening method for detection of precancerous and cancerous changes in cervical epithelium. But, histopathology remains the gold standard for definitive diagnosis.

Objectives: The aim of this study is to correlate abnormal Pap smears findings with histopathological findings with cervical biopsy and endocervical curettage in patients with premalignant lesions of the uterine cervix on our material.

Materials and methods: In a retrospective study we analysed data from Par smears and histopathological diagnosis after cervical biopsy and endocervical curettage of 440 patients with premalignant lesions of the uterine cervix on University clinic for gynecology and obstetrics in Skopje in the period between 01.01.2025 to 31.12.2025.

Results: A total of 440 women aged between 19 and 72 years presenting with abnormal cervical cytology were included. Pap smears results were classified using Bethesda system, and cervical biopsies and endocervical curettage were performed for histopathological examination. LSIL (HPV cervicitis, CIN-1) was confirmed in 55 cases with LSIL on Pap smears. In 18 patients with LSIL on PAP histopatology confirmed HSIL lesions (CIN2,CIN3,CIS). HSIL had 30 patients in which

histopatology confirmed HSIL lesions (CIN 3, CIS) in 24 cases, LSIL lesions in 5 cases, and invasive carcinoma in one case. In patients with ASC-US on Pap smears (39cases) histopathology confirmed LSIL lesions in 27 patients, and HSIL lesions in 12 patients. In patients with ASC-H on Pap smears (7 cases) LSIL was confirmed in 4 cases and HSIL in 3 cases. In tree patients with AGC on Pap smear histopathology confirmed adenocarcinoma of the uterine cervix. In patients with HPV cervicitis on Pap smears in 21 cases histopatology confirmed HSIL lesion v.s.49 patients with LSIL lesions. The overall concordance rate between cytology and histopathology was about 75%. At the same time results from HPV testing were available for 323 patients. High risk types of HPV were detected in 255 cases (78,9%), HPV type 16 was detected in 79 cases (24,5%), HPV type 18 in 25 cases (7,7%) and HPV type 31 in 35 cases (10,8%).

Conclusions: Pap smear is an effective preliminary screening tool, but histopathological confirmation is essential for accurate diagnosis and treatment planning for the patients with premalignant lesions of the uterine cervix. Infections with high risk types of HPV (especially types 16,18,31) are associated with premalignant cervical lesions. Integration of cytology with biopsy and HPV testing can enhance early detection and improve patients outcomes in cervical cancer prevention programs.

Key words: Premalignant lesions of uterine cervix, Pap smear, HPV testing

HPV VACCINATION COVERAGE IN NORTH MACEDONIA: PROGRAM EVOLUTION AND ONGOING CHALLENGES

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Human papillomavirus (HPV) vaccination is a cornerstone of cervical cancer prevention and a key element of the World Health Organization (WHO) strategy for cervical cancer elimination. In North Macedonia, HPV vaccination has been included in the national immunization program since 2009; however, achieving and sustaining high vaccination coverage remains a challenge. This abstract presents an overview of HPV vaccination coverage trends and program evolution in North Macedonia between 2009 and 2025, based on national immunization program information, publicly available reports, and professional experience related to vaccine implementation. Since its introduction, vaccination coverage has remained variable and below levels required for population-wide impact and alignment with WHO elimination targets. From 2009 to 2023, the national program utilized bivalent and quadrivalent HPV vaccines. In 2024, the program transitioned to the nonavalent HPV vaccine, in accordance with WHO

recommendations favoring broader oncogenic HPV genotype coverage. Although this transition expands the potential scope of protection against HPV-related disease, vaccination uptake continues to be influenced by program organization, public awareness, vaccine confidence, regional variability, and healthcare provider engagement rather than vaccine formulation alone. Strengthening organized vaccination delivery, improving communication on vaccine safety and effectiveness, and reinforcing healthcare professional involvement are essential to increase coverage nationwide.

Keywords: HPV vaccination; cervical cancer prevention; immunization coverage; nonavalent HPV vaccine; North Macedonia; public health

HUMAN PAPILLOMAVIRUS INFECTION AND BACTERIAL VAGINOSIS IN WOMEN WITH SQUAMOUS CELL ABNORMALITIES OF THE UTERINE CERVIX

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Introduction: The aim of the study was to determine the association between HPV-DNA infection and bacterial vaginosis in women with squamous cell abnormalities of the uterine cervix.
Material and Methods: The material of the study is represented by 128 sexually active women, aged 21 to 59, with an abnormal cervical cytological finding, ie a PAP test with a squamous intraepithelial lesion or squamous invasive cervical cancer. In all 128 women we done: HPV DNA-testing and Nugent's scoring system.
Results: HPV-DNA infection was detected in 75.00% (96/128) of the examined patients. Out of a total of 128 patients, bacterial vaginosis was found in 56 (43.75%) patients. Out of a total of 128 patients, the presence of bacterial vaginosis and HPV-DNA infection was found in 50 (39.06%) patients. Out of a total of 96 HPV-DNA positive patients, bacterial vaginosis was present in 50 (52.08%) patients, and the absence of bacterial vaginosis was noted in 46 (47.92%) of the HPV-DNA positive patients. Data analysis showed an association between bacterial vaginosis and DNA-HPV infection (chi-square test=10.836, $p=0.009$, $p<0.05$). Among the high-risk HPV-DNA genotypes,

HPV-16 was the most common (56.00%; 28/50), followed, in descending order, by: HPV-31 (20.00%; 10/50), HPV- 18 (16.00%; 8/50), HPV-33 and -45 (with 8.00% each; 4/50), HPV-35, -42 and -52 (with 4.00% each; 2/ 50) etc. Among low-risk HPV-DNA genotypes, the most common was HPV-6 (10.00%; 5/50), followed by HPV-11 and HPV-61 (4.00% each; 2/50). Bacterial vaginosis was detected in 28 (56.00%) patients with single HPV-DNA infection and in 22 (44.00%) patients with mixed HPV-DNA infection.
Conclusion: The results of our study confirmed that there is a positive correlation between HPV-DNA infection and bacterial vaginosis in women with squamous cell abnormalities of the uterine cervix.

Key words: HPV DNA testing, bacterial vaginosis, squamous cell abnormalities

HUMAN PAPILLOMAVIRUS AND SQUAMOUS CELL ABNORMALITIES OF THE UTERINE CERVIX

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Introduction. The aim of the study was to confirm the existence of an association between human papillomavirus-deoxyribonucleic acid infection and squamous cell abnormalities of the uterine cervix.

Material and Methods. Cross-sectional study, conducted of 128 sexually active women, age groups of 21 to 59 years with squamous cell abnormalities on the cervical cytology, who came to their annual gynecological exam at University Clinic for Gynecology and Obstetrics in Skopje. In all patients was done: human papillomavirus-deoxyribonucleic acid testing and colposcopic cervical biopsy with endocervical curettage for histopathological analysis.

Results. Data analysis showed an increase in the presence of human papillomavirus-deoxyribonucleic acid infection in parallel with an increase in the cytopathological (p=0.029) and histopathological (p=0.029) grade of cervical lesion. The data analysis showed an association between the oncogenic potential of the virus and the cytopathological (p=0.001) and histopathological (p=0.001) grade of cervical lesion. HPV-DNA infection was detected in 75.00% of the examined women. The relationship between the prevalence of high-risk and low-risk HPV-DNA genotypes was 56.25%:10.94%. Mixed HPV-DNA infection was detected in 32.03% of all

patients, in 42.71% of HPV-DNA positive patients. The most common HPV-DNA genotypes, in descending order, were: HPV-16 (43.75%), HPV-31 (15.62%), HPV-18 (10.4%), HPV-45 (9.37%), HPV-33 (7.29%), etc.

Conclusion. There was an association between HPV-DNA infection and squamous cell abnormalities of the uterine cervix. Young women under 30 years of age was the most affected age group.

Key words: human papillomavirus, squamous cell abnormalities, uterine cervix

HISTOPATHOLOGICAL ASSESSMENT OF LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION OF THE CERVIX IN A 26-YEAR-OLD PATIENT WITH CHRONIC CERVICITIS

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Abstract

Background:

Low-grade squamous intraepithelial lesion (LSIL) is commonly associated with transient HPV infection and frequently regresses spontaneously. Persistence or progression is more likely with chronic cervical inflammation or high-risk HPV. Case

Presentation:

A 26-year-old female, born in 1998, presented with two prior abnormal Pap tests (LSIL) and clinical signs of inflammatory disease of the cervix uteri. Colposcopy revealed mild acetowhite areas without atypical vessels. Directed cervical biopsy confirmed LOW-GRADE SIL (dysplasia epithellii gradus levis). No high-grade lesions or glandular involvement were observed. HPV testing was recommended for risk stratification.

Management:

Following current guidelines (ASCCP/ESGO), conservative management with observation is indicated due to high rates of spontaneous regression. Cervical inflammation should be treated with targeted antimicrobials, and patient counseling on HPV vaccination and lifestyle modifications is recommended.

Follow-up includes repeat Pap and HPV testing at 12 months; colposcopy if persistent HPV or cytologic abnormalities occur; excisional therapy only if progression to high-grade lesions is detected.

Conclusion:

LSIL in young women, especially with concurrent cervical inflammation, warrants careful monitoring rather than immediate invasive therapy. Early identification, treatment of inflammation, HPV testing, and structured follow-up are key to preventing progression to high-grade lesions.

MANAGEMENT OF HPV-ASSOCIATED HSIL DURING THE SECOND TRIMESTER OF PREGNANCY

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Background: Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide and is frequently diagnosed in women of reproductive age. The detection of high-grade squamous intraepithelial lesions (HSIL) during pregnancy represents a clinical challenge, requiring a careful balance between oncological safety and maternal–fetal well-being. According to international guidelines, colposcopy with directed biopsy can be safely performed during pregnancy, particularly in the second trimester, while definitive treatment is usually deferred until after delivery unless invasive carcinoma is suspected.

Objective: To present a case demonstrating the safety and clinical value of diagnostic cervical biopsy performed during the second trimester of pregnancy in a patient with HPV-associated HSIL.

Methods: A conservative diagnostic approach was applied. Following cytological detection of HSIL (CIN III), targeted cervical biopsy was performed at 27+1 weeks of gestation. No excisional or ablative treatment was undertaken during pregnancy. Maternal and fetal monitoring followed standard obstetric protocols, and definitive treatment was planned for the postpartum period.

Results: A 34-year-old patient with one previous cesarean section underwent cervical biopsy due to HSIL detected on cervical cytology. Histopathological examination confirmed a high-grade squamous intraepithelial lesion without evidence of invasive carcinoma. Obstetric ultrasound showed normal fetal growth and anatomy. At 31+2 weeks of gestation, the patient was rehospitalized because of vaginal bleeding and pregnancy-induced hypertension. Cervical length was normal, with no signs of cervical insufficiency or preterm labor. Conservative management resulted in clinical stabilization, and the patient was discharged in good condition.

Conclusion: This case supports current international recommendations that diagnostic cervical biopsy during the second trimester of pregnancy is safe when HSIL is suspected. In the absence of invasive disease, conservative management with postponement of definitive treatment until the postpartum period remains an appropriate and evidence-based strategy.

Keywords: HPV, HSIL, pregnancy, cervical biopsy, conservative management

EPIDEMIOLOGICAL PROFILE OF HUMAN PAPILLOMAVIRUS GENOTYPES IN AN HPV-POSITIVE SCREENING POPULATION

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Background:
Persistent infection with high-risk human papillomavirus (HPV) is the main etiological factor for cervical cancer. Knowledge of genotype distribution in screened populations is essential for evaluating vaccination strategies and optimizing cervical cancer prevention programs.
Methods:
A total of 2,587 women undergoing HPV testing at the Gynecology and Obstetrics Clinic in Skopje were included in the analysis. HPV DNA detection and genotyping were performed using a multiplex real-time PCR-based assay capable of identifying both high-risk and low-risk HPV types. Among them, 819 women (31.7%) were HPV positive and were further analyzed for age distribution, single versus multiple infections, and genotype prevalence.
Results:
The mean age of HPV-positive women was 37.1 years (median 35.5 years). Multiple HPV infections were detected in 258 patients (31.5%), while 561 (68.5%) had a single genotype infection. The most frequently detected genotypes were HPV16 (n=173), followed by HPV53 (n=79), HPV31 (n=72), HPV51 (n=68), HPV52 (n=64), HPV66 (n=63), and HPV18 (n=57). A high proportion of infections were caused by high-risk HPV types, with HPV16 being the dominant genotype across all age groups. Low-risk types, including HPV6 and HPV42, were also

present, mainly in younger women and often in combination with high-risk genotypes.

Conclusion:

In this large cohort of HPV-positive women, high-risk genotypes predominated, with HPV16 as the leading type, followed by several other oncogenic types such as HPV31, 51, 52, and 53. The substantial rate of multiple infections highlights the complexity of HPV epidemiology in the screened population. These findings provide important baseline data for monitoring the impact of HPV vaccination and for tailoring cervical cancer screening strategies in North Macedonia.

ABNORMAL UTERINE BLEEDING IN PERIMENOPAUSE PATIENTS WITH INCREASED HOMA INDEX

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Abstract
Introduction: Perimenopause as a clinical entity is characterised by a series of symptoms that occur due to estrogen deficiency in multiple organs and systems. Obesity is a risk factor that favours all these changes, especially endometrial hyperplasia. Glucose homeostasis is often impaired, with increased both insulin and HOMA IR.
Goals: to detect endometrial hyperplasia in obese perimenopausal patients with abnormal uterine bleeding, to determine insulin levels, HOMA IR, and to determine the association between endometrial hyperplasia and HOMA IR.
Material and methods: This was a prospective cohort study, performed at the OB/GYN Clinic, over a period of 1 year(2020-2021). 100 patients with abnormal uterine bleeding during the perimenopause were involved, aged 45–50, divided into two groups based on BMI. The control group consisted of 40 asymptomatic patients. 1group-patients with BMI above 30, 2 group-patients with BMI under 30 and the control group consisted of 40 asymptomatic patients
The patients were examined with ultrasound, laboratory analysis, and curettage was performed in the first and the second group of patients with abnormal bleeding.
Results: The average value of glycemia in the first group was higher, 5.7 mmol/l, cut-off value was 5,5. The average value of

the HOMA-IR insulin resistance index in the first group was highest, 2.8(the cut-off value was 1.8). Endometrial hyperplasia was registered in the first group at 40.9%.

Discussion: The first group registered a significant association between HOMA IR and hyperplasia, the risk of endometrial hyperplasia was eight times higher. The first group registered a significant association between glycemia and endometrial hyperplasia. High levels of glycemia increase the risk of endometrial hyperplasia occurring by three times.

Conclusion: In menopausal transition, patients with abnormal uterine bleeding have an increased incidence of endometrial hyperplasia, hyperglycemia, and increased HOMA IR. There is a strong association between these changes and the risk of cardiovascular disease. Menopause is a period in a woman's life that requires a multidisciplinary approach to diagnostics and treatment.

Keywords: HOMA IR, perimenopause, abnormal bleeding, hyperplasia

HPV INFECTION IN LOW-GRADE CERVICAL CYTOLOGY (ASC-US AND LSIL) PATIENTS TREATED WITH AN ABSORPTIVE AND ANTIOXIDANT VAGINAL GEL

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Abstract

Background:

Low-grade cervical cytological abnormalities, such as atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesions (LSIL), are frequently associated with cervical inflammation and high-risk human papillomavirus (hrHPV) infection. Non-invasive therapeutic approaches aimed at reducing inflammation and supporting cervical epithelial healing may contribute to cytological improvement.

Objective:

To evaluate the clinical and cytological outcomes of treatment with an absorptive and antioxidant vaginal gel (DeflaGyn®) in women presenting with ASC-US or LSIL, with or without hrHPV infection.

Methods:

Seventy-two women presenting with congestive cervix and/or cervical bleeding were enrolled. Baseline cervical cytology identified cervicitis (25.0%), ASC-US (41.7%), and LSIL (33.3%). Among women with ASC-US or LSIL, 20 patients underwent hrHPV testing, of whom 18 (90.0%) were positive. All patients were treated with DeflaGyn® vaginal gel

according to the recommended protocol. A subgroup of 24 patients with ASC-US or LSIL underwent follow-up evaluation after 3 months, including repeat Pap smear and clinical examination.

Results:

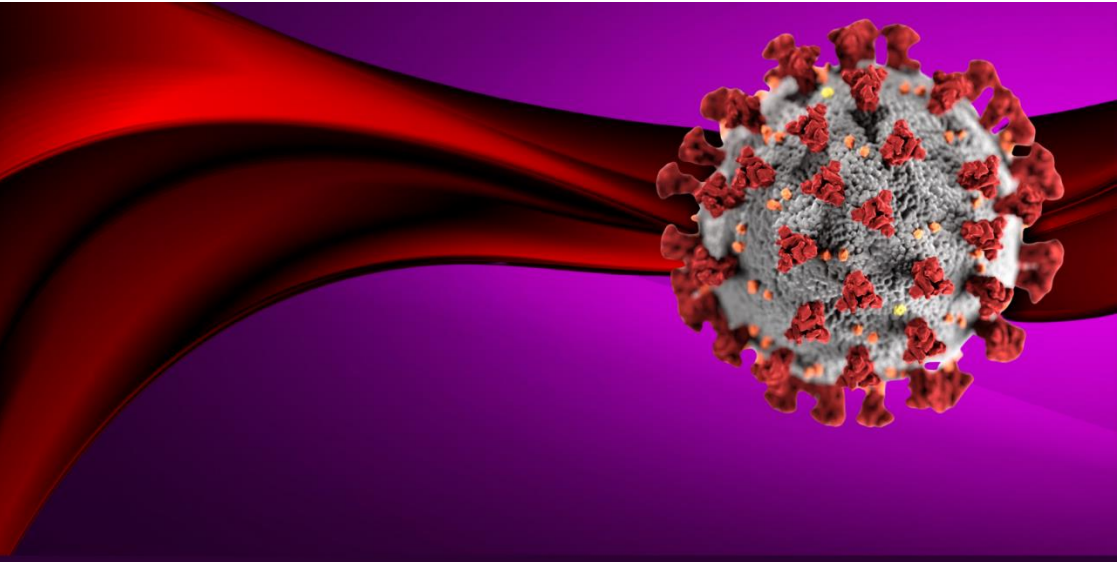
At 3-month follow-up, cytological normalization was observed in 20 of 24 patients (83.3%). Four patients (16.7%) showed improvement to inflammatory or borderline findings without persistence of LSIL. No progression to higher-grade lesions was observed. Clinically, resolution of cervical inflammation and bleeding was reported in the majority of followed patients, with normalization of cervical appearance on examination.

Conclusion:

Treatment with an absorptive and antioxidant vaginal gel was associated with high rates of cytological improvement and favorable clinical outcomes in women with low-grade cervical abnormalities, including hrHPV-associated lesions. These findings support its potential role as a non-invasive therapeutic option in the management of ASC-US and LSIL.

Keywords:

DeflaGyn®, ASC-US, LSIL, HPV infection, cervical cytology, vaginal gel



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