

**1st EDITION**

**PRACTICAL TRAINING**

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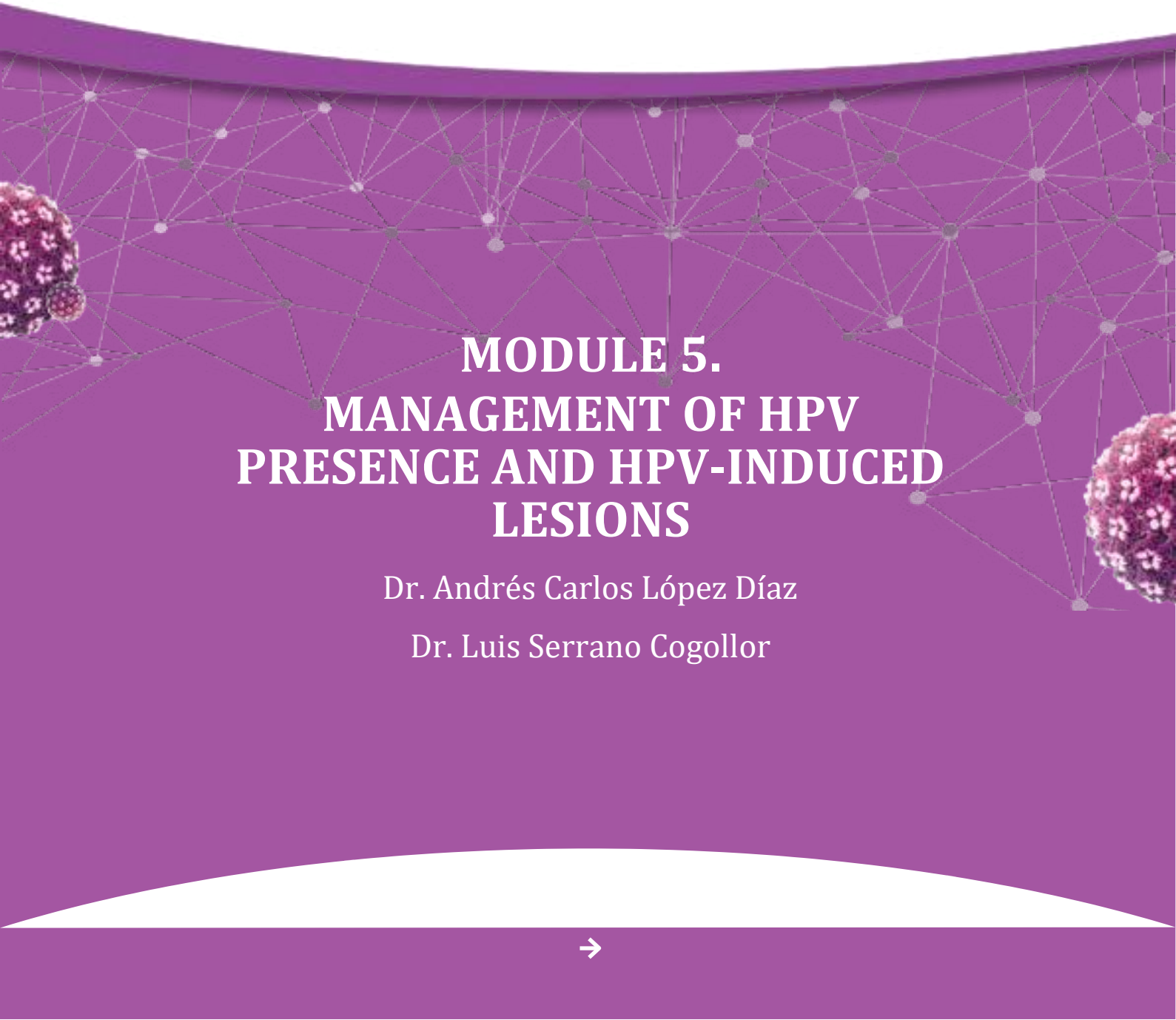
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# **HUMAN PAPILLOMAVIRUS**

**PRACTICAL CASES**

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## **MODULE 5. MANAGEMENT OF HPV PRESENCE AND HPV-INDUCED LESIONS**

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# INDEX

<b>AUTHORS</b> .....	¡Error! Marcador no definido.
<b>INTRODUCTION</b> .....	¡Error! Marcador no definido.
<b>OBJECTIVES</b> .....	¡Error! Marcador no definido.
<b>1. PRESENCE OF HPV: MANAGEMENT</b> .....	¡Error! Marcador no definido.
<b>2. HPV-INDUCED LESIONS: MANAGEMENT</b> .....	¡Error! Marcador no definido.
<b>3. CONCLUSIONS</b> .....	¡Error! Marcador no definido.
<b>BIBLIOGRAPHY</b> .....	¡Error! Marcador no definido.



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## INTRODUCTION

Human papillomavirus (HPV) detection in cervical mucous or infection (HPV integration in the cellular genome) is very common. In Spain, three out of every ten women under the age of 30 and one out of ten women over 30 are HPV-positive at any given time. At some point in their lives, eight or nine of every ten Spanish women will be HPV-positive<sup>1</sup>. In Spain, approximately one hundred thousand intraepithelial cervical lesions are diagnosed each year<sup>2</sup>. This imposes a significant burden on both public and private health care systems, costing €147,284,811<sup>3</sup>.





## OBJECTIVES

The objective of this module is to understand the current guidelines for managing various HPV-associated clinical situations and the cervical lesions resulting from HPV integration (infection).

## 1. PRESENCE OF HPV: MANAGEMENT

- » HPV determination tests should never be carried out before 30 years of age. As mentioned before, HPV is very prevalent in women under 30 in Spain. There are also high rates of spontaneous clearance in that population. Performing determination in that group has low positive predictive value for intraepithelial cervical lesions and cervical cancer<sup>3</sup>. As a reminder, and as specified in Module 3 of this course, the technique used to determine the presence of HPV must be validated. HPV determination results influence management actions, so we need to ensure that this result is reliable, and comes from a validated technique.
- » After 30 years of age, with a positive HPV determination, it is recommended to perform cytology as a decision-driving strategy<sup>4,5</sup> and then proceed according to the cytology result (see more below). If determination is negative, tests for the presence of HPV should be annual, never less.
- » “Evidence-based medicine” does not provide recommended measures to facilitate eliminating HPV present in the cervix. Because of the well-established increased risk of cervical cancer in smokers<sup>6</sup>, the first advice to give an HPV-positive smoker is to cease smoking. Professional help through *ad hoc* smoking cessation classes<sup>7</sup> is essential.
- » A vaginal gel based on *Coriolus versicolor* demonstrated benefits for cervical re-epithelialization, balancing vaginal microbiota, and improving vaginal immunity<sup>8-9</sup>. Actually a clinical study is on goin in fase IIb the objective of it is demonstrate the efficacy in clearance HPV in the cervix. Inicial data are so good with 56% of HPV clearance at 6 months in the treatment group than 30% in the control group. This tendence is more evidence in the subpopulation of women with HR-HPV: 50 vs 17% .

## 2. HPV-INDUCED LESIONS: MANAGEMENT

The following recommendations are based on those formulated in the *2014 Spanish Cervical Cancer Screening Guidelines*<sup>4</sup> and in the *2014 SEGO Oncoguide for Cervical Cancer Prevention*<sup>5</sup>. These references obtained a broad consensus from eight Spanish scientific societies, and should be considered required guidelines. In both publications, the supporting literature base can be consulted.

Health care practice is governed by specific recommendations<sup>15</sup> that allow preventive cytology screens from the time sexual relations are initiated (16 is the average age in Spain)<sup>16</sup>. For this reason, it is necessary to also establish management recommendations for anomalous cytology results in women under 30 (below).

Additionally, the management indications for women in special situations, menopause or pregnancy are also included:

- » **Cytological result: “Atypical Squamous Cells of Undetermined Significance” (ASC-US).**
  - Under 30 years of age: cytology in one year and follow-up according to result. If normal, test every three years.
  - Over 30 years of age: HPV determination.
    - a) HPV-positive: colposcopy.
    - b) HPV-negative: cytology and HPV test (co-test) in three years.
- » **Cytological result: “Atypical Squamous Cells cannot rule out a High-grade lesion” (ASC-H).**
  - Follow-up for women under or over 25-30 years of age with this cytological result have demonstrated the same risk of developing a High-grade Squamous Intraepithelial Lesion (HSIL) for both age groups.
  - Recommendation: colposcopy. If negative, conduct co-test in one year.
- » **Cytological result: “Low-grade Squamous Intraepithelial Lesion” (LSIL).**
  - Colposcopy is required, proceeding according to results.
  - In menopausal women, it is acceptable to perform an HPV test to rule out cases where hypotrophy could have caused over-diagnosis of LSIL.
    - a) HPV-positive: colposcopy.
    - b) HPV-negative: co-test in 3 years.
  - In pregnant women, the preferred option is to perform a colposcopy, but it is acceptable to postpone to six weeks after birth.



- » **Cytological result: “High-grade Squamous Intraepithelial Lesion” (HSIL).**
  - Colposcopy is required in all age groups, proceeding according to results. If negative, perform another cytological-colposcopic check-up in 6 months.
  
- » **Cytological result: “Atypical Glandular Cells” (AGC).**
  - From endocervical cells: colposcopy.
  - From endometrial cells: endometrial biopsy.
  - The presence of benign endometrial cells in the vaginal tract does not require any further exploration, except in post-menopausal women, in which case the endometrial study is required.
  
- » **Histological diagnosis: “Low-grade cervical intraepithelial neoplasia” (CIN1).**

CIN1 is not a precancerous lesion, it is the histological response to infection with HPV. The possibility of a woman with a CIN1 diagnosis developing cancer does not exceed 30%, so the preferred action is appropriate monitoring and testing.

  - With previous cytology of ASC-US or LSIL: co-test (if > 30 years old) or cytology-colposcopy at one year or when postpartum if pregnant.
  - With previous cytology of ASC-H, AGC, or HSIL:
    - a) Co-test (if > 30 years old) or cytology-colposcopy at one year or when postpartum if pregnant.
    - b) Review previous cytological material.
    - c) Excisional treatment is reserved for those at risk of loss to follow-up or repeated atypical cytology. Never perform in pregnant women.
  
- » **Histological diagnosis: “High-grade cervical intraepithelial neoplasia” (CIN2/3).**

One of every three high-grade intraepithelial lesions progresses to cancer, so treating these lesions is necessary, except:

  - If it is a small lesion, controllable via colposcopy, without endocervical affectation, with possible follow-up.
  - During pregnancy when there is:
    - a) No colposcopic suspicion of invasion.
    - b) Possibility of cytological-colposcopic check-up every three months.



### 3. CONCLUSIONS

Determining whether the patient is an HPV carrier is appropriate after age 30. HPV is very common and transient under age 30, making testing inefficient.

For patients with HPV presence and low-grade cytological-colposcopic alterations, use of a *Coriolus versicolor*-based vaginal gel is recommended. This recommendation is based on early clinical trial data availability, real-world use, a robust benefit-risk ratio, and the lack of alternatives in routine clinical practice.

## BIBLIOGRAPHY

1. Castellsagué X, Iftner T, Roura E, Vidart JA, Kjaer SK, Bosch FX, et al.: Prevalence and genotype distribution of human papillomavirus infection of the cervix in Spain: the CLEOPATRE study. *J Med Virol*. 2012;84:947-56.
2. Bosch FX. Presented at EUROGIN 2015. Seville, Spain.
3. Castellsagué X, San Martín M, Cortés J, González A, Remy V. Impacto de la vacuna teravalente frente al virus del papiloma humano (VPH) tipos 6, 11, 16 y 18 en las enfermedades asociadas al VPH en España [Impact of the tetravalent vaccine against human papillomavirus (HPV) types 6, 11, 16 and 18 in diseases associated with HPV in Spain]. *Prog Obstet Ginecol*. 2008;51:520-30.
4. Torné A, del Pino M, Cusidó M, Alameda F, Andía D, Castellsagué X, et al. Guía de cribado del cáncer de cuello de útero en España [Spanish Cervical Cancer Screening Guidelines] 2014. *Prog Obstet Ginecol*. 2014;57(supl.1):1–53.
5. Oncoguía SEGO: Prevención del cáncer de cuello de útero [SEGO Oncoguides: Cervical cancer prevention]. Guías de práctica clínica en cáncer ginecológico y mamario [Practical clinical guidelines in gynecological and breast cancer]. Publicaciones SEGO, October 2014. ISBN: 978-84-612-7418-2–Vol.9.
6. Lee PN, Thornton AJ, Hamling JS. Epidemiological evidence on environmental tobacco smoke and cancers other than lung or breast. *Regul Toxicol Pharmacol*. 2016;80:134-63.
7. Asociación Española contra el Cáncer [Spanish Association Against Cancer]: <https://www.aecc.es/TeAyudamos/informaryconcienciar/Programas/Paginas/Dejardefumar.aspx> Last accessed: 11/16/2017.
8. Palacios S, Losa F, Dexeus D, Cortés J. Beneficial effects of a *Coriolus versicolor*- based gel on cervical epithelization, vaginal microbiota and vaginal health: a pilot study in asymptomatic women. *BMC Women's Health* [Internet]. 2017. Doi: 10.1186/s12905-017-0374-2.
9. Gálvez J, González SP, Serrano L, Vezza T, Garrido-Mesa J, Algieri F; Rodríguez- Cabezas ME Rodríguez-Nogales A. Effect of a *Coriolus versicolor*-based vaginal gel on cervical epithelization and vaginal microbiota in HPV-positive women with normal cytology and colposcopy: a pilot study. *BMC Women's Health* (pending publication with reference BMWH-D-19-00067R1).

10. Palacios S, Dexeus D, Serrano L, González SP, López AC, Centeno C, et al.: Design of a phase 2 randomised, controlled, parallel-group, open-label multicenter trial to explore the effectiveness of a *Coriolus versicolor*-based gel on restoration of cervicovaginal mucosal lesions caused by human papilloma virus (The PALOMA Clinical Trial). *ClinicalTrials.gov* Identifier: NCT04002154.
  
11. Seydoux G, Cortés J, Serrano L, López AC, González S, Palacios S, Dexeus D, Centeno C, Coronado P, de la Fuente J, López JA, and Vanrell C. Efficacy of a Multi-Ingredient Vaginal Gel in Normalizing HPV-Dependent Cervical Lesions and HR-HPV Clearance. *J Low Genit. Tract Dis.* 2020 April; 24(1S):S16. doi:10.1097/LGT.0000000000000538
  
12. Multicenter, randomized, open, parallel, control group clinical trial to explore Papilocare Gel efficacy to repair cervical mucosa with HPV high-risk lesions (PALOMA 2). *ClinicalTrials.gov* Identifier: NCT04199078
  
13. Emsellem C, Cortés J, de Santiago J, Cos A, Lago I, Espinosa G, Olalla MA, Fiol G, Lozada C, García C, and Agenjo M. Efficacy of a Multi-Ingredient Vaginal Gel in Repairing HPV-Dependent Cervical Lesions in Real-Life: Interim Analysis. *J Low Genit. Tract Dis.* 2020 April; 24(1S):S16-S17. doi:10.1097/LGT.0000000000000538
  
14. Gaslain Y, Cortés J, Dexeus D, Palacios S, Serrano L, Seydoux G, Gajino C, Marín E, and Riera M. Effect of a Multi-Ingredient Vaginal Gel in High-Risk HPV Infected Patients: Results of Different Studies. *J Low Genit. Tract Dis.* 2020 April; 24(1S):S15-S16. doi:10.1097/LGT.0000000000000538
  
15. Cortés J, Dexeus D, Palacios S, Serrano L. La Prevención del Cáncer Ginecológico en la Asistencia Privada [The Prevention of Gynecological Cancer in Private Care]. *Prog Obstet Ginecol.* 2017;60: 160–75.
  
16. Bosch FX, Catellsagué X, Cortés J, Puig-Tintoré LM, Roura E, de Sanjosé S, et al. Estudio AFRODITA [AFRODITA Study]. GSK Eds. 2009. ISBN: 978-84-691-8490-5.
  
17. Serrano L, López A, González S, et al. Efficacy of a *Coriolus versicolor*-based vaginal gel in repairing HPV-dependent cervical lesions (ASCUS/LSIL) in three patients groups according to the risk of HPV strains. *Int J Gynecol Cancer* 2019;29:A154.