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Impact of the HPV Vaccine in Women Treated for High-Grade Cervical Intraepithelial Neoplasia. Is it Equally Effective in All Patients?

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ABSTRACT

Objectives: To evaluate the role of the human papillomavirus (HPV) vaccination in terms of clinical relapse prevention in women treated for high grade cervical intraepithelial neoplasia (HSIL) in relation to different clinical factors.

Material and Methods: A retrospective review of 242 patients diagnosed with HSIL and who had undergone loop diathermy conization (LEEP) in the Obstetrics and Gynecology Department at Santa Lucia University Hospital (HUSL) between January 2011 and May 2015. 42.6% of the patients received the HPV vaccine (bivalent or tetravalent) immediately before or after conization. Follow up was conducted at 3,6,12,18, and 24 months during the first two years, and then annually to detect any recurrence of HSIL disease. For this review, we took into account the HPV type at the time of diagnosis and the state of the conization margins to analyze vaccine effectiveness.

Results: Of the 242 patients, 27 (11.1%) developed H-SIL recurrence post-LEEP. Recurrence was detected during follow-up in 5 of the vaccinated patients (4.8%), versus 22 of the 139 unvaccinated patients (15.8%) ($p<0.05$). The median age was 6 years higher in the unvaccinated group. The multivariate lineal regression analysis shows that the only two variables that act as independent indicators of HSIL recurrence are age at the time of conization ($p<0.05$) and not being vaccinated for HPV ($p<0.05$). Regards the HPV type, patients infected with a vaccine virus (16/18) and vaccinated showed lower risk of clinical relapse (5.8%) than patients unvaccinated (26.3%) ($p<0.01$). When surgical margins are free of disease, the risk of having a recurrent lesion is lower in patients who had received the vaccine (2.5%) as opposed to those who had not (17%) ($p<0.01$).

Conclusion: HPV vaccination appears to be a recommendable preventative strategy in reducing the risk of recurrent disease for patients treated for HSIL. This protective power of the vaccine seems to be greater in women infected with 16/18 virus and for those with unaffected conization margins.

Keywords: Human papillomavirus, Vaccine, Recurrent disease, Conization

Abbreviations: VBAC : Vaginal birth after caesarean; TOLAC: Trial of labor after cesarean; CS: Cesarean section; PROM: Premature rupture of membranes; ARM : Artificial rupture of membranes; GDM : Gestational diabetes mellitus; C: Catheter; O: Oxytocin

INTRODUCTION

Infections by the Human Papillomavirus (HPV) are associated with a significant burden of morbidity and mortality worldwide [1]. HPV genotypes 16 and 18 cause approximately 70% of cervical cancers and 50% of precancerous cervical lesions [2]. The effect of HPV vaccination against infection and HPV-related clinical signs has been clearly demonstrated after more than ten years of phase III clinical trials with more than 30,000 women, including those older than 26 years [3]. Up until now three different vaccines, which vary in the number of HPV types they contain and target, have been clinically developed (bivalent, quadrivalent and 9-valent vaccine) [4-6]. The efficacy of these vaccines is explained by the induction of neutralizing antibodies that prevent infection by binding to virions and preventing them from entering the host cell [7].

Women after treatment for high-grade cervical intraepithelial

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neoplasia (HSIL) are 4-5 times more at risk than general population up to 10-20 years [8] and the level of HSIL recurrence is 5-17% for any of the ablation or excisional treatments [9]. The average relapse time is between 9-10 months approximately, within a range from 3 to 23 months [10]. After using cervical conization as a treatment, HPV clearance occurs in 50% of patients [11]. Post treatment HPV persistence is considered the major factor of relapse [12]. Testing HPV 6 months after conization, could be a recurrent disease score with more sensitivity and specificity than cytology [13]. There are factors that had been associated with a major risk of relapse or virus persistence, such as surgical margins [14], immunosuppression [15] and advanced patient age [16].

There are different studies that suggest that vaccine could be helpful for preventing cervical lesions relapse after excisional treatment [17-21]. This fact led some international guidelines [22] to recommend HPV vaccination in order to prevent the disease appearing again after the treatment. The Autonomous Community of the Region of Murcia started following this procedure in April 2014 [23], becoming the first Spanish Region to implement this measure.

The purpose of this review is to evaluate if HPV vaccine is equally effective in all patients after excisional treatment to reduce the recurrence of HSIL or if there would be clinical factors that would advise vaccination.

MATERIALS AND METHODS

This is a retrospective review of the digitized medical records of 242 patients, who were between 18 and 65 years of age, diagnosed with HSIL and who had undergone loop diathermy conization (LEEP) in the Obstetrics and Gynecology Department at Santa Lucia University Hospital (HUSL) between January 2011 and May 2015.
The 242 who were included in the study fit the following criteria:

- HSIL histologically confirmed after conization (LEEP)
- Patients diagnosed with HPV pre-conization
- Patients who had not received HPV vaccination before developing HSIL

Twelve patients were excluded for hysterectomies post conization due to an infiltrative cervical cancer and 10 for residual HSIL (≤ 6 meses). Conization was performed with loop diathermy and local anesthetic, obtaining a piece that was referenced at 12 hours accompanied by endocervical curettage.
We recommended both of the two vaccines (bivalent or quadrivalent) at the moment of the conization. The first dose of any of both vaccines had been administered 0-1 month before or 0-1 month after conization. Patients were classified in two groups: unvaccinated and vaccinated, the latter were subdivided into two subgroups based on the type of vaccine received, bivalent or tetravalent. Patients underwent post-operative examination after 3,6,12,18, and 24 months during the first two years, and then annually at the Cervical Pathology Unit at HUSL to detect any recurrence of disease caused by HPV. The criteria to define residual disease or recurrent disease was determined by the histological HSIL diagnosis in the colposcopy-guided biopsy or endocervical biopsy at ≤6m (residual disease) orat≥12m (recurrence disease). For the statistical analysis, the results of the cervical biopsy during follow-up were grouped in negatives (normal, cervicitis or LSIL) or positives (HSIL or greater degree of lesion).

For this review, we took into account the HPV type (16/18 or no 16/18) at the time of diagnosis and the state of the conization margins (contacted/ no-contacted) to analyze the results.

STATISTICAL METHODS

The primary event was the appearance of CIN 2-3 recurrence after conization. The normality of continuous variables was tested by Kolgomorov-Smirnov of Shapiro-Wilk tests, as appropriate continuous variables are presented as the median (interquartile range [IQR]) for non-normally distributed data or mean (standard deviation [SD]) for normally distributed data. Comparisons of group differences for continuous variables were made by the Mann-Whitney U-test or the Student's t-test, as appropriate. Categorical variables are presented as a number and percentage in each category. The significance of differences in percentages was tested by the Chi-squared test. Univariate and multivariate binary logistic analyses were performed with the previously defined variables for the prediction of recurrence disease and the odds ratios (OR) were displayed. The statistical analysis was performed using SPSS v. 20.0. All P- values < 0.05 were considered statistically significant.

RESULTS

A total of 242 patients met the requirements of the study to be included, of whom had follow-up care for at least two years. The median age of the 242 patients was 36 years. Of these, 28 patients (11.6%) were between 18-25 years old, 92 patients (38%) between 26-35 years old, 62 patients (25.6%) between 35-45 years old and 60 patients were older than 45 years. 88.8% of the patients were of Spanish nationality. Of the 242 patients, 27 (11.1%) had recurrence. The average time between recurrence and conization was 14.2 months (6-24 months). Of the 242 patients included in the analysis, 103 patients (42.6%) had been vaccinated, of them 70 patients (68%) received the bivalent vaccine and 33 patients (32%) the tetravalent vaccine. The moment of vaccination was 0-1 month before conization in 46 patients (44.6%) and 0-1 month after conization in 57 patients (55.4%).

The baseline characteristics of the patients included in the different study groups were fairly homogeneous in terms of country of origin, reasons for conization, state of cone margins and positivity for 16/18 genotypes. Regarding HPV test, 96.7% (234/242) of the total of patients were positive for high risk-HPV (HR-HPV), 51.4% (120/234) were positive for HPV 16/18 and 48.7% (114/234) were positive for other HR-HPV types. The median age was 6 years higher in the unvaccinated group, being identical in the two vaccinated groups. We found that age has a significant influence on recurrence (1.037 per additional year of the patient at the time of conization).

Recurrence was detected during follow-up in 5 of the vaccinated patients (4.8%), versus 22 of the 139 unvaccinated patients (15.8%) ($p<0.05$). Among the vaccinated patients that showed recurrence, 3 patients had received the tetravalent vaccine (60%) and 2 the bivalent vaccine (40%). The univariate analysis demonstrated significant differences between the age variation at the time of conization and the vaccination variable ($p<0.05$) **(Table 1)**. The multivariate lineal regression analysis shows that the only two variables that act as independent indicators of HSIL recurrence are age at the time of conization ($p<0.05$) **(Table 1)** and not being vaccinated for HPV ($p<0.05$) **(Table 1)**. Neither the type of vaccine nor the time of vaccination showed a significant association with the onset of recurrence.

Table 1. Uni and multivariate analysis.

Univariate Analysis	**Multivariate Analysis**			
Variable	OR (IC 95%)	p	OR (IC 95%)	**p**
Age	1.050 (1.014-1.088)	0.006*	1.037(1.0-1.076)	**0.04***
Positive Margins	1.844 (0.795-4.276)	0.154		
Vaccination	0.271 (0.099-0.743)	0.011*	0.360(0.125-1.032)	**0.03***
Type of Vaccine (Tetravalent vs Bivalent)	3.4(0.54-21.41)	0.192		
Time of Vaccination (after vs before)	0.521(0.083-3.529)	0.486		
Type of HPV baseline (16,18 vs other RA)	**2.059 (0.884-4.794)**	**0.094**		

Influence of basal virus type on the relationship between vaccination status and the development of recurrent disease

As **Table 2** displays, if patient has 16 and/or 18 HPV serotype, the risk of having a recurrent lesion is clearly lower in vaccinated patients (5.8%) comparing to the ones who are not (26.3%). This difference is statistically significant even after adjustment for age ($p<0.01$).

However, when there are other virus serotypes present, there is not a statistical significance for having relapse between the two study groups ($p=0.646$).

Influence of margin status on the relationship between vaccination status and the development of recurrent disease

As **Table 3** shows when surgical margins are free of disease, the risk of having a recurrent lesion is lower in patients with vaccine (2.5%) than ones who does not (17%). This is statistically significant even after adjustment for age ($p< 0.01$). However, when surgical margins are affected there is no statistical significance found for relapse between patients vaccinated and patients not ($p= 0.889$).

Lesión residual/Recurrente

Table 2. Percentage of patients with residual/recurrent lesions depending on vaccine and stratifying by being infected with 16 and/or 18 at conization time. P-values are obtained using logistic regression for age conizations adjusted.

Virus 16 y/o 18	Vacuna	Datos	Casos	%	P-valor
		(C)	(D)	(D/C)	
No	Si	50	2	(4.0%)	**0.646**
	No	58	6	(10.3%)	
Si	Si	52	3	(5.8%)	**<0.01**
	No	**57**	**15**	**(26.3%)**	

Lesión residual/Recurrente

Table 3. Percentage of patients with recurrent lesion, depending on vaccine and stratifying by the status of surgical margins. P-values are obtained using logistic regression for age conizations adjusted.

Márgenesafectados	Vacuna	Datos	Casos		%	P-valor
		(C)		(D)	(D/C)	
No	Si	79	2		(2.5%)	**<0,01**
	No	88	15		(17.0%)	
Si	Si	25	3		(12.0%)	**0.889**
	No	**28**	**6**		**(21.4%)**	

DISCUSSION

The increased risk of cervical cancer in women treated for HSIL may be due to new HPV infections or residual lesions after an incomplete treatment [24].

The prevention of recurrences has an important impact on economical saving in health systems by reducing clinical follow-up and second treatments. Besides, a second conization is associated with a two times higher likelihood of premature birth [25].

Although evidence shows that the vaccine may have a protective role for the recurrence of HSIL [17-21], there are also studies against this idea [26]. So far, the SPERANZA study is the only prospective evaluation of the clinical effectiveness of HPV vaccine in reducing CIN2+ recurrent disease in women who underwent cervical conization for cervical HSIL and FIGO stage Ia1 cervical cancer. Quadrivalent HPV-vaccination injected 30 days after conization for CIN2+ (HSIL) lesion reduced the risk of subsequent HSIL recurrence by 81.2% (95% CI, 34,3-95,7), irrespective of causal HPV type. Thus, it can be assumed that, when the cells with integrated HPV in the primary lesion are removed by surgery, the antibodies evoked by the HPV-vaccine, performed after the surgical treatment, can prevent the HPV reactivation/ re- infection or the de novo HPV infection [20].

Unlike other studies, in ours, two types of vaccine were analyzed. We observed that much of the influence of vaccination on the prevention of recurrence, was due to the younger age of the patients. However, when we selected patients by vaccine virus type at the time of diagnosis or by the affection of the surgical margins, the protective power of vaccination was clearly increased despite the age of the patients. It is likely that a non-personalized HPV vaccine administration during the post conization follow-up was expensive and unnecessary [27].

CONCLUSION

HPV vaccination can be considered as a preventative strategy for patients after HSIL treatment reducing the cases of recurrence and the overall risk of any related HPV disease. This protective power of the vaccine seems to be greater in women infected with 16/18 virus and for those with not affected margins of conization.

Nevertheless, a randomized, placebo-controlled study, with a larger number of patients, would be required to confirm our findings.

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