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Cervical Pathology Following HPV Vaccination in Greece: A 10-year HeCPA Observational Cohort Study

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Abstract. *Background: In Greece the population-level impact of HPV vaccination is unknown due to lack of official registries. This study presents in a pragmatic frame the comparison of cervical pathology data between HPV-vaccinated and unvaccinated women referred for colposcopy. Patients and Methods: This is an observational prospective cohort study performed in 7 academic Obstetrics and Gynaecology Departments across Greece between 2009-2019. Cases were women that had completed HPV vaccination before coitarche and were referred for colposcopy due to abnormal cytology. For each vaccinated woman an unvaccinated matched control was selected. Results: A total of 849 women who had been vaccinated before coitarche and 849 unvaccinated controls were recruited. The combination of cytological, colposcopic and molecular findings necessitated treatment in only a single case among vaccinated (0.1%) and in 8.4% among unvaccinated. Conclusion: HPV vaccination at a proper age can markedly reduce development of severe cervical precancers and consequently the need for treatment, as well as their long-term related obstetrical morbidity.*

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Cervical cancer had been one of the most common malignancies in females prior to introduction of Pap test and initiation of screening. Screening programmes (secondary prevention) have led to reduced cervical cancer incidence and mortality rates (1, 2), thanks to the early discovery of pre-invasive cervical lesions and their treatment before progression to cancer. Human papillomavirus (HPV) vaccination (primary prevention) promises to further reduce, or even eliminate, cervical cancer burden (3). The efficacy of HPV vaccines has been documented in randomised clinical trials and is up to 99% for prevention of cervical intraepithelial neoplasia (CIN2+) related to vaccine-specific HPV types in HPV-naïve women (4). Observational data have also shown a reduction of CIN2+ lesions in the general population (5).

Coverage of cervical cancer screening varies around the globe and is approximately 20% for developing and 60% for developed countries (6). The same pattern is also observed for HPV vaccination, with higher uptake rates in high-income countries (more developed *vs.* less developed countries: 5.4% *vs.* 0.5% for all ages; 33.6% *vs.* 2.7% for ages 10-20 years) (7). In Greece there are no official registry-based records for coverage with regards to screening (which is opportunistic) or HPV vaccination (which, albeit being state-funded until 18 years of age, is not based on a national school-based programme but rather on parents' initiative). Nonetheless, most authorities accept that coverage for both screening and HPV vaccination lies around 30-40%.

The aim of this study was to present cervical pathology data (*i.e.* cytological and colposcopic results) for vaccinated women who were referred to academic colposcopy clinics across Greece due to abnormal cytology of any grade, and compare them to the findings of matched unvaccinated controls.

Patients and Methods

This observational prospective cohort study took place in the colposcopy clinics of the majority of academic Departments of Obstetrics and Gynaecology in Greece (Ioannina, Alexandroupolis, 3 Departments in Thessaloniki, Larissa and Patras), during 2009-2019. The coordinating centre was the academic Department of Obstetrics and Gynaecology in Ioannina.

For women that had completed HPV vaccination before sexual debut and were referred to the colposcopy clinics due to abnormal cytology of any grade, demographic data (age, education level), lifestyle risk (age at onset of sexual intercourse, number of sexual partners, smoking, frequency of condom use), as well as the results of the referral cytology, were recorded. All colposcopic evaluations were performed by the lead colposcopist in each Department. If necessary, HPV biomarkers (especially HPV mRNA test but also HPV DNA test or p16) were ordered. The policy in all clinics was not to perform punch biopsies unless a high-grade lesion was suspected cytologically or colposcopically, but instead take into account cytology, colposcopy, HPV biomarkers (mostly mRNA, if indicated) and lifestyle risk before deciding whether treatment (usually large loop excision of the transformation zone; LLETZ) is warranted.

For each HPV-vaccinated patient, an unvaccinated control (1:1) matched for age (±3 years), education (tertiary or secondary), lifestyle (low-, middle- or high-risk) and date/place of referral (*i.e.* as close as possible after the referral of the case at the same Department), was selected. Women who initiated HPV vaccination after coitarche or who had started but not completed the full HPV vaccination course at coitarche or time of referral were excluded from the study.

Results

A total of 849 vaccinated women that had completed the full HPV vaccination course before onset of sexual intercourse and were referred for colposcopy due to abnormal cytology of any grade were eligible. A total of 849 matched unvaccinated controls were also selected.

Table I. *Results of referral cytology.*

Cytology	Vaccination before coitarche (n=849)	Controls (n=849)
HPV	313 (36.9%)	280 (33%)
ASC-US	306 (36%)	209 (24.6%)
LSIL	228 (26.9%)	301 (35.5%)
HSIL	2 (0.2%)	59 (6.9%)

ASC-US: Atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial neoplasia; HSIL: high-grade squamous intraepithelial neoplasia.

The percentage of cytological high-grade squamous intraepithelial lesion (HSIL) increased from 0.2% (2/849) for women vaccinated before coitarche to 6.9% for unvaccinated women (Table I). Respectively, the colposcopic impression was HSIL for 0.2% (2/849) of vaccinated women and 8.7% of unvaccinated controls (Table II).

Only one woman (0.1%) who had been vaccinated before onset of sexual intercourse required treatment (LLETZ), after taking cytology, colposcopy and HPV mRNA test into consideration. Her final histopathological diagnosis was cervical intraepithelial neoplasia grade 2 (CIN2). The other vaccinated woman with cytological and colposcopic HSIL was adolescent and there was no suspicion of CIN3+. Because CIN2 is very likely to spontaneously regress at a young age (8, 9), a decision for conservative management was made. On the other hand, 71 controls (8.4%) underwent treatment, in whom the final histopathological diagnosis was CIN3 in 37 women (4%) (Table III).

Discussion

This was an observational study comparing cervical pathology between HPV-vaccinated women at the appropriate age (*i.e.* before onset of sexual intercourse) and unvaccinated controls matched for several known risk factors of cervical carcinogenesis. Our results showed that cytological and colposcopic findings in women who were referred for colposcopy and had been vaccinated before coitarche, tended to be much less severe than in unvaccinated women. Respectively, only one woman (0.1%) in the group vaccinated before coitarche needed treatment, while treatment was warranted for a significantly higher percentage in unvaccinated women (8.4%, >80-times higher). Although CIN treatments are highly effective and only 5-10% of treated women are diagnosed with residual or recurrent disease (10-13), they are associated with an increased risk of preterm birth and other adverse pregnancy outcomes in subsequent pregnancies (14-19). Less radical treatments might decrease the risk of reproductive morbidity

Table II. *Results of colposcopy.*

Colposcopy	Vaccination before coitarche (n=849)	Controls (n=849)
No AWE	180 (21.2%)	119 (14%)
Metaplasia	34 (4%)	21 (2.5%)
HPV	471 (55.5%)	491 (57.8%)
LSIL	162 (19.1%)	144 (17%)
HSIL	2 (0.2%)	74 (8.7%)

AWE: Aceto-white epithelium; LSIL: low-grade squamous intraepithelial neoplasia; HSIL: high-grade squamous intraepithelial neoplasia.

Table III. *Final histopathological diagnosis in women undergoing treatment.*

Histological examination of excised cone	Vaccination before coitarche (n=849)	Controls (n=849)
Treatment not needed	848 (99.9%)	778 (91.6%)
CIN1	0	9 (1.1%)
CIN2	1 (0.1%)	25 (2.9%)
CIN3	0	37 (4.4%)

but potentially compromise oncological outcomes; this balance between obstetrical and oncological outcomes can be better comprehended by a clinical ranking of CIN treatments through a network meta-analysis (20, 21). HPV vaccination at the appropriate age (*i.e.* before beginning of sexual life) greatly reduces the risk that a women will be diagnosed with CIN2+ and will require treatment during her lifetime.

HPV vaccines are more effective in HPV-naïve women (22). HPV vaccines are also more effective in younger compared to older individuals (regardless of sexual history), because their immunogenicity has been found to be stronger in ages under 15 years compared to older adolescents/adults (23, 24). Therefore, children aged 11-13 years should be the target group of HPV vaccination programmes. HPV vaccines can still be administered to sexually-active unvaccinated women, since they provide full protection against HPV types to which these women have not been exposed yet and limited protection against HPV types for which they are HPV DNA-negative, but seropositive (22). However, vaccination of sexually-active women is generally less cost-effective (25) and should be considered only on an individual basis taking into account relationship status and other lifestyle parameters. The role of HPV vaccination in unvaccinated women undergoing CIN treatment is not clear due to lack of evidence from randomised studies, but observational studies have shown that it decreases the risk of preinvasive recurrence (26, 27). A recent systematic review and meta-analysis showed that women previously treated for CIN are at increased long-term risk of invasive cervical and other HPV-related cancers (28), thus HPV vaccination after CIN treatment could also reduce the incidence of these HPV-related cancers in this population.

Our conclusions agree with a meta-analysis of observational studies that showed that HPV vaccination has reduced CIN2+ diagnoses in the general population by 51% in ages 15-19 and 31% in ages 20-24 (5). A recent Scottish observational study showed that vaccinating 90% of girls reduced CIN2+ diagnoses in first screening round by 88%. CIN2+ diagnoses were reduced not only in vaccinated but also in unvaccinated individuals by an impressive 67% thanks to herd immunity (29). HPV vaccination has been also found to reduce cervical HPV infections (HPV 16/18 by 83% in ages 15-19, 56% in ages 20-24 and 37% in ages 25-29; HPV 31/33/45 by 54% in ages 15-19) and anogenital warts (by 67% in ages 15-19, 54% in ages 20-24 and 31% in ages 25-29) (5). Because of the long natural history of HPV infection (30), it is still early to document a reduction in cervical cancer diagnoses. However, it is projected that cervical cancer will be eradicated in some countries within 20 years (3). In Greece, the Hellenic Society of HistoPathology has been running a pathology-based cancer registry since 2009 (31) with participation of almost all pathology laboratories in the public and private sector, recording the data of pre-invasive and invasive cervical disease diagnoses. Preliminary and unpublished data have shown that between the years 2009 and 2016 there has been a reduction of CIN diagnoses, probably due to HPV vaccination.

Unfortunately, HPV vaccination coverage in Greece is low and estimated at around 30-40%, and HPV prevalence is still high (32). The reason for this low coverage is the fact that there is no national school-based programme and the onus of HPV vaccination lies on the parents. The main source of information for parents is paediatricians and gynaecologists, many of whom give a lukewarm (or even a negative) response when asked whether their children should be vaccinated against HPV, citing ignorance or even possible side-effects. Another source of information is the Internet where many websites deter parents from vaccination. However, more than 270 million doses have been administered in the last 10 years since HPV vaccination introduction and the evidence is clear that HPV vaccines are very safe (33, 34). Clinicians should be better informed so that they strongly encourage parents to vaccinate their children. Our study could also be an impetus for higher coverage rates in Greece.

Strengths and limitations. One strength of our study is that we selected controls matched for age, education and all known lifestyle risk factors associated with a higher risk of HPV infection and cervical cancer (age at onset of sexual intercourse, number of lifetime sexual partners, smoking, frequency of condom use). In addition, this study took place soon after the introduction of HPV vaccination up to now in many academic colposcopy clinics across Greece with a high volume of referrals. One limitation of this study is that it is at risk of selection bias, since we were able to show a reduction of high-grade abnormalities after HPV vaccination only in a specific population referred for colposcopy and not in the general population. To document a reduction of CIN2+ in the general population, official nationwide registries recording CIN2+ diagnoses from public and private health sector linked with vaccination status are needed. There is a lack of such records not only in Greece but also in many other developed countries, although an initiative to collect data from all pathology laboratories has started in Greece. Finaly, it is possible that this relatively small subgroup of Greek society vaccinated before coitarche is better informed of prevention policies or health issues in general due to other potential confounders we did not adjust for. Despite these shortcomings, this Greek reality is comparable to other developed countries and the conclusions of the present study are likely applicable globaly.

Conflicts of Interest

The Authors have nothing to disclose.

Authors' Contributions

This study was designed by EP. Data from the participating hospitals were collected by EP, and were interpreted by all authors. The manuscript was drafted by EP and AA, and was revised by all authors. EP is the guarantor.

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