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Practice Guideline

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Updated clinical guideline for human papillomavirus vaccine: the Korean Society of Gynecologic Oncology guidelines

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ABSTRACT

Since the human papillomavirus (HPV) vaccine guidelines were developed by the Korean Society of Gynecologic Oncology (KSGO) in 2011, 2016, and 2019, several recent studies on the efficacy and safety of HPV vaccines in middle-aged women and men have been reported. Furthermore, there has been an ongoing debate regarding the efficacy of the HPV vaccine in women with prior HPV infection or who have undergone conization for cervical intraepithelial neoplasia (CIN). We searched and reviewed studies on the efficacy and safety of the HPV vaccine in middle-aged women and men and the efficacy of the HPV vaccine in patients infected with HPV and those who underwent conization for CIN. The KSGO updated their guidelines based on the results of the studies included in this review.

Keywords: Papillomavirus Vaccines; Practice Guideline; Middle Aged; Female; Male

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Conflict of Interest

Kyung-Jin Min and Seok Ju Seong serve as editors or editorial advisor of the Journal of Gynecologic Oncology (JGO), but have no role in the decision to publish this article. No other conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: C.H.W., M.K.J., L.J.K., L.K..H., L.J.W.; Data curation: C.H.W., M.K.J., K.S.H., K.K., K.S., S.S.J., S.Y.J., L.K.H., L.S.W., L.J.W., J.W., K.Y.T., L.J.K.; Formal analysis: C.H.W., M.K.J., K.S.H., K.K., K.S., S.S.J., S.Y.J., L.K.H., L.S.W., L.J.W., J.W.; Investigation: C.H.W., M.K.J., K.S.H., K.K., K.S., S.S.J., S.Y.J., L.K.H., L.S.W., L.J.W., J.W.; Methodology: C.H.W., M.K.J.; Project administration: L.J.K.; Software: C.H.W., M.K.J.; Supervision: L.J.K.; Writing - original draft: C.H.W., M.K.J.; Writing - review & editing: C.H.W., M.K.J., K.S.H., K.K., K.S., S.S.J., S.Y.J., L.K.H., L.S.W., L.J.W., J.W., K.Y.T., L.J.K.

1. Key question 1: what is the recommended age for the 3-dose schedule of the HPV vaccine?

- The optimal age for the 3-dose schedule of the quadrivalent HPV vaccine is 9–45 years in girls and women and 9–26 years in boys and men (IA).
- The optimal age for the three-dose schedule of the bivalent HPV vaccine is 9–45 years in girls and women (IA) and 9–25 years in boys and men (IIC).
- The optimal age for the three-dose schedule of the nonavalent HPV vaccine is 9–45 years in girls and women and 9–26 years in boys and men (girls and women aged 9–26 years, IA; women aged 27–45 years, IIIB; and boys and men aged 9–26 years, IA).

2. Key question 2: is the HPV vaccine effective in women already infected with HPV?

- In HPV-infected women already, the administration of the quadrivalent HPV vaccine can lower the risk of infection with an uninfected HPV subtype (IIB).
- In HPV-infected women already, the administration of the bivalent HPV vaccine can lower the risk of infection with an uninfected HPV subtype (IIB).
- In HPV-infected women already, the administration of the nonavalent HPV vaccine can lower the risk of infection with an uninfected HPV subtype (IIB).

3. Key question 3: is the HPV vaccine effective in preventing the recurrence of HPV-related diseases in patients who underwent conization?

- In women who underwent conization, the administration of the quadrivalent HPV vaccine can reduce the risk of recurrence of HPV-related diseases by preventing infection with the corresponding viral subtype (IIB).
- In women who underwent conization, the administration of the bivalent HPV vaccine can reduce the risk of recurrence of HPV-related diseases by preventing infection with the corresponding viral subtype (IIB).
- In women who underwent conization, the administration of the nonavalent HPV vaccine can reduce the risk of recurrence of HPV-related diseases by preventing infection with the corresponding viral subtype (IVB).

INTRODUCTION

High-risk human papillomavirus (HPV) infection is associated with the incidence of cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers and is responsible for 5%–10% of all cancers [1]. In particular, cervical cancer accounts for 80% of HPV-related cancers [2]. HPV is the most widespread sexually transmitted infection, with a prevalence of approximately 11%, and persistent HPV infection is a major cause of cervical precancerous lesions and cancer [3,4]. Prophylactic vaccination against high-risk HPV can prevent precancerous lesions of cervical cancer and cervical cancer, as well as cancers that occur in men, such as oropharyngeal cancer, anal cancer, and penile cancer [5-8].

To date, three HPV vaccines have been approved; they can prevent infection with HPV types 16 and 18, which cause approximately 70% of cervical cancers and other HPV-related tumors [6,9-16]. The quadrivalent vaccine can further prevent infection with HPV types 6 and 11, which account for 90% of genital warts [17]. The most recently introduced 9-valent vaccine can protect against infection with 5 additional types of high-risk HPV (31, 33, 45, 52, and 58), in addition to these 4 types of HPV [18].

The Korean Society of Gynecologic Oncology (KSGO) provided and updated the clinical recommendations for HPV vaccines in 2011 and 2016 [19,20] and announced a recommendation for the 9-valent HPV vaccine in 2019 [8].

However, many studies have been recently reported on the effectiveness of HPV vaccines in middle-aged women and men. Additionally, the effectiveness of HPV vaccines in women already infected with HPV or who have undergone conization for precancerous cervical lesions is controversial. Therefore, updated recommendations for HPV vaccines are required.

METHODS

1. Developing the recommendations for HPV vaccine

The key questions and scope of guideline were derived through a meeting of the committee. The committee tried to develop a guideline by systematically searching for the latest literature related to vaccines and evaluating evidence.

2. Strategy of literature search

According to the criteria for selection and exclusion criteria of all key questions, 2 reviewers per document independently selected and excluded the literature. The primary selection and exclusion were made by looking at the title and the abstract, and the literature selected by even 1 reviewer was searched for the original article. After that, the committee members selected and excluded based on the original article, and if there was no agreement between the members, the final selection and exclusion was decided through discussion. Articles were searched on Ovid-MEDLINE, Ovid-Embase, and Cochrane Library.

3. Quality assessment of literature

In the selected literature, randomized controlled clinical researches were evaluated using risk of bias (ROB) of Cochrane, and non-randomized observational studies were assessed by NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES. The quality of the literature is assessed independently by 2 members, and it was determined by an agreement between the 2 members if the quality of the literature is different.

4. Summary of evidence and data extraction

Data extraction from the final selected literature was carried out independently by 2 working-level members according to the predetermined data extraction form. If data extracted were different between the 2 members, final settlement was made by discussion. A summary of evidence is attached to the **Data S2**. Classification of evidence and recommendations are displayed in **Tables 1** and **2**.

Table 1. Level of evidence

Level	Type of evidence
I	RCTs, or overwhelming evidence from observational studies
II	RCTs with important limitations, or exceptionally strong evidence from observational studies
III	Observational studies, or RCTs with notable limitations
IV	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations
V	No evidence or difficult to analysis or based on expert opinion

RCT, randomized controlled trial.

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Table 2. Grade of recommendations

Grade	Descriptor
A	Strongly recommended, strong evidence
B	Generally recommended, moderate evidence
C	Optional, insufficient evidence
D	Generally not recommended
E	Never recommended

EVIDENCE OF HPV VACCINES

The process of developing clinical guidelines and an evidence table for each key question is addressed in the Supplementary Materials (**Data S1** and **S2**).

1. Key question 1: what is the recommended age for receiving the HPV vaccine via a 3-dose schedule?

In 2016, the KSGO recommended 9–26 years of age as the appropriate age for receiving the three doses of the 4-valent vaccine and 9–25 years of age as the appropriate age for receiving the three doses of the 2-valent vaccine in girls and women [21]. Additionally, in 2019, girls and women aged 9–26 years were recommended as appropriate for receiving the three doses of the 9-valent vaccine [8]. In this guideline, the effectiveness and safety of the three doses of the HPV vaccine in middle-aged women and men have been investigated.

The quadrivalent HPV vaccine

To date, 2 randomized controlled trials (RCTs) for women over 20 years of age have been published, and 5 papers have been identified. [22-26]. In a multinational clinical trial published in 2009 (Protocol 019, NCT00090220), an interim analysis was performed in women aged 24–45 years over an average follow-up period of 2.2 years. The vaccine's efficacies against infection or disease associated with 4 types of HPV (6, 11, 16, and 18) and 2 types of HPV (16 and 18) were 90.5% (95% confidence interval [CI]=73.7, 97.5) and 83.1% (95% CI=50.6, 95.8), respectively [22]. After 4 years of follow-up, the efficacies against diseases related to the 4 types of HPV were 88.7% (95% CI=78.1, 94.8), and 66.9% (95% CI=4.3, 90.6) in women who were not infected with the 4 types of HPV and those who were vaccinated at least once, respectively [23]. The seropositivity rates for antibodies against HPV types 6, 11, 16, and 18 at 48 months after the first vaccination were 91.5%, 92.0%, 97.4%, and 47.9%, respectively, and no serious side effects were reported [22,23].

In the study V501-041 (NCT00834106), the vaccine's efficacy against cervical intraepithelial neoplasia (CIN) ≥2 related to HPV types 16 and 18 over a 78-month follow-up period in Chinese women aged 20–45 years was 100% (95% CI=32.3, 100) and that against CIN grade 1+ related to HPV types 6, 11, 16 and 18 was also 100% (95% CI=70.9, 100). Additionally, its efficacy against persistent infection with HPV types 16 and 18 was 97.5% (95% CI=85.1, 99.9), and the efficacy against abnormal cytology related to HPV types 6, 11, 16, and 18 was 94.0% (95% CI=81.5, 98.8) [26]. No serious adverse reactions were observed [25].

An RCT involving adolescent male aged 9–15 years and 2 RCTs involving male participants aged 16–26 years have been published. In V501-018 (NCT00092547), the seropositivity rate in adolescent boys aged 9–15 years at 10 years after vaccination was 89.96%, and the antibody titer was 16%–42% higher in boys aged 9–12 years than in boys aged 13–15 years [5]. In the Merck protocol 020 trial (NCT00090285) for boys and men aged 16–26 years, the vaccine's efficacies

against anal epithelial neoplasia related to HPV types 6, 11, 16, and 18 after a follow-up period of 2.2 years were 77.5% (95% CI=39.6, 93.3) and 50.3% (95% CI=25.7, 67.2) in the per protocol and intention to treat populations, respectively. Additionally, the incidence of anal intraepithelial neoplasia 2 and 3 in men who received the vaccine decreased by 74.9% (95% CI=8.8, 95.4) and 54.2% (95% CI=18.0, 75.3) in the per protocol and intention to treat populations, respectively [27]. In phase II study for boys and men aged 16–26 years, the vaccine's efficacies against external genital warts were 90.4% (95% CI=69.2, 98.1) and 65.5% (95% CI=45.8, 78.6) in the per protocol and intention to treatment populations, respectively [6].

For the 4-valent vaccine, 2 doses were recommended from the age of 9 to 13 years, based on previous studies (level of evidence I, recommendation level B).

The above results determined the following recommendation for target of quadrivalent HPV vaccine:

- The optimal age for the 3-dose schedule of the 4-valent HPV vaccine is 9–45 years in girls and women and 9–26 years in boys and men (IA).

The bivalent HPV vaccine

Three RCTs [28-30] and three observation studies [31-33] on middle-aged women were identified. A RCT (VIVIANE study, NCT00294047) in women over 25 years of age evaluated and compared the efficacy of the vaccine in the following age groups: 26–35, 36–45, and 46–55 years [30]. The efficacy of the 2-valent vaccine against 6-month-long infection or mild cervical epithelial dysplasia associated with HPV types 16 or 18 was 81.1% (97.7% CI=52.1, 94.0) in all age groups, 83.5% (97.7% CI=45.0, 96.8) in the 26–35 years age group, and 77.2% (97.7% CI=2.8, 96.9) in the 36–45 years age group. In an RCT (study HPV-010, NCT00423046) comparing the 2-valent and 4-valent vaccines in women aged 18–45 years, the seropositivity rate for HPV type 16 at 60 months after vaccination was 100% in the 2-valent vaccine group and 97.5–100% in the 4-valent vaccine group. The seropositivity rate for HPV type 18 was 99.0–100% in the 2-valent vaccine group and 72.3%–84.4% in the 4-valent vaccine group [29]. However, the antibody titer and the duration of antibody production against HPV type 16 or 18 were found to decrease in women aged 27–35 years and 36–45 years compared with that in women aged 18–26 years (HPV 16 and 18: women aged 18–26 years, 68.2 and 40.6 years, respectively; women aged 27–35 years, 57.3 and 9.5 years, respectively; and women aged 36–45 years, 31.0 and 1.9 years, respectively). No serious adverse effects were observed. In men, a phase I/II RCT was noted [7]. Seven months after vaccination in boys aged 10–18 years, seropositivity was 100%, and no serious side effects were observed. Additionally, for the 2-valent vaccine, the 2 doses were recommended at the age of 9–14 years based on previous research outcomes, including those from RCTs, and the 2016 KSGO recommendation (level of evidence I, recommendation level B).

According to the aforementioned results, the recommendation was as follows:

- The optimal age for the three-dose schedule of the 2-valent HPV vaccine is 9–45 years in girls and women (IA) and 9–25 years in boys and men (IIC).

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The nonavalent vaccine

A recently published phase III RCT (NCT03158220) that evaluated the efficacy and safety of the 9-valent vaccine was identified [34]. In this RCT, the immunogenicity and stability of the 9-valent vaccine were evaluated in women aged 27–45 years compared with those in women aged 16–26 years. At 7 months of vaccination, antibody titers against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 were not significantly different between women aged 27–45 years and women aged 16–26 years (0.60–0.67). The seroconversion rate was 99% or higher for all HPV types. No serious vaccine-related side effects have been reported to date. In boys and men, in the recommendations published in 2019 by the KSGO the 9-valent vaccine was recommended for boys and men aged 9–26 years (level of evidence I, recommendation level A) [8].

Based on this information, the recommendations was as follows:

- The optimal age for the three-dose schedule of the 9-valent HPV vaccine is 9–45 years in girls and women and 9–26 years in boys and men (girls and women aged 9–26 years, IA; women aged 27–45 years, IIIB; and boys and men aged 9–26 years, IA).

2. Key question 2: is the HPV vaccine effective in women already infected with HPV?

The quadrivalent HPV vaccine

In a randomized pilot study, 10 women aged 27–45 years who tested positive for HPV 16 were divided into the vaccinated and non-vaccinated groups. In the vaccination group, antibody titers increased by 24–930-fold, and the number of memory B cells increased by 3–27-fold [35].

Based on the above results, the following was recommended:

- In HPV-infected women already, the administration of the quadrivalent HPV vaccine can lower the risk of infection with an uninfected HPV subtype (IIB).

The bivalent vaccine

A phase III RCT (PATRICIA study, NCT00122681) in girls and women aged 15–25 years was identified. According to this study, when the 2-valent HPV vaccine was administered to women infected with HPV type 16 or 18 at the beginning of the study, the efficacy against CIN grade 2+ related to an HPV type other than the one causing infection was 90% (95% CI=31.8, 99.8) [36].

Based on the above results, the recommendation was as follows:

- In HPV-infected women already, the administration of the bivalent HPV vaccine can lower the risk of infection with an uninfected HPV subtype (IIB).

The nonavalent vaccine

A combined study of three RCTs (9-valent Vaccine Study Protocol V503-001, Quaternary Vaccine Study Protocol V501-013, and V501-015) was identified. In this study, the incidence of cervical lesion related to HPV 31, 33, 45, 52, and 58 was decreased among women who tested positive at baseline for HPV 6, 11, 16, or 18 but tested negative for HPV 31, 33, 45, 52, and 58

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(all grades: 95.1%; high grades: 91.1%). Similarly, in women who tested positive at baseline for HPV 31, 33, 45, or 52 but tested negative for HPV 6, 11, 16, and 18, the incidence of cervical disease related to HPV 6, 11, 16, and 18 was also significantly reduced (all grades: 97.4%; high grade: 95.8%) [12].

Based on the above results, the recommendation was as follows:

- In HPV-infected women already, the administration of the nonavalent HPV vaccine can lower the risk of infection with an uninfected HPV subtype (IIB).

3. Key question 3: is the HPV vaccine effective in preventing the recurrence of HPV-related diseases in patients who have undergone conization?

The quadrivalent vaccine

In an RCT of 312 patients who received treatment such as conization for CIN grade 1–3, the recurrence rate of CIN grade 1–3 was significantly decreased (58.7%) in the vaccinated group compared with that in the control group [37]. In a prospective case-control study of patients who underwent cone resection for CIN, the risk of high-grade cervical epithelial tumors in vaccinated patients was reduced by 81.2% (95% CI=34.3, 95.7) [38]. In a retrospective study of 20–45-year-old Korean women who underwent cone resection for high-grade CIN, the recurrence rate of high-grade CIN was decreased in the vaccinated group (vaccinated group, 2.5%; unvaccinated group, 7.2%), and the recurrence risk of high-grade CIN was significantly higher in the unvaccinated group than in the vaccinated group (hazard ratio=2.84; 95% CI=1.335, 6.042) [39]. In a single-center retrospective study of women who underwent conization for cervical dysplasia, the recurrence of cervical dysplasia was less common in the vaccinated group than in the unvaccinated group (7.1% vs. 16.5%, p=0.02), and vaccination after conization was a significant factor in preventing recurrence (odds ratio [OR]=0.2; 95% CI=0.1, 0.6) [40].

Based on the above, the following was recommended:

- In women who underwent conization, the administration of the quadrivalent HPV vaccine can reduce the risk of recurrence of HPV-related diseases by preventing infection with the corresponding viral subtype (IIB).

The bivalent vaccine

In an RCT (PATRICIA, NCT00122681) including girls and women aged 15–25 years, vaccine efficacy against the recurrence of CIN grade ≥2 was 88.2% (95% CI=14.8, 99.7) in women who underwent conization after vaccination [41]. However, in a analysis of RCT (Costa Rica HPV Vaccine Trial, NCT00128661), no vaccine efficacy was noted against cervical precancerous lesions in patients who underwent conization for cervical lesions after vaccination (efficacy: high-grade squamous intraepithelial lesion + –163.3% [95% CI= –742, 18]; CIN2+ –55.5% [95% CI=–834, 74]) [42]. In a meta-analysis that included the above 2 studies (2 studies on the 2-valent vaccine and three studies on the 4-valent vaccine), vaccination before and after conization could reduce the recurrence of CIN grade ≥2 (pretreatment vaccination: OR=0.4; 95% CI=0.21, 0.78; post-treatment vaccination: OR=0.28; 95% CI=0.14, 0.56) [43].

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Based on the above results, the following recommendations were made:

- In women who underwent conization, the administration of the bivalent HPV vaccine can reduce the risk of recurrence of HPV-related diseases by preventing infection with the corresponding viral subtype (IIB).

The nonavalent vaccine

In a retrospective study of women who were vaccinated after conization (2-valent: 19.6%; 4-valent: 4.6%; 9-valent: 64.1%), the incidence of persistent or recurrent high-grade CIN was significantly lower in the vaccinated group than in the unvaccinated group (3.3% vs. 10.7%, p=0.015), and the risk of persistent or recurrent high-grade CIN was significantly decreased in the vaccinated group (OR=0.2; 95% CI=0.1, 0.7) [44].

Based on the above results, the following was recommended:

- In women who underwent conization, the administration of the nonavalent HPV vaccine can reduce the risk of recurrence of HPV-related diseases by preventing infection with the corresponding viral subtype (IVB).

DISCUSSION

The presented recommendations are based on evidence but have several controversial aspects. Although this guideline recommends HPV vaccination in middle-aged women, the optimal age for vaccination is between 9 and 26 years in girls and women. In women aged 27–45 years, vaccination safety has been sufficiently proven, but the vaccine may be less effective because these women may have already been exposed to the virus [45]. In addition, because only one RCT has been performed for the 9-valent vaccine in middle-aged women, the evidence is insufficient for this vaccine. Therefore, doctors should fully discuss the benefits of vaccination with the patient prior to vaccination. Moreover, further research is required to identify middle-aged women who can benefit from vaccination and to study the cost-effectiveness of vaccination in this population.

HPV vaccines are administered via a 2-dose schedule for most persons who initiate vaccination at 9–14 years of age. Based on several RCTs, 2 doses of the 4-valent and 2-valent vaccines are recommended for boys and girls aged 9–13 years and 9–14 years, respectively [21,46,47].

This guideline recommends a 2-valent vaccine for boys and men aged 9–25 years. However, only one phase I/II randomized study has evaluated immunogenicity in boys aged 10–18 years [7]. Owing to insufficient evidence, further studies on 2-valent HPV vaccines in adolescent boys and young adult men are required.

These guidelines recommend that the administration of the HPV vaccine can lower the risk of infection with an HPV subtype other than the ones causing the infection in women already infected with HPV. This must be interpreted carefully, as it can be misunderstood as the vaccine leading to HPV clearance in women after infection. Clinical studies have

demonstrated that vaccination does not eliminate HPV already present in women [12,35,36]. In addition, evidence to support the effectiveness of vaccination in patients who have already undergone conization is still inconclusive. In a analysis study of an RCT, no vaccine efficacy was observed against cervical precancerous lesions in patients who underwent conization for cervical lesions after vaccination [42]. Although recent meta-analysis shows a significant risk reduction of recurrence or persistence of CIN2+ after conization [43,48,49], well-designed RCTs are needed in future.

Regarding the safety of the HPV vaccine, no associations with multiple sclerosis, other disorders of the central nervous system, demyelinating disorders, Guillain-Barré syndrome, neurological diseases, venous thromboembolism, and autoimmune diseases have been revealed in observational studies and randomized clinical studies [50-53]. In addition, in a recently published registry-based study on 11–14-year-old Korean girls, 33 serious complications, including Hashimoto's thyroiditis, rheumatoid arthritis, and malignant headache, were demonstrated to not be associated with HPV vaccination [54].

The present recommendation requires further updates based on further research on men and middle-aged women or on controversial aspects.

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SUPPLEMENTARY MATERIALS

Data S1

Development process of human papillomavirus (HPV) vaccine guideline

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Data S2

Evidence table of key question

Click here to view

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