NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

Menopause e-Consult®

May 2020

This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Mindy S. Christianson, MD, the Editor of *Menopause e-Consult*, encourages your suggestions for future topics. The opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Christianson.

Question

A 65-year-old nulliparous divorced woman presents for her annual examination. She reports that she has been in a new sexual relationship for the past year. Her gynecologic history is notable for uterine fibroids. She has no history of abnormal Pap tests or human papillomavirus (HPV) infections. She is not a smoker, has had three total lifetime partners, and has no history of sexually transmitted infections. At the woman's insistence, a Pap test was performed and showed a high-grade intraepithelial lesion with high-risk HPV detected. Subsequent Pap tests showed cervical dysplasia, and she eventually opted to proceed with a hysterectomy. Although this situation is extreme in terms of the woman's age, what are the guidelines for Pap tests and the HPV vaccine for midlife women and beyond? How old is too old for cervical cancer screening?

Submitted by Wen Shen, MD, MPH, FACOG, Baltimore, Maryland

Commentary by

Vivien Brown, MDCM, CCFP, FCFP, NCMP
Assistant Professor
University of Toronto
VP Medical Affairs,
Medisys Health Group
VP North America,
Medical Women's International Association
Toronto, Ontario, Canada

This question is very interesting because it reflects issues of both screening and prevention.

Per screening guidelines in both the United States and Canada, this patient could be offered routine screening up until the age of 65 or 70 years. The US Preventive Services Task Force, in their 2018 recommendation statement, recommends against screening for cervical cancer in women aged 65 years and older who have had adequate prior screening and are otherwise not at high risk for developing cervical cancer (grade D).[1]

The Canadian Task Force on Preventive Care advises that screening Pap tests may stop at age 70 years after three successive negative PAP results.[2] However, the Canadian guideline does say that for women aged older than 70 years who have not been adequately screened, there is a recommendation to continue screening until three negative tests have been obtained (weak recommendation; low-quality evidence).

The Canadian guideline states that

- There is little evidence regarding at what age to stop screening, although other countries have a policy to stop screening women aged older than 65 or 70 years given adequate previous screening.[3-5]
- Evidence for the definition of adequate previous screening is unclear. The US

combined societies: the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology (ACS/ASCCP/ASCP) report acknowledged lack of evidence and used a modeling study that suggested that for women who had not undergone screening, "a few" screens resulted in extra life expectancy.[6]

- European policy advises that two tests with negative results are sufficient.[7]
- There is limited evidence for the benefits of screening older women, largely because of the exclusion of this age group from most of the studies reviewed.
- Given these possibilities, healthy women in this age group may derive some benefit from screening if they have not undergone adequate screening previously.
- Where recommendations are weak, healthcare providers should discuss the balance between potential benefits and harms of screening with PAP tests to help each woman make an informed decision that is consistent with her values and preferences.

And what is adequate screening? From the American societies:

- Adequate prior screening. ACS/ASCCP/ ASCP define adequate prior screening as
  - Three consecutive negative cytology results or two consecutive negative cotesting results within 10 years before stopping screening, with the most recent test occurring within 5 years.
  - Furthermore, even though our patient now has a new partner, routine screening is not recommended in her age group. "Once screening has stopped, it should not resume in women older than 65 years, even if they report having a new sexual partner."[8]

It is reasonable to review when this woman last had routine negative screening because this is not clear from the history, and that timing is very important. Given her personal concern, her understanding of exposure to a new partner, and her clear preference, the clinician agreed and did a PAP test, with worrisome results.

In terms of prevention, the HPV vaccine is a major factor to consider and is a common clinical question. Both in the United States and Canada, the product monograph for HPV immunization has the upper age limit as 45 years. Any use of the vaccine after that would be considered off-label use. In Canada, the National Advisory Commission on Immunization advise immunization for those "age 26 and above," essentially not giving an end age for usage.[9]

The Centers for Disease Control and Prevention (CDC) advises that for adults aged 27 through 45 years, clinicians can consider discussing HPV vaccination with those who are most likely to benefit.[10] Thus, there are no clear guidelines for this patient, age 64, with respect to primary prevention.

There are, however, a number of interesting publications focused on the benefit of immunization in those patients with identified disease aimed at reducing risk of recurrence or de novo infection in another location. This is now aimed at secondary or even tertiary prevention. These studies reflect international assessments, demographics, and variable underlying criteria for inclusion or exclusion in the studies.

Joura and colleagues in 2012 showed that previous vaccination in women who had surgical treatment for HPV disease significantly reduced the incidence of subsequent HPV-related disease.[11] Kang and associates in 2013 published data showing

significant decreased risk of recurrence of disease in a group of patients after loop electrosurgical excision procedures (LEEP).[12] And in 2018, Ghelardi and colleagues showed that reduction of risk of recurrent disease in women with cervical intraepithelial neoplasia grade 2+ (CIN2+) can reduce the risk of recurrent disease on the order of 80% in any location.[13]

Although there may be variable demographics and variation in extent and location of disease in these and other studies, given the high-grade nature of this woman's disease, the ongoing exposure to possible new partners in a sexually active woman, and her own active participation in her healthcare decisions, it seems reasonable to have the discussion with her about the options around HPV vaccination so that she can make an informed decision about her care.

References

1. US Preventive Services Task Force; Curry S, Krist AH, et al, Screening for cervical cancer: US Preventative Services Task Force recommendation statement. *JAMA*. 2018;320(7):674-686
2. Dickinson J, Tsakonas E, Gorber SC, et al; Canadian Task Force on Preventive Health Care. Recommendations on screening for cervical cancer. *CMAJ*. 2013;185(1):35-45.
3. National Health Service. Cervical screening: programme overview. April 1 2015. Last updated November 18, 2019. www.gov.uk/guidance/cervical-screening-programme-overview. Accessed May 14, 2020.
4. Moyer VA; US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;156(12):880-891.
5. Australian Government Department of Health. National cervical screening program. www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-screening-1. Accessed May 14, 2020.
6. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol* 2012;137:516-42.
7. Arbyn M, Anttila A, Jordan J, et al. European guidelines for quality assurance in cervical cancer screening second edition—summary document. *Ann Oncol*. 2010;21(3):448-458.
8. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *J Low Genit Tract Dis*. 2012;16(3):175-204.
9. Tunis M, Ismail S, Deeks S. Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV Vaccine 2-Dose Immunization Schedule and the Use of HPV Vaccines in Immunocompromised Populations. Public Health Agency of Canada Publication 160301. May 2017.
10. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;69(32):698-702.
11. Joura EA, Garland SM, Paavonen J, et al; FUTURE I and II Study Group. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ*. 2012;344:e1401.
12. Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? *Gynecol Oncol*. 2013:130(2):264-268.
13. Ghelardi A, Parazzini F, Martella F, et al. SPERANZA project: HPV vaccination after treatment for CIN2. *Gynecol Oncol*. 2018;151(2):229-234.

Disclosures: Dr. Brown reports Speaker for GSK, Merck, Pfizer, and Sanofi-Pasteur.

Case

A 25-year-old woman presents to you for evaluation of irregular menstrual cycles for the past 4 years. She also reports associated hot flashes, night sweats, mood swings, poor sleep, and hair loss over the last 6 months. She is planning to get married in 10 months and would like to conceive within the year.

Her menarche was at age 11. Her cycles occurred every 27 days with a moderate flow that lasted 4 to 5 days. She began to skip monthly cycles when she was 21 until the last year when she skipped 5 to 6 months and started to experience her symptoms.

Her physical examination shows a well-nourished woman with a height of 65 in and weight of 128 lb. Her examination is unremarkable except for evidence of vulvovaginal atrophy. She brought her labs to the visit, which were notable for follicle-stimulating hormone of 49, luteinizing hormone of 42, estradiol of 15, and antimüllerian hormone of 0.01.

She tried to investigate her symptoms online and found a possible association between HPV and primary ovarian insufficiency. She remembered that she had two doses of the HPV vaccine over the last 6 months. What information can you give her about the HPV vaccine, and how do you advise her about her current situation?

Submitted by Barbara A. Soltes, MD, FACOG, NCMP, Chicago, Illinois

Commentary by

Mindy S Christianson, MD
Assistant Professor
Medical Director, Johns Hopkins Fertility Center
Division of Reproductive Endocrinology and Infertility
Department of Gynecology and Obstetrics
Johns Hopkins University School of Medicine
Lutherville, Maryland

It's not uncommon for women to ask about the human papilloma virus (HPV) vaccine and ovarian failure. This often stems from antivaccination material they've read on social media or even from coverage in the popular press. It's critical for women's health providers to know that this association is not warranted and to tell their patients that we currently do not have any substantive data that suggest or support that the HPV vaccine can cause primary ovarian insufficiency (POI).[1]

Each year, approximately 500,000 women worldwide are diagnosed with cervical cancer, and high-risk strains of HPV cause 70% of cervical cancers.[2,3] Fortunately, an HPV vaccine exists that can prevent most cervical cancer cases. The Centers for Disease Control and Prevention (CDC) recommends HPV vaccination for adolescents and adults, with routine vaccination starting at age 11 to 12 years and catch-up vaccination through age 26 years. Vaccination for persons aged 27 to 45 years that are not adequately vaccinated is also recommended, with shared decision-making.[4]

Even though the HPV vaccine has been available for more than 10 years, its vaccination rate lags behind other vaccines, with public safety fears identified as a major barrier.[5,6] Concerns about the HPV vaccine causing POI is a myth with no supporting data. Unfortunately, a few case reports of young women being diagnosed with POI after receiving the vaccine has provided fuel for antivaccination proponents to scare women from receiving the vaccine.

The woman in our case has a presentation consistent with POI, defined as loss of ovarian function in women aged younger than 40 years and characterized by amenorrhea or irregular menses and menopause-level serum follicle-stimulating hormone levels. It is relatively rare in younger women, affecting 1 in 10,000 women aged younger than 20 years and 1 in 1,000 women aged younger than 30 years. Primary ovarian insufficiency affects approximately 1% of women aged younger than 40 years.[7,8]

There are multiple etiologies for POI, including prior chemotherapy or radiation treatment, X chromosome abnormalities such as Turner syndrome or Turner syndrome mosaicism, the Fragile X permutation, and

autoimmune issues such as antiadrenal antibodies. However, in most cases, a cause is not identified even after an extensive evaluation.[7]

The standard-of-care treatment for women with POI is physiologic estrogen and progestin treatment up until the age of natural menopause. In terms of fertility, the chance of spontaneous pregnancy is less than 5% for women with POI, and a donor egg is typically the recommended option to have a baby.[9] For young women, POI is obviously in most cases a devastating and shocking diagnosis.

Many women diagnosed with POI are eager to find a cause. It's important to reassure the woman that the HPV vaccine most likely did not cause her POI, and it may be helpful to know about the handful of cases that triggered the public fears in some.

In 2012, a case report was published in which a 14-year-old received the HPV vaccine and 2 years later was diagnosed with POI.[10] In 2014, a published case series by the same author reported on three young women with POI diagnoses temporally associated with the HPV vaccine. One of the women was the patient in the original case report.[11] In 2013, another case series reported on three young women who developed POI 1 to 2 years after receiving the HPV vaccine.[12]

Since the case reports and case series, published epidemiologic studies have refuted an association between the HPV vaccine and POI. In 2014, Pellogrino and colleagues analyzed national surveillance databases for adverse events after vaccine administration. Regarding POI, they found one case in Australia, two cases in Europe, and four cases in the United States. They estimated the reported rate of POI as 0.065 cases per million doses of HPV vaccine in the United States.[13]

In 2018, a postlicensing safety analysis of the HPV vaccine in the United States evaluated the Adverse Reporting System. They calculated a rate of 0.28 reported cases of POI per million HPV vaccines given.[14] A final epidemiologic study examined the US Vaccine Safety Datalink to estimate the risk of POI in females who received the HPV vaccine. Of approximately 60,000 females who received the HPV vaccine, they identified 28 women with confirmed POI, yet only one had received the HPV vaccine before symptom onset. The authors did not find an increased risk of POI after the HPV vaccine, and the age-adjusted hazard ratio of POI after the HPV vaccine was 0.30.[15]

From the six reported cases of POI after the HPV vaccine, there was no evidence other than the timing of symptom onset after the vaccine to suggest a causal association. The American College of Obstetrics and Gynecology, the CDC, the American Cancer Society, and other professional organizations strongly recommend the HPV vaccine for both male and female patients. At this point, with the information we have to date, healthcare providers can confidently counsel their patients that there is no significant data that suggest the HPV vaccine can cause POI.[1]

References

1. Christianson MS, Wodi P, Talaat K, Halsey N. Primary ovarian insufficiency and human papilloma virus vaccines: a review of the current evidence. *Am J Obstet Gynecol*. 2020;222(3):239-244.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
3. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12-19.
4. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):698-702.

5. Elam-Evans LD, Yankey D, Jeyarajah J, et al; Immunization Services Division, National Center for Immunization and Respiratory Diseases; Centers for Disease Control and Prevention (CDC). National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2014;63(29):625-633.
6. Calvet GA, Grinsztejn BG, Quintana Mde S, et al. Predictors of early menopause in HIV-infected women: a prospective cohort study. *Am J Obstet Gynecol*. 2015;212(6):765.e1-765.e13.
7. Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med*. 2009;360(6):606-614.
8. Rebar RW. Premature ovarian failure. *Obstet Gynecol*. 2009;113(6):1355-1363.
9. van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. *Hum Reprod Update*. 1999;5(5):483-492.
10. Little DT, Ward HR. Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination. *BMJ Case Rep*. 2012;2012: pii: bcr2012006879. doi: 10.1136/bcr-2012-006879.
11. Little DT, Ward HR. Adolescent premature ovarian insufficiency following human papillomavirus vaccination: a case series seen in general practice. *J Investig Med High Impact Case Rep*. 2014;2(4) :2324709614556129.
12. Colafrancesco S, Perricone C, Tomljenovic L, Shoenfeld Y. Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants. *Am J Reprod Immunol*. 2013;70(4):309-316.
13. Pellegrino P, Carnovale C, Perrone V, et al. On the association between human papillomavirus vaccine and primary ovarian failure. *Am J Reprod Immunol*. 2014;71(4):293-294.
14. Arana JE, Harrington T, Cano M, et al. Post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the Vaccine Adverse Event Reporting System (VAERS), 2009-2015. *Vaccine*. 2018;36(13):1781-1788.
15. Naleway AL, Mittendorf KF, Irving SA, et al. Primary ovarian insufficiency and adolescent vaccination. *Pediatrics*. 2018;142(3): pii: e20180943. doi: 10.1542/peds.2018-0943.

Disclosures: Dr. Christianson reports no relevant financial disclosures.

30100 Chagrin Blvd, Suite 210
Pepper Pike, OH 44124, USA
Tel 440-442-7550 • Fax 440-442-2660 • info@menopause.org
www.menopause.org