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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. Peter F. Schnatz, DO, FACOG, FACP, NCMP, the Editor of *Menopause e-Consult*, encourages your suggestions for future topics. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz.

Question:

We recently screened a postmenopausal woman whose results showed atypical squamous cells of undetermined significance and high-risk human papillomavirus (HPV). She has been monogamous with her husband for 23 years. How do we explain this mysterious infection to her with what we know about HPV around the time of menopause?

Commentary by:



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History. Ever since HPV was determined to be a necessary cause of invasive cervical cancer, HPV DNA testing has been increasingly incorporated into routine Papanicolaou (Pap) screening, particularly in women over age 30. Historically, women with abnormal Pap tests were counseled about the risk of malignancy and cancer prevention and were largely unaware that these abnormalities were caused by a sexually transmitted infection. The addition of HPV testing to routine screening makes this connection more explicit. As a result, our case patient is likely to experience significant anxiety

upon learning she is positive for HPV and she will probably have questions about how and when she acquired the infection. Because she has been monogamous for 23 years, concerns about her partner's fidelity may surface. Clinicians should appropriately contextualize the test results for her in order to minimize any psychological harm.

In the United States, the prevalence of HPV infection declines with increasing age. In a nationally representative sample of women in the 2003 to 2004 US National Health and Nutrition Examination Survey, HPV was highest in young women near the average age of sexual debut (44.8%), and lowest in older women ages 50 to 59 (19.6%).¹ This decline in HPV occurrence in women as they age has long been attributed to a combination of: 1) protective immunity from previous infection, which guards against reinfection; and 2) a decrease in new sexual partners, hence less HPV exposure.

The discovery of HPV in routine screening in older women can be the result of either long-term infection or new infection. In women who have their first HPV test at an older age, a positive result is likely to reflect a persistent infection, which has a higher risk of continuing than HPV first detected in younger women.² In contrast, in older women with a history of negative HPV, newly detected HPV is not more likely to persist than in younger women. However, the risk of progression to cervical

intraepithelial neoplasia grades 2/3 is relatively similar for both older women ages 45 and older (9%) and younger women ages 18 to 25 (7%). These data suggest that management of HPV-positive women for prevention of cervical cancer does not need to be modified in older women.

Counseling. Answering the question of “where and when was I infected” is challenging, particularly for the perimenopausal, monogamous woman. However, based on the data described above, HPV detected in an older woman on her first test is more likely to represent an infection that has persisted for some time. As women are repeatedly tested for HPV in routine screening, an infection history will accrue. For our case patient, who probably had previous negative results or was never screened before, her questions about the source of this newly detected infection are likely to be intense. Certainly, women remain at risk for HPV acquisition across the lifespan, and women who report a new sexual partner are at a higher risk even among women over age 40.^{3,4} A recent population-based study, however, reported that new sexual partnerships explained only about 20% of incident HPV in women ages 45 to 75.³ Does this mean that the remaining HPV detections are attributed to new infections in a woman’s long-term male partner?

While this possibility cannot be answered with certainty, it is unlikely that recent transmission from the male sex partner is the only explanation (in the absence of the woman herself reporting a new exposure). In the same study described above, the investigators estimated that another 21% of incident infection could be attributed to past sexual behavior and 12% to diminished systemic immune function.³ The association with past sexual behavior could represent a marker of general sexual risk and possibly the likelihood that the male partner had formed new sexual partnerships. However, data increasingly support the notion that a fraction, perhaps a substantial fraction, of incident HPV may not reflect a recent acquisition in older women but rather a reemergence of a previously acquired infection that had been suppressed to

viral loads below the limit of detection by a competent immune response.

Several studies have now demonstrated repeat HPV type-specific detection in women following long periods of undetectable viral DNA.⁵⁻⁷ While this could represent reinfection with the same HPV type, the observation of the same phenomenon in sexually inactive women suggests that this is not the only possibility. For example, HPV “incidence” in HIV-infected women after 18 months of sexual abstinence ranged from 5% to 22%, and increased significantly with increasing immune suppression as measured by peripheral CD4+ T-cell count.⁸ Older women with new HPV detection had reduced lymphoproliferative response of peripheral blood mononuclear cells following general immune activation.³

Is the risk of reactivation higher in older women? Although several US surveys show a continuous decline in HPV prevalence with increasing age, larger meta-analyses have demonstrated a second “peak” prevalence of HPV around the age of menopause,⁹ raising new questions about HPV natural history during the menopause transition. A small study reported an independent association between menopausal stage and prevalent HPV detection in women ages 40 to 60 after adjustment for sexual behaviors.¹⁰ Because of the well-described interaction between female sex hormones and immune function, it is possible that the second peak occurs specifically around the age of menopause because of immune suppression secondary to the hormonal fluctuations characteristic of this transition.

Summary. While data describing the natural history of HPV during the menopause transition are limited at present, the collective evidence suggests that our case patient can be reasonably assured that her newly detected HPV infection was acquired years earlier. Even if a patient had history of negative HPV test results (but now has a positive test result), she may have had a prior infection that was immunologically controlled to levels below the limits of detection (ie, the virus becomes dormant in the woman

with a strong immune system), as emerging data suggest.

Disclosure: Dr. Gravitt reports: Advisory Board—Qiagen

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Case:

A 56-year-old woman in our practice recently stopped hormone therapy (HT) but is now suffering again from hot flashes and night sweats. In light of the common recurrence of menopausal symptoms after discontinuation of HT, what approaches might work best for

managing patients who have discontinued treatment and are again experiencing discomfort?

Management issues by:



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Individualizing management: Individualizing counseling for a peri- or postmenopausal woman is one of the most important themes in the 2010 NAMS position statement on hormone therapy.¹ Clinicians need objective endpoints when treating women who have discontinued HT, after a conversation with the patient about her goals. If the woman continues to have distressing symptoms, resolution of those problems should be the focus of her management.

The review of symptoms should include questions about her sense of well-being, vasomotor symptoms, fatigue, depression, sleep quality, vaginal dryness, libido, dyspareunia, and other quality-of-life problems.

Health maintenance issues are equally important to discuss, including appropriate screening tests (ie, lipid profile, bone density, colonoscopy), vaccinations (ie, herpes zoster, flu, Pneumovax), and diet and exercise regimens. Clinicians should also encourage women to have regular eye and dental examinations.

Since we have abandoned the concept of HT being a “magic bullet,” management for this patient will likely have several components, not one.

- Lifestyle modification should be the basis for management. Relaxation techniques such as yoga or meditation may be effective. Reducing the temperature at bedtime is

helpful for those with bothersome night sweats. Obesity not only contributes to the risk of diabetes, hypertension, cardiovascular disease, and cancer, but also increases the severity and frequency of hot flashes.² An appropriate exercise program and individualized diet to attempt to reduce weight by approximately 10% is a reasonable, healthy goal. But this needs to be a lifelong commitment rather than a short-term sprint in order to be beneficial.

- Over-the-counter remedies have failed to show a meaningful reduction in vasomotor symptoms for most patients. Most of the products have little or no record of safety or appropriate dosing for age or weight differences. Interestingly, virtually all vasomotor studies demonstrate a 30% to 50% reduction in hot flashes with placebo!
- Manifestations of stress may mimic menopausal symptoms. Screening for depression is essential and prescribing such therapies as selective serotonin reuptake inhibitors (SSRIs) may be effective. Fatigue and depression may be secondary to sleep disturbances. Sleep apnea needs to be considered, as it affects as many as 15% of postmenopausal women.
- For the woman who has hypoestrogenic symptoms, restarting HT may be reasonable. Because of the vast amount of information published in the lay literature about the risks of HT, it is important to have a detailed discussion with the patient about her concerns. You may allay unfounded fears and improve her compliance with the ultimate therapy.³

Restarting treatment. The decision to restart HT should be based on the severity of symptoms and her benefit-risk ratio considerations. Prescribing therapy at a lower dose than was used previously is likely to result in relief that is just as effective as the previous regimen. The route of administration is important as well. Oral HT has been well studied but will raise

triglyceride levels and may yield a higher risk of thromboembolic events. Consider the specific goal, the ease of use, and the cost to the patient when making the choice with her.

Although very low doses of estrogen may ultimately not require the addition of progestogen, women with an intact uterus need it for endometrial protection. The combined regimen does not have to be continuous. With very low doses, I have found that 12 days of micronized progestogen (200 mg every 3 mo) is sufficient to prevent endometrial hyperplasia in most patients.

Clearly, one of the common fears women have about HT is the risk of breast cancer. Remember, exercise reduces the risk of breast cancer in most patients. In select patients, it may be appropriate to consider a risk-reduction strategy that includes tamoxifen or raloxifene. These preparations may increase hot flashes and have a similar thromboembolic risk as HT. Explaining the current data will be crucial. On a very positive note, estrogen alone appears to have no negative effect on breast cancer risk,^{4,5} although there appears to be increased risk for invasive cancer with combined therapy. There is currently no model that accurately predicts risk for the individual patient. In fact, in the Continuing Outcomes Relevant to Evista study, 43% of patients with invasive breast cancer had a score below the threshold.⁴

Osteoporosis may be another concern or medical issue that needs to be managed for midlife women stopping HT. There is some recent literature suggesting that HT could be a reasonable first-line therapy for osteoporosis.⁶ Other therapeutic agents for bone loss such as bisphosphonates, raloxifene, or denosumab need to be included in the discussion.

Two difficult areas in counseling the patient are the possible cognitive effects and cardiovascular effects around the time of menopause. There is a clear difference in both of these concerns before and after menopause. HT cannot return a woman to her premenopausal state, but as new estrogen receptors are being discovered in the

heart (eg, GPR30) and changes are found after menopause in the hippocampal region in the brain, we find that the story is still evolving.^{7,8}

Recommendations. Here is a reasonable set of steps to present to this woman after discontinuance:

1. Determine her individual goals.
2. Encourage lifestyle modifications, which might work to reduce menopausal symptoms and have other significant health benefits as well.
3. Treat other medical conditions such as depression or sleep apnea.
4. Discuss potential alternative medications such as SSRIs.
5. Some nonhormonal treatments, such as gabapentin, might meet her needs without restarting HT.
6. Restart HT at a lower-dose that meets her goals, if appropriate. Consider alternative delivery routes, such as transdermal.
7. Add an appropriate amount of progestogen for uterine protection.

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