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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. Kathryn M. Macaulay, MD, 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 by Dr. Macaulay.

Question

Can hormone therapy (HT) be used safely in women with a history of migraine with aura? What would be the preferred HT regimen in women with this condition?

Commentary by

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Migraine with aura (MA) accounts for about 20% to 30% of attacks of pulsating head pain preceded by transient and progressive focal neurologic symptoms (mostly visual but also sensory, aphasic, or motor), lasting no more than 1 hour and resolving before migraine occurs.

To recognize aura in ob/gyn practice is essential, because reproductive milestones, especially pregnancy, and manipulation with exogenous hormones, namely estrogens, may be causal factors (ie, combined hormone contraception worsens MA in more than half of users).

Migraine with aura usually presents before the age of 40 years because high estrogen levels seem predisposed to aura by modulating the threshold for cortical spreading depression, the neurobiologic event underlying MA. Moreover, estrogens affect the vascular system in many ways, including endothelial dysfunction, hemostatic balance, and neuroendocrine and metabolic factors, and their fluctuations likely explain the striking preponderance of migraine in women across the life span.[1]

With advancing age, incidence generally decreases, and about two-thirds of patients no longer have any type of migraine and its associated phenomena by age 65. De novo diagnosis over the age of 40 may require investigation to exclude other causes (transient ischemic attacks, neoplasm, temporal arteritis, epilepsy, pituitary macroadenoma). However, during a long menopause transition, erratic estrogenic secretion and unbalanced estrogenic exposure because of anovulatory cycle and/or progesterone deficiency may increase the frequency and severity of migraine or even initiate it.

In addition, the intensity of menopause symptoms such as hot flashes, palpitations, night sweats, disturbed sleep, and negative emotions may contribute to the burden of migraine, explaining why the fifth decade of life is extremely critical for first consultations. That being so, the clinician must face the challenge of pharmacologic management at the same time as the

symptoms related to the hypoestrogenic state of menopause and migraine, in particular with aura, which is sensitive to the estrogenic milieu.[2]

Indeed, caution is mandatory in the prescription of HT because MA is an established marker of roughly a double risk of ischemic stroke (IS). Risk increases further in women aged younger than 45 years, who smoke, and/or who are using combined hormone contraception. Even younger menopause age and the high frequency of MA attacks increase the risk of IS. Migraine with aura and hemorrhagic stroke have been associated, as well as with an increased prevalence and progression of silent brain lesions in women.

By contrast, migraine status has not been associated with faster rates of cognitive decline. It is worth mentioning that the increased risk of IS in MA is most apparent in young women, likely because they have few or no additional risk factors, and migraine is prevalent in fertile life, whereas stroke is a disease of the elderly. Thus, with increasing age, traditional cardiovascular risk factors are predominant in driving the association between MA and IS.

Finally, the hypothesized increased risk of cardiovascular events remains questionable in migraine sufferers, and it may be related to their peculiar vascular vulnerability in the presence of other cardiovascular and metabolic risk factors.[3]

In the context of menopause medicine, there are not absolute contraindications to the use of HT for symptomatic women with MA. At variance with the World Health Organization Medical Eligibility Criteria against the use of combined hormone contraception in fertile women, an individualized approach is the best practice. Clinicians should take into account the cardiovascular and metabolic profile as well as MA disease activity at menopause and beyond.[2,4,5]

Hormone therapy in perimenopausal patients with MA has been associated with an increase in severity of pain and visual auras. Moreover, estrogen users reported a greater use of antimigraine preparations than did nonusers, and current HT use was associated with higher rates of migraine compared with no use.

Prescribing the lowest effective dose of estrogen seems to prevent this undesired effect, bearing in mind that if aura starts for the first time in a woman with no history of migraine, a neurologic consultation is needed. If aura becomes more frequent or starts again after a long period of remission in a previous migraine sufferer, the indication is to reassess cardiovascular and metabolic risk factors and to stop estrogen for clinical reevaluation.

Weight loss and lifestyle changes are the first-line indications for the management of short- and long-term consequences of menopause and may be beneficial for migraine. Nonhormonal strategies, such as selective serotonin reuptake inhibitors (fluoxetine, paroxetine), serotonin nor-epinephrine reuptake inhibitors (ven-lafaxine), and gamma-aminobutyric acid analog (gabapentin), may be used for management of vasomotor symptoms, showing some dose-dependent evidence of efficacy for migraine prevention.

In nonhysterectomized women with MA who are in need of endometrial protection, the best HT option should aim to 1) stabilize estrogenic fluctuations, 2) avoid “estrogen withdrawal,” and 3) achieve amenorrhea by using continuous combined estrogen-progestin regimens. Hysterectomized women may use estrogens alone.

The preferable estrogen is transdermal bioidentical estradiol (patches, gels), which provides more physiologic estrogen levels and avoids the "first pass" liver metabolism. Its low metabolic and thrombotic effect is relevant not only to the clinical management of MA but also to the higher cardiovascular and cerebrovascular risk of these postmenopausal women. Progestins with little metabolic effect or micronized bioidentical progesterone are preferred for safety. The levonorgestrel intrauterine system may also be used as a continuous progestogen component of HT.

Hormone therapy use in women with MA is possible and safe by tailoring the best estrogen-progestin combination at the lowest dose to manage menopause symptoms effectively and to contain MA disability and potential associated risk.

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Case

A 45-year-old woman has been treated about 5 years ago for cervical intraepithelial neoplasia (CIN) 2/3. She is questioning her risk of recurrence, her risk of disease from HPV in other regions, and the benefit of being vaccinated. Or is it too late?

Commentary by

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This is an important question, because prevention in this age group is still very relevant. We know that mature women will continue to be sexually active and that there remains a risk of acquiring human papillomavirus (HPV).

In fact, the cumulative risk of HPV infection in a woman increases over time, irrespective of age. Furthermore, HPV prevalence has been shown to have a bimodal age distribution, with a second prevalence peak occurring in women aged older than 50 years.

Will sexually active women benefit from HPV vaccination? Will women treated for previous HPV infection and/or HPV-related cervical or genital disease benefit from HPV vaccination? These questions were recently asked and answered by the Society of Gynecologic Oncology Group of Canada in a review published at the end of 2015.[1]

According to Canada's National Advisory Commission on Immunization (NACI), women who are sexually active, including those with cervical cancer, anogenital disease, or known HPV infection, will benefit from HPV vaccination.[2]

We know that the likelihood of being exposed to more than one HPV type is low, and current vaccines offer protection for up to 9 HPV types. Moreover, HPV antibodies do not always develop in a timely manner after natural infection; therefore, even with previous exposure, natural infection does not guarantee protection.[3] Suffice it to say, it is very possible to become reinfected.

In large randomized, controlled trials, both the bivalent and quadrivalent vaccines demonstrated efficacy in preventing diseases related to HPV types to which women had been previously exposed (measured by baseline seropositivity).[3-5]

Vaccines were also effective in preventing recurrent HPV-related disease among women with previous HPV infection or disease (CIN or anogenital warts).[6,7] Therefore, results suggest that women with prior infection and/or treatment still derive benefit from vaccination.

Vaccine efficacy has been demonstrated in the following groups:

- Women up to 45 years of age, with no restriction on lifetime partners (> 85% disease reduction)[5]
- Women with evidence of previous infection; in pivotal clinical trials, vaccine recipients had a reduction of up to 100% of disease caused by the same HPV type[3]
- Women with a history of previous disease
  - Women who were vaccinated and then had cervical surgery were 64.9% less likely to develop subsequent disease of CIN 2 or worse[6]
  - Women who were vaccinated after loop electrosurgical excision procedure (LEEP) therapy for CIN 2/3 had an approximately 66% reduction in recurrent disease[7]

Kang and colleagues investigated the benefit of vaccination post-treatment in 737 women aged between 20 and 45 years.[7] Results indicated that immunization with the quadrivalent vaccine post-LEEP reduced the recurrence of CIN 2/3. Furthermore, risk of recurrence was found to be higher for women who were not vaccinated (hazard ratio [HR], 2.840; $P<.01$), had cone margin involvement (HR, 4.869; $P<.01$); or had positive endocervical involvement (HR, 3.102; $P=.01$).

In all studies, no differences with regard to age, previous cytological abnormalities, and CIN grade at the time of the LEEP were noted among women who did or did not have recurrent disease.

What can we as practitioners conclude from the various studies?

Although the studies and approval for the vaccines are limited to age 45, the Canadian guidelines (NACI) state no upper age limit for vaccination. This can be seen as an off-label decision for the older patient and her caregiver. There is data to support a decreased risk of disease recurrence in a vaccinated cohort. There is also data to support a decreased risk of disease in other locations (ie, vaginal, vulvar, etc) in women who have had cervical cancer and then been vaccinated.[6]

Although we still do not have sufficient data to understand why some women clear the oncogenic virus easily and others are burdened with persistence, we do know that persistence can lead to disease. Therefore, in my understanding, a patient with disease at the cervix has demonstrated that she is at risk for HPV persistence and may therefore

benefit from vaccination in order to decrease her risk of recurrent disease (at the cervix as well as at a new location). This warrants our attention and discussion with the patient so that she can be aware of the options and make an informed decision.

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Note on HPV Vaccination From the NAMS Executive Director

The US Food and Drug Administration rejected Merck's request to market its HPV vaccine, Gardasil, to US women aged between 27 and 45 years.

Data from the quadrivalent HPV vaccine trial indicated that vaccine efficacy in the per-protocol analysis was high, indicating that some women could benefit from vaccination.[1] However, identifying specific groups or individual adult women who might benefit from vaccination has not yet been felt possible, because most women clear their HPV infection, and more than half of women with HPV infection developed an antibody response. Individual choice might suggest that it is selectively appropriate to discuss or offer.

Reference

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What do you think about HPV vaccination for women aged older than 26 years? Visit our Member Forum to discuss the January *Menopause e-Consult*.

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