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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Early Initiation of Postmenopausal Estrogen Therapy: Cardioprotective at the Right Dose?

By Jeffrey T. Jensen, MD, MPH, with Commentary by Rebecca Allen, MD

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Dr. Jensen reports he is a consultant for Teva Pharmaceuticals and MicroChips; and is a consultant for and receives grant research support from HRA Pharma, Bayer Healthcare, Merck, Agile Pharm, Population Council, AbbVie, Evofem, and ContraMed. Dr. Allen reports she is a Nexplanon trainer for Merck and a Liletta trainer for Actavis, and she has served on advisory boards for Bayer and Pharmanest.

SYNOPSIS: Women randomized to oral estradiol therapy within six years after onset of menopause showed less progression of subclinical atherosclerosis than those who received placebo. This effect was not seen when therapy was initiated 10 or more years after onset of menopause.

SOURCE: Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016;374:1221-1231.

The National Institute on Aging supported the Early versus Late Intervention Trial with Estradiol (ELITE) study, a randomized, double-blind, placebo-controlled study designed to test the hypothesis that time of onset of hormone therapy affects the relationship to cardiovascular health in postmenopausal women. More specifically, the primary hypothesis of the study was that postmenopausal hormone therapy would reduce the progression of subclinical atherosclerosis when therapy was initiated soon after menopause (< 6 years) but not when initiated at a later time (≥ 10 years).

The ELITE study, conducted at the University of Southern California, recruited healthy (no diabetes or clinical evidence of cardiovascular disease) postmenopausal women. Enrollment was stratified according to the number of years past menopause: < 6 years (early) or ≥ 10 years (late). Subjects were randomized to

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In Memoriam

On May 4, 2016, Dan Mishell, MD, passed away at home surrounded by family. An internationally recognized leader in our field, Dr. Mishell's legacy includes more than 30 years of service as Chair of Obstetrics & Gynecology at the University of Southern California, founder and Editor-in-Chief of *Contraception* from 1970-2012, and founding member of the Population Council's International Committee for Contraception Research with service from 1970-2014. He performed innovative research, published widely, and made a major impact on all areas of our specialty. Examples include the co-development of contraceptive implants, the LNG IUS, and the Copper T380 IUD. Dan was also a great gentleman, collaborator, and friend. Women worldwide are better off due to the lifelong efforts of Dr. Mishell. Let us remember him by carrying on this important work.

— Jeffrey T. Jensen, MD, MPH, Editor

receive oral 17ß-estradiol (1 mg daily) or matching placebo. Additional randomization stratification factors included baseline carotid-artery intima–media thickness (CIMT) (< 0.75 or ≥ 0.75 mm) and hysterectomy status (yes or no). Women with an intact uterus received daily micronized progesterone (45 mg) as a 4% vaginal gel (estrogen arm) or placebo gel (placebo arm) for 10 days during each 30-day cycle. The primary outcome was the rate of change in CIMT, assessed every six months during trial follow-up. Secondary endpoints included measurements of cognition (not reported in this paper) and the degree of coronary atherosclerosis assessed by computed tomography (CT) scan. Out of 2,243 postmenopausal women screened, 643 were randomized. Of these, 248 (123 in the placebo group and 125 in the estradiol group) in the early postmenopause (median age, 55.4 years) cohort and 348 women (176 in the placebo group and 172 in the estradiol group) in the late postmenopause (median age, 63.6 years) cohort contributed CIMT data for analysis of the primary endpoint.

The overall adherence to the study regimen was excellent (98%). After a median five-year intervention, there was a significant difference in the effect of hormone therapy on CIMT progression between the early and late postmenopause groups. In the early cohort, the mean rate of change in the estradiol group (0.0044 mm/yr) was significantly lower than placebo (0.0078; $P = 0.008$). In contrast, in the late group, the rate of change did not differ (0.010 estradiol, 0.0088 placebo; $P = 0.29$). In post-hoc analyses, the results were similar in women who received estradiol alone or in combination with progesterone, and in women who used lipid-lowering or antihypertensive therapy. There were no significant differences in cardiac CT outcomes between the estradiol and placebo groups in either the early or late postmenopause groups.

Taken together, these results support the validity of the "timing" hypothesis. Initiation of estradiol therapy within 6 years of menopause offers protection against subclinical atherosclerosis (as measured by CIMT), but initiation 10 or more years after menopause does not have a similar benefit.

■ COMMENTARY BY JEFFREY T. JENSEN, MD, MPH

One of the major criticisms of the Women's Health Initiative (WHI) study is that the population studied was asymptomatic and approximately 10 years postmenopausal — a decade older than the age at which women commonly start hormone replacement therapy. One explanation for the negative cardiovascular effects observed in WHI and the positive benefits seen in observational studies is that a critical window for initiation of treatment may exist, the "aging" or timing hypothesis. Evidence in support of a critical window comes from a follow-up re-analysis of the WHI combined conjugated equine estrogen/medroxyprogesterone acetate treatment group.[1] A nonsignificant trend toward protection from cardiovascular disease was observed in women less than 10 years postmenopausal in contrast with the elevated risk observed in women starting therapy more than 20 years after menopause.

Other studies support this timing hypothesis. The Estrogen in Prevention of Atherosclerosis Trial (EPAT) showed a reduction of atherosclerosis progression in postmenopausal women without coronary heart disease who were treated with oral estradiol.[2] In contrast, a companion study, the Women's Estrogen Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), found no benefit of estrogen therapy in women with an existing coronary lesion. Together, these studies suggest that estrogen therapy helps prevent the development of atherosclerotic

plaques, but does not reduce the size or progression of existing lesions. Based on these findings, the group, led by Howard Hodis at USC, received funding for the ELITE to more directly explore the timing hypothesis.

The primary outcome of ELITE was the change in CIMT, a measure of progression of atherosclerosis. The authors found that initiation of estrogen therapy within six years of onset of menopause reduced the progression of atherosclerosis, an effect not seen when therapy was initiated after 10 years. There was no difference between early and late initiation of estrogen therapy in the secondary outcome of CT angiogram findings. Although positive findings from this measure would have provided additional evidence to support hormonal therapy, this measure reflects baseline cardiac disease, so the finding is consistent with other studies that have shown no benefit of hormonal therapy on existing lesions. All the more reason to treat early.

A key limitation of the study is the use of surrogate measures rather than actual cardiac events. However, the CIMT method has been validated to correlate with the progression of coronary artery disease.[3] Additionally, only oral estradiol was studied, and the regimen of sequential micronized vaginal progesterone gel for women with an intact uterus is not widely used. Still, the results are highly supportive of the validity of the timing hypothesis. To answer the question using cardiac outcomes would require enrolling thousands of women in a multiyear, randomized study. Don't hold your breath for another large-scale clinical study of postmenopausal therapy sponsored by the National Institutes of Health.

Can we accept the results of ELITE? The recently published Kronos Early Estrogen Prevention Study (KEEPS) also evaluated the aging hypothesis.[4] This study showed no difference in CIMT progression in women within 36 months of the onset of menopause randomized to receive received oral conjugated estrogens 0.45 mg/d or transdermal estradiol 50 mcg/d (plus oral micronized progesterone capsules 200 mg/d on days 1 to 12 of each month in women with an intact uterus) or placebo. The difference in outcomes between KEEPS and ELITE suggests that dose may play a role in mediating the effect of estradiol on the vessel wall independent of route of administration. One result of the WHI has been a consistent pressure to find the "lowest effective dose" of estrogen. In general, the dose response for bone drives the discussion. While levels of estradiol around 40 pg/mL are considered bone protective, this may be insufficient to produce cardiovascular benefits. I am not a fan of the minimum dose approach that has been advanced by many following the WHI. Keeping serum estradiol in the 50-80 pg/mL range seems appropriate. The advantage of estradiol over conjugated estrogens is the availability of serum assays at clinical labs that can help in the management of patients.

The ELITE study provides additional information in support of the timing hypothesis. Although reduction in cardiovascular disease is not a primary indication for hormone replacement therapy, these results support absence of a negative effect and are highly encouraging that protection may exist when appropriate doses of estrogen are used. Women and clinicians should feel reassured by these results.

■ COMMENTARY BY REBECCA ALLEN, MD

The ELITE study was conducted to test the timing hypothesis of menopausal hormone therapy (HT): Initiation of HT in early menopause (within 10 years) is not harmful (and possibly helpful) to cardiovascular health, whereas initiating HT in late menopause is associated with greater risk. The results of this study add to the growing body of literature that the timing of HT initiation makes a difference in the degree of cardiovascular risk a woman experiences. Scientists have theorized that estrogen has favorable endothelial effects in women recently menopausal but has adverse effects on advanced atherosclerotic lesions in older menopausal women.[5] ELITE demonstrated that estradiol may actually slow the progression of atherosclerosis in women less than six years from menopause. The results of this study agree with a re-analysis of WHI data published in 2013.[6] This re-analysis showed that among women in the estrogen-only group, those aged 50 to 59 years actually had a net reduction in mortality and cardiovascular disease outcomes, while those aged 60 to 69 years were no different than placebo, and those aged 70 to 79 years experienced greater mortality and cardiovascular events compared to placebo.

The limitations of this study are significant, however, mainly due to the use of a surrogate endpoint. CIMT measurement has been used in past studies as a predictor of coronary artery disease.[7] Nevertheless, the study was not powered to assess actual clinical coronary artery disease events nor was the duration of follow-up likely long enough to detect significant differences. So the results of this study must be interpreted cautiously. There are not yet enough data for a return to use of HT for prevention of cardiovascular disease.

I find this study reassuring, however, regarding the use of HT in women who are perimenopausal or recently postmenopausal. Estrogen therapy remains the most effective treatment for vasomotor symptoms, but the dissemination in the media of the WHI trial results has dramatically reduced the number of women using HT. The North American Menopause Society (NAMS) and the American College of Obstetricians and Gynecologists agree that HT should be individualized using the lowest effective dose for the shortest duration to treat symptoms.[8,9] NAMS also states that "the benefits outweigh the risks for most healthy, symptomatic women aged younger than 60 years or within 10 years of the final menstrual period." ELITE supports this recommendation. ■

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ABSTRACT & COMMENTARY

Pessaries in Patients with Short Cervices

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

SYNOPSIS: The largest multicenter, randomized, controlled trial so far has found no significant benefit of pessaries to prevent preterm birth or to decrease neonatal morbidity in patients with short cervices.

SOURCE: Nicolaides KH, Syngelaki A, Poon LC, et al. A randomized trial of cervical pessary to prevent preterm singleton birth. *N Eng J Med* 2016;374:1044-1052.

Previous Alerts have been devoted to preterm birth (PTB) because it remains one of our biggest obstetrical problems. After many years of a frustrating inability to put a dent in the rate of PTB, the good news is that recently there has been a trend downward from our peak rate of 12.8% in 2006 to 9.6% in 2014.[1]

Possible reasons for this heartening change might include the use of progesterone, screening with cervical length (CL), judicious use of cerclage, or simply an increased awareness of its possible presence. While looking for yet another treatment option, practitioners have been awaiting more news on the newest method for prevention of PTB: the pessary.

An article in the March *New England Journal of Medicine* may help in decision-making by clinicians for patients noted to have short cervices in the mid trimester. Nicolaides et al undertook a randomized clinical trial (RCT) involving patients with singleton pregnancies with CLs < 2.5 cm between 20 and 24 weeks.[2] A total of 935 patients were recruited from hospitals in 16 countries, although most (n = 746) were from England. The authors randomly assigned 467 patients to have an insertion of an Arabin pessary and 465 patients were designated as controls. If the cervix was < 1.5 cm, both groups were given vaginal progesterone daily. The pessary was removed empirically at 34 weeks.

Delivery at less than 34 weeks occurred in 55 controls (12.0%) vs. 50 in the pessary group (10.8%) (odds ratio [OR], 1.12; 95% confidence interval [CI], 0.77-1.65). After adjusting for various confounding factors, such as "iatrogenic intervention" (antibiotics, progesterone, and past obstetrical history), significance was still not attained (OR, 1.09; 95% CI, 0.73-1.61). There were no differences in neonatal outcomes between the two groups. Adverse outcomes included vaginal discharge (46.8% vs. 13.8%) and pelvic discomfort (11.4% vs. 3.4%). Although 24.5% had the pessary removed because of premature rupture of membranes, preterm labor, and indicated early deliveries, another 10% of patients were bothered by the pessaries enough to request that they be removed.

■ COMMENTARY

This study represents the largest of only three RCTs that have addressed pessary use in singletons whose mothers have short cervices. One study[3] has suggested benefit and another[4] has not, so this study represents a "tiebreaker" of sorts, which will have to sit until new information surfaces. It is interesting that while two out of three studies showed no benefit of pessaries in singletons, the same mixed bag of results are popping up with pessaries in twins, where there is a desperate need for prevention of PTB. Although a very recent small case control study in the *Green Journal*[5] showed a significant benefit from pessaries in patients with twins whose CL < 2.0 cm, other studies, including another RCT from Nicolaides et al,[6] found no difference in PTB prior to 34 weeks with pessaries. Another RCT showed no difference in neonatal outcomes in twins when pessaries were empirically placed.[7] Secondary analysis in this study, however, showed some improvement in outcome in patients with CL < 3.8 cm. Nevertheless, the predominance of evidence points toward no benefit from pessaries in twins.

The following is a summary of information to date on various methods to prevent PTB:

1. The original, and largest, study shows 17 alpha-hydroxyprogesterone caproate (17P) to be effective in preventing recurrent PTB in patients with a past history.[8]
2. Meta-analysis shows vaginal progesterone to be useful in patients with short cervices, irrespective of history, but the weakest effect occurred in patients with CL < 1.0 cm.[9]
3. Two RCTs show vaginal progesterone to outperform IM progesterone in decreasing PTB.[10,11]
4. Meta-analysis shows that cerclage decreases PTB in patients with short cervices (< 2.5 cm) who have a history of PTB, with its greatest effect in patients with CL < 1.5 cm. However, significant benefit was not seen in those without a history.[12]
5. Two out of three studies show that pessaries are not effective in preventing PTB in singletons with short cervices.[2,3,4]
6. Twins: While waiting for more data to be published, thus far there is no compelling evidence that progesterone, cerclage, or pessary are useful in preventing PTB in twins. ■

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ABSTRACT & COMMENTARY

Colpocleisis: Body Image, Satisfaction, and Regret at 24 Weeks

By Chiara Ghetti, MD

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Dr. Ghetti reports no financial relationships relevant to this field of study.

SYNOPSIS: Colpocleisis is an effective surgical treatment for pelvic organ prolapse. Women report high satisfaction and low regret.

SOURCE: Crisp CC, Book NM, Cunkelman JA, et al; Society of Gynecologic Surgeons' Fellows' Pelvic Research Network. Body image, regret, and satisfaction 24 weeks after colpocleisis: A multicenter study. *Female Pelvic Med Reconstr Surg* 2016;22:132-135.

The objective of this study was to determine the effect of colpocleisis on body image, regret, and pelvic floor symptoms 24 weeks after surgery. This was a multicenter prospective cohort study of 88 women choosing to undergo colpocleisis for surgical management of prolapse. The primary outcomes were body image, measured by the modified Body Image Scale; pelvic floor symptoms, measured by the Pelvic Floor Impact Questionnaire and the Pelvic Floor Disorders Inventory; satisfaction, measured by the modified Satisfaction with Decision Scale and a Visual Analog Scale that measured satisfaction with surgical outcome; and regret, measured using the Decision Regret Scale. Six-week outcomes were reported in a prior study. Outcomes for this study were measured 24 weeks after surgery. Women with dementia or mental status changes impeding completion of study questionnaires were excluded, as were subjects who did not ultimately undergo a colpocleisis.

Eighty-eight women underwent colpocleisis. Seven subjects were deceased at the time of 24-week follow up. Body image and pelvic floor symptoms bother scores were significantly improved at 24 weeks compared to preoperative scores. Subjects reported high satisfaction and low regret. Of the

six subjects who expressed regret, three reported regret due to urinary complaints, one due to prolapse, one due to a perioperative complication, and one reported regret due to loss of the ability to have vaginal intercourse.

■ COMMENTARY

For patients and physicians, choices surrounding surgical management of pelvic organ prolapse are influenced by numerous factors. These factors are unique to each patient and include pelvic floor symptoms, anatomic extent of prolapse, medical comorbidities, and the patient's desire to restore vaginal anatomy to maintain vaginal function (penetrative sex).[1] For older patients who do not desire vaginal patency, a colpocleisis is a viable option with excellent anatomic outcome. This obliterative procedure can be used both in the treatment of post-hysterectomy apical prolapse or uterovaginal prolapse. In a woman with a uterus, a total colpocleisis can be performed after vaginal hysterectomy. A total colpocleisis involves a total colpectomy (removal of the majority of the vaginal epithelium) and imbrication of the fibromuscular layer, and ideally is followed by restriction of the genital hiatus with a concurrent levator myorrhaphy. The resulting vaginal length is usually approximately 3 cm. In women retaining their uterus, a partial, or Le Fort, colpocleisis can be performed. During a Le Fort colpocleisis, rectangles of anterior and posterior vaginal epithelium are excised and the underlying fibromusclar layer is sutured together. As the prolapsing uterus and vagina are progressively reduced, drainage tunnels are created from the cervix to the introitus bilaterally. These tunnels allow passage of vaginal discharge and uterine bleeding. Compared to reconstructive approaches, the possible benefits of a colpocleisis include decreased operative time, decreased blood loss, decreased operative adverse events, and decreased recovery time.[2,3]

In this study of patients undergoing colpocleisis, subjects demonstrated significant improvements in pelvic floor symptoms and body image 24 weeks after surgery. Subjects also reported high satisfaction and low regret. Similar findings were reported in this cohort at six weeks. This study provides the long-term follow-up of the initial short-term postoperative findings.

There is a paucity of literature addressing the indication of additional procedures at time of colpocleisis. Specifically, there is very little to guide the decision of whether to perform a hysterectomy at time of obliterative procedure in women with uterovaginal prolapse. Concomitant hysterectomy has been shown to lead to increased operative time and blood loss.[3] Some surgeons routinely perform a hysterectomy due to concerns about possible future endometrial cancer; others choose to perform a Le Fort and to evaluate the endometrium via endometrial biopsy or ultrasound prior to the procedure, and/or dilatation and curettage at time of Le Fort's colpocleisis. Long-term prospective data are lacking to establish a standard of care. A recent decision analysis suggests that a Le Fort colpocleisis should be the preferred option in a patient with uterovaginal prolapse undergoing an obliterative procedure.[4] However, many individual factors affect this decision, and a Le Fort is never appropriate in a patient with postmenopausal bleeding.

In our practice, the preferred obliterative procedure is a vaginal hysterectomy with total colpectomy, colpocleisis, and levator myorrhaphy. We believe the most critical part of the procedure is the levator myorrhaphy, which significantly reduces genital hiatus size. In colpocleisis failures referred to us, a levator myorrhaphy was not performed.

Despite several limitations, including absent description of standardized surgical methodology, use of a non-condition specific body image scale, and lack of anatomic outcomes, this study adds to existing literature supporting colpocleisis in appropriate patients. Colpocleisis is a reliable option for elderly women with pelvic organ prolapse who are not and do not plan to be sexually active and should be included in surgical counseling of patients. ■

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SPECIAL FEATURE

Vulvar Squamous Intraepithelial Lesions

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck and a Liletta trainer for Actavis, and she has served on advisory boards for Bayer and Pharmanest.

In 2012, the American Society for Colposcopy and Cervical Pathology and the College of American Pathologists introduced the Lower Anogenital Squamous Terminology (LAST).[1] The goal of LAST was to unify the diagnosis of human papilloma virus (HPV)-related diseases of the entire lower anogenital tract for both females and

males. The LAST system divided HPV-associated squamous lesions into low-grade and high-grade including vulvar lesions. Low-grade squamous intraepithelial lesion (LSIL) of the vulva represented the old term vulvar intraepithelial lesion 1 (VIN 1) and high-grade squamous intraepithelial lesion (HSIL) of the vulva represented VIN 2-3. However, there were a couple of issues with this classification according to the International Society for the Study of Vulvovaginal Disease (ISSVD).[2] First, albeit focusing on HPV only, LAST did not include the entity known as differentiated VIN (DVIN), which has a higher risk of progression to cancer than HPV-associated VIN. DVIN usually is not associated with HPV, and it is important to note that the vulva has no transformation zone like the cervix and anus. DVIN is often related to preexisting lichen planus or lichen sclerosus of the vulva. In a recent worldwide review of 2000 cases of VIN and vulvar cancer, HPV DNA was found in 86.7% of VIN and 28.6% of vulvar cancer.[3] In a smaller U.S. review, HPV DNA was found in 97.1% of VIN 3 and 69% of invasive vulvar cancer.[4] Second, by including vulvar LSIL, there was concern that the LAST system would lead to overdiagnosis and treatment of an essentially benign lesion with no risk of progression to HSIL or cancer. Vulvar LSIL or VIN 1 is not considered a precancerous lesion, but rather "the reaction of the skin to HPV infection."[2] To resolve these two concerns, the ISSVD adapted LAST to the specifics of the vulva and released the new 2015 ISSVD terminology (*see Table 1*). Vulvar LSIL is benign and includes HPV effect and flat condyloma. Vulvar HSIL is the usual HPV-associated type of high-grade vulvar intraepithelial neoplasia and the non-HPV-associated type is labeled differentiated-type vulvar intraepithelial neoplasia.

Now that the classification is clear, what about diagnosis and treatment? The most common presenting symptom of vulvar HSIL/DVIN is pruritis.[5] However, lesions may be asymptomatic; therefore, a careful vulvar exam at each annual gynecologic visit is important. For those groups who advocate abandoning the yearly pelvic exam, I would argue that an external vulvar exam should not be omitted, regardless of whether a speculum or bimanual exam is being performed. A vulvar biopsy should be performed for lesions of uncertain etiology, lesions that do not respond to therapy as expected, and lesions for which dysplasia or malignancy cannot be excluded. It is important to remember that vulvar HSIL/DVIN may be found concomitantly with vulvar carcinoma, so the threshold for vulvar biopsy should be low.

Vulvar LSIL does not require any treatment unless the patient is symptomatic or desires removal for cosmetic reasons.[2] Vulvar HSIL and DVIN should be treated, as it is impossible to predict progression to vulvar carcinoma. Treatment choices include wide local excision (WLE), laser ablation, and medical therapy. It is important to counsel patients that, for all treatments, there is a high incidence of recurrence (30-50%) and a risk of progression to cancer.[5] One retrospective study of 303 patients with VIN 2-3 found that 87 patients (28.7%) developed recurrent disease, which was associated with smoking, larger lesion size, and positive margins. Seven women (2.3%) developed invasive disease a median of 109 months (range 12-327 months) from initial diagnosis.[6] For surgical modalities, an excisional margin of at least 5 mm is recommended.[5] Candidates for laser ablation should be selected carefully, as occult squamous cancer was found in 22% of patients in one review of 73 cases.[7] Additionally, in one study of 50 women, those undergoing WLE were more likely to be free of recurrences at 5 years compared to those who underwent laser vaporization (91% for surgery vs. 51.3% for ablation).[8]

Table 1. 2015 International Society for the Study of Vulvovaginal Disease Terminology

- Low-grade squamous intraepithelial lesion of the vulva (vulvar LSIL)
- High-grade squamous intraepithelial lesion of the vulva (vulvar HSIL)
- Differentiated-type vulvar intraepithelial neoplasia (DVIN)

Medical therapy most commonly uses 5% imiquimod cream, an immune response modifier that triggers a local immune response. A recent review examined imiquimod therapy for vulvar HSIL.[9] The authors identified 14 studies encompassing 780 women, of which 354 were treated with imiquimod. All the patients had histologically confirmed VIN 2-3 and there were two randomized, controlled trials, eight prospective uncontrolled studies, and four retrospective cohort studies. The most common regimen used was escalating doses of cream application, starting once a week and then increasing to three times a week for 12-20 weeks, depending on response and side effects. Overall, complete clinical response ranged from 16% to 76%, depending on the study.[9] Looking at just the randomized, controlled trials that compared imiquimod to placebo, one study of 52 women showed a complete response of 35% compared to 0% for placebo, and the other study of 32 women showed an 81% response rate compared to 0% for placebo. The difference in response rate was not explained by dosing regimen, smoking, or lesion grade. Adverse effects of treatment included vulvar burning, pruritis, and pain that required dose reductions or pauses in treatment among 8% to 85% of patients, depending on the study.[9] Other topical agents such as cidofovir are being studied. There are no quality trials comparing medical and surgical treatment. The most recent Cochrane review on the subject concluded that "topical treatment (imiquimod or cidofovir) may effectively treat about half of vulvar HSIL cases after a 16-week course of treatment, but the evidence on whether this effect is sustained is limited."[10] Ultimately, the decision to proceed with topical therapy rather than surgery will have to be individualized, taking into account the number of lesions, lesion size, and whether occult cancer is suspected.

Finally, in terms of prevention, the HPV vaccine holds the most promise to reduce the incidence of vulvar HSIL. In a review of 244 cases of VIN 3 and invasive vulvar

cancer in the United States before HPV vaccine introduction, HPV 16 was present in 48.6% of invasive vulvar cancer cases and 80.9% of VIN 3 cases; other high-risk HPV was present in 19.2% of invasive vulvar cancer cases and 13.2% of VIN 3 cases.[4] The new 9-valent HPV vaccine, which includes HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, was found to reduce the risk of high-grade cervical, vulvar, and vaginal disease by 96.7% in the per protocol efficacy population.[11] It is anticipated that the HPV vaccine will play a large role in reducing the incidence of vulvar HSIL in the future. For prevention of differentiated type-VIN, a recent study demonstrated that women with vulvar lichen sclerosus who were compliant with preventive topical corticosteroids were significantly less likely to develop VIN and squamous cell carcinoma.[12] ■

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CME/CE QUESTIONS

1. What was the primary objective of the ELITE study of postmenopausal hormone therapy?

a. Evaluate the rates of cardiovascular mortality in users of oral estrogen.

b. Evaluate all-cause mortality following use of vaginal progesterone.

c. Evaluate progression of surrogate markers of cardiovascular disease.

d. Evaluate quality of life and sexual function with combined hormone replacement therapy.

2. Which of the following has not been proven effective in preventing preterm birth (PTB)?

a. 17P in patients with a history of PTB.

b. Cerclage in patients with CL < 2.5 cm.

c. Cerclage in twins with CL < 2.0 cm.

d. 17P in patients with a history of PTB.

e. All of the above are correct.

3. Women who undergo colpocleisis express:

a. a large amount of regret following the procedure.

b. a significant decrease in body image following obliterative procedure.

c. high satisfaction 24 weeks after surgery.

d. persistent pelvic floor symptoms following surgery.

4. The 2015 International Society for the Study of Vulvovaginal Disease Terminology includes which of the following?

a. VIN 3

b. VIN 1

c. Condyloma acuminata

d. Vulvar HSIL