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Financial Disclosure: *OB/GYN Clinical Alert's* editor, Jeffrey T. Jensen, MD, MPH, is a consultant for Agile Pharmaceuticals, Bayer Healthcare, HRA Pharma, and Merck; is a speaker for Bayer Healthcare and Merck; and receives research support from Agile Pharmaceuticals, Abbott Pharmaceuticals, Bayer Healthcare, HRA Pharma, and Medicines360. Peer reviewer Catherine Leclair, MD; executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Screening for Preeclampsia with Uterine Artery Dopplers

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synposis: *Data from a large trial in patients at low risk for preeclampsia show that uterine artery waveforms analysis has little value as a screening method for preeclampsia.*

Source: Myatt L, et al. The utility of uterine artery Doppler velocimetry in prediction of preeclampsia in a low-risk population. *Obstet Gynecol* 2012;120:815-822.

Ever since Stuart Campbell introduced the concept of using ultrasound waveforms of the uterine artery to screen for preeclampsia (PE), single studies and meta-analyses have emerged to address its efficacy — with inconsistent results. Investigators in the NICHD perinatal network recently decided to study the screening potential of uterine artery Dopplers in a low-risk patient population, the results of which were published in the October 2012 issue of *Obstetrics & Gynecology*.[1]

In this study, 2188 second-trimester nulliparous patients who had no risk factors for PE were selected. All had uterine artery waveforms obtained prior to 21 weeks (average of 16 weeks). Interestingly, these patients were members of a cohort group that was formed as part of a randomized clinical trial to determine if antioxidant supplementation prevented PE. Uterine artery waveforms were obtained in standardized fashion with Doppler ultrasound, and results were analyzed based on the presence or absence of a notch in a diastolic portion of the waveform or the demonstration of increased resistance in the spiral arteries by a high average resistance index (RI) according to gestational age. PE was diagnosed clinically by standard clinical definitions.

VOLUME 29 • NUMBER 8 • DECEMBER 2012 • PAGES 57-64

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PE occurred in 165 of the 2188 patients screened (7.5%) — a surprisingly high rate in this population. Using a threshold RI of the 75th percentile, the sensitivity for PE was 43% (95% confidence interval [CI], 35-51) with a specificity of 67% (95% CI, 65-69) for all forms of PE. However, an increased RI was more predictive of early onset PE (< 34 weeks) with a sensitivity of 78%, a specificity of 66%, and an increase in odds ratio (OR) of 6.9. The presence of notches did not correlate with the overall incidence of PE, but was correlated with early PE. The authors concluded that the method has "a poor sensitivity for prediction of PE overall in a well-characterized, low-risk nulliparous population." However, the authors indicated that the method did predict "trophoblastic invasion of spiral arteries of a magnitude that compromises utero-placental flow that gives early onset disease."

■ COMMENTARY

Remodeling of the spiral arteries occurs in two waves. During the first wave (before about 14 weeks), the decidual (surface) portion of the spiral arteries in the basal plate of the placenta normally are invaded by the adjacent trophoblast. The second wave occurs in the second trimester and involves deeper invasion into the myometrial portion of the spiral arteries, resulting in a wide-open pathway that allows blood to flow freely into the inter-villus space. In PE, this invasion does not occur, especially the second wave of invasion. Since uterine artery waveforms represent an upstream reflection of the status of the spiral artery bed, they have the potential to provide information to predict PE. However, study results have been variable, depending on the population studied. The largest meta-analysis was undertaken by the World Health Organization and involved 43 studies (22 were in low-risk patients and 18 in high-risk patients).[2] The analysis included 42,000 patients. The likelihood ratio for PE overall was 4.2 for a high uterine artery RI and 3.5 to 6.6 for a single notch or double notch, respectively. Most importantly, the likelihood ratio for early PE (< 34 weeks) was 7.94 for a single notch and 15.9 for bilateral notches. Another very recent small study in high-risk pregnancies dealt with using uterine artery waveforms in the first and second trimesters.[3] It showed that an increased RI in the second trimester was more predictive of PE (overall) (36%; OR = 2.9) and early PE (18.2%; OR = 11.9) than first trimester waveforms. First trimester waveforms picked up only one case of PE (overall) and no cases of early PE if the second trimester Dopplers were normal later. However, if both first and second trimester waveforms were abnormal, the risk of PE (overall) was 57% (OR = 6.7) and for early PE was 28% (OR = 29.1).

From the data available, there is little evidence that screening a low-risk population with uterine artery Dopplers is useful. However, in high-risk patients, the evidence does suggest a reasonable ability of uterine artery waveform analysis to predict overall PE and a very good ability to predict severe, early PE.

Actually, the question of whether to screen for PE becomes moot if there is nothing we can do to prevent it in susceptible patients. Here there is evidence that increased surveillance and stepped-up prenatal care can improve outcome.[4] Also, most importantly, some studies show that we may be able to decrease overall PE and early PE with carefully timed administration of low-dose aspirin (ASA).

In 2003, Coomarasamy et al published a meta-analysis of 14 studies using low-dose ASA to prevent PE in women with risk factors.[5] They found that treating with low-dose ASA resulted in a statistically significant, but non-dramatic, drop in PE (OR = 0.86), perinatal death (OR = 0.79), and preterm birth (OR = 0.86), and a sizable increase in average infant weight of 215 g. The same group did a meta-analysis of five studies to evaluate the use of low-dose ASA in patients with abnormal uterine artery waveforms and found a reduction in overall PE by 50%.[6]

Perhaps the most significant contribution recently came from Montreal. Bujold analyzed outcome data from 22 randomized trials in which ASA randomization was begun after 16 weeks and compared these results with those from 12 studies in which randomization was begun before 16 weeks.[7] There was a modest, non-significant, reduction in PE (0.81) in the > 16-week group compared with a significant reduction (0.47) in PE in those in whom

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
SENIOR VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***OB/GYN Clinical Alert***, P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
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Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

Summary Points

1. Using uterine artery waveforms to screen for PE in a low-risk population is not effective.

2. All high-risk patients might benefit from low-dose ASA (84 mg OD) after 12 weeks. These would include:
   - Those with a previous history of PE.
   - Those with chronic hypertension (whether or not they are on antihypertensives).
   - Those who have delivered a growth restricted infant.
   - Those with any form of thrombophilia.

3. If all of the above patients are on, or will be on, low-dose ASA, there would be no need to do uterine artery analysis in the first trimester.

4. Second trimester uterine artery waveforms may be useful in identifying those high-risk patients who have the greatest chance for PE, and the pattern of management can be adjusted accordingly.

5. If the second trimester uterine artery waveforms are normal, these patients can be managed in the usual low-risk fashion and given some reassurance that their risk of severe PE is very low.

6. There are no data to determine how long patients should be on ASA, but I have been discontinuing ASA after 34 weeks (some anesthesiologists are reluctant to offer epidurals to patients on low-dose ASA), and by that time it probably has done its job.

ASA was begun < 16 weeks. Most importantly, there was a highly significant drop in early, severe PE (0.09) in the < 16 week group, suggesting that if one were to optimize the ability of ASA to prevent severe PE, it should be on board before 16 weeks.

Since ultrasound evaluation of uterine artery waveform analysis involves increased cost and expertise, would it not make sense to finesse the ultrasound and simply prescribe low-dose ASA for all high-risk patients? Since there is no evidence that ASA delivered in this dosage causes harm, I think an argument could be made for this approach. There are two benefits of the ultrasound step that could impact the outcome and the psyche of the patient. As mentioned above, there is evidence that enhanced perinatal care can benefit patients at risk for PE[4] (and this would include those with abnormal uterine artery waveforms). Also, having a negative uterine artery result can have very beneficial spinoff. Every study so far has shown an extremely low chance of PE developing after a reassuring result (negative predictive values of 98-100%). In the vast majority of high-risk patients, the second trimester waveforms will be normal (80% in the most recent study).[3] In these patients, we should be able to loosen up on our surveillance and give the patient some reasonable reassurance that she will not have PE, and most importantly, a severe form of it — an experience that usually leaves an indelible impression on every patient having previously experienced it. ■

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Clinical Considerations for Uterine Serous Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Uterine (papillary) serous cancer is a genomically unstable cancer associated with poor survival even in stage I. It is also frequently associated with a secondary malignancy, particularly breast cancer. Comprehensive surgical staging is recommended since extrauterine disease can be present without other high-risk uterine features, like myometrial invasion. How-*

ever, an optimal adjuvant treatment protocol remains to be defined.

Source: Growdon WB, et al. Prognostic determinants in patients with stage I uterine papillary serous carcinoma: A 15-year multi-institutional review. *Int J Gynecol Cancer* 2012;22:417-424.

To evaluate the impact of surgical staging on survival of women with early stage (Stage IA and Stage IB) uterine papillary serous cancer (USC), a retrospective analysis was undertaken on patients treated over a 15-year period at two institutions. Over this time period, 84 cases of early stage cancer were identified. The diagnosis was based on histologic l features, including papillary architecture with tuft stratification, marked nuclear pleomorphism, high nuclear-to-cytoplasmic ratio, and a high mitotic count. Of the 84 identified cases, the majority were stage IA (n = 71); 37 patients (44%) had a history of a second cancer (22 breast tumors, 9 synchronous müllerian cancers). Surgical staging with at least hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic lymph node dissection was performed in 60 (71%) of 84 patients. The median survival for all patients was 10 years. Univariate analysis revealed that surgical staging ($P < 0.001$), normal preoperative CA-125 ($P < 0.001$), and absence of a secondary malignancy ($P < 0.01$) were associated with improved survival. Age-adjusted multivariate analysis incorporating these factors revealed that surgical staging (hazard ratio, 0.18; $P < 0.001$), substage (hazard ratio, 4.59; $P < 0.05$), and history of a second malignancy (hazard ratio, 2.75; $P < 0.04$) were independent factors associated with reduced overall survival. The former two remained independent factors if secondary malignancy was excluded. Treatment approach (observation, radiation, chemotherapy, or both) did not impact survival. It was concluded that independent of adjuvant therapy, early substage of disease, comprehensive surgical staging, and the presence of a second malignancy significantly impacted overall survival.

■ COMMENTARY

Uterine papillary serous, now termed uterine serous cancer, is widely recognized as unique histology, distinguished from "common" type or endometrioid adenocarcinoma by its frequent metastatic disease at presentation, frequent recurrence, and poor overall survival. Classically, it has underscored the two-class nomenclature frequently seen in textbooks, which highlight a disease (type II) that is associated with older age at presentation, absence of obesity, disassociation from estrogen use, and deep myometrial invastion.[1] USC accounts for just 10% of all primary uterine cancers but is responsible for 40% of the cancer-related deaths. The rarity of presentation has hindered clear treatment guidelines, particularly from Phase 3 adjuvant trials. This has led to a series of reports, like the current, which are retrospective in nature, generally with small patient cohorts, and gathered over long periods of time. However, from these types of studies, hypotheses can be generated which, until better information is available, can help foster rational treatment approaches. For most gynecologic oncologists, the most significant is recognition that uterine factors, such as size, location, and depth of myometrial invasion, are poorly associated with the probability of extrauterine spread. This is common practice for endometrioid, particularly early-stage, low-grade tumors where the risk of extrauterine spread is < 5% and formal staging may be overtreatment and unnecessary. In USC, even tumors confined to a polyp are associated with extrauterine or peritoneal dissemination (particularly the omentum) in one-third of patients.[2] The Society of Gynecologic Oncology and the National Comprehensive Cancer Network both have issued guidelines recommending surgical staging in all such cases if medically feasible.

The high rate of secondary tumors, particularly breast cancer, is curious but consistent across USC studies. The Cancer Genome Atlas (TCGA) has characterized USC to be not only distinct from its endometrioid counterpart, but in many ways, similar to high-grade serous ovarian cancer, with frequent P53 mutation and E-cadherin loss. The relationship between breast and ovarian cancer is well documented, but the association of BRCA germline mutation carrier status and USC is much less clear. Although more investigation is needed, the frequency of USC and breast cancer does raise the question of hysterectomy at the time of risk-reducing ovarian/tubal surgery for high-risk individuals.

In all, the USC population represents an important and distinct entity of disease challenged by much of the same clinicopathological features seen in ovarian malignancy. It is hoped that information emerging from the TCGA and other genomic interrogation efforts will help identify novel targets for future intervention.[3] ■

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Use of Long-acting Reversible Contraception Is Increasing: Have You Changed Your Recommendations?

ABSTRACT & COMMENTARY

By Jeffrey Jensen, MD, Editor

Synopsis: *Although the pill and female sterilization remain the most popular methods of contraception, fewer women report using condoms as a primary method and more are using intrauterine devices. Still, 11% of women at risk for unintended pregnancy report using no method.*

Source: U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Jones J, et al. Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995. National Health Statistics Reports; No 60. Hyattsville, MD: National Center for Health Statistics. 2012. Available at: http://www.cdc.gov/nchs/data/nhsr/nhsr060.pdf. Accessed Oct. 29, 2012.

The national survey of family growth (NSFG) is a national representative survey designed to provide data that supplement and complement the National Vital Statistics by collecting information on the factors that affect birth rates — including sexual activity, marriage, divorce, cohabitation, contraceptive use, and infertility. The NSFG originally was conducted as a periodic survey designed to interview a large number of women within a short period of time. Beginning in 2006, the design was changed to continuously interview smaller numbers of men and women for a longer period. The current report compares data using both of these methodologies involving the largest samples of women in the NSFG's history — 10,847 interviewed in 1995, and 12,279 interviewed between June 2006 and June 2010. These large numbers permit detailed comparisons that were not possible in previous reports. The key results from the 2006-10 cycle are that 62% of reproductive age (defined as 15-44) women report current use of a contraceptive method. Among women using a contraceptive method in the month of the interview, the most common methods used are the pill (28%, or 10.6 million women) and female sterilization (27%, or 10.2 million women). Big changes in use patterns occurred with certain methods, principally use of intrauterine devices (IUDs; increased from 0.8% in 1995 to 5.6% in 2006–2010) and condoms (decreased from 20.4% in 1995 to 16.4% in 2006-10). On a discouraging note, 11% of women at risk for pregnancy report not currently using any method of contraception.

■ COMMENTARY

This report provides important information on family planning trends in the United States. Established in 1973 by the National Center for Health Statistics, the NSFG contributes important representative data of factors affecting the formation, growth, and dissolution of families, including contraception, sterilization, and sexual activity. The NSFG was conducted five times (1973, 1976, 1982, 1988, 1995) with a national representative sample of women only. A sixth periodic survey, conducted in 2002, included both men and women. Beginning in 2006, the NSFG shifted to a continuous survey design that interviewed both men and women, and the current cycle for analysis concluded in June 2010. The present analysis permits a detailed comparison of trends in family planning over the last 15 years.

First the positives: Results from the 2006-10 survey show that use of more effective contraceptive methods is up. Particularly encouraging is the use of the most effective long-acting methods like IUDs. Compared to 1995, where fewer than 1% of women reported current use of an IUD, this has increased to almost 6% in 2010. The increase in IUD use is associated with a roughly equivalent decrease in the number of women reporting use of male condoms as a primary method of contraception (from 20.4% in 1995 to 16.4% in 2006-10). Since typical use failure of condoms (17%) is substantially higher than that of an IUD (< 1%), this is an excellent trade that should be driving down rates of unintended pregnancy and abortion.

Now the bad news: Current users of a contraceptive method at the time of the 2006-10 survey represented 62.2% of the sample, a drop of 2.0% since 1995. This translates to an estimated 1,235,100 fewer contraceptive users (2% of 61,755,000 women aged 15-44). Since an increase in the number of women desiring pregnancy might explain this decrease, it is important to point out that the decline is absorbed instead by a 2.4% boost in the proportion of women most at risk (e.g., those who report being sexually active within the last 3 months before the interview, not using a method, and not intending pregnancy) from 5.2% to 7.7%. This 2.5% increase in women not using contraception translates into an additional 1.5 million women at risk of unintended pregnancy. This is a continuation of a disturbing trend; the uptick in nonuse was 7.4% in the 2002 survey.[1]

The public health implications of this increase are noteworthy; it has been estimated that the 5.2% of nonusers in the 1995 sample contributed 54% of all unintended pregnancies (the rest occurred as a consequence of contraceptive failure).[2] Although national vital statistics data have not yet been correlated with the 2006-10 fig-

ures, conservatively running the numbers would support that the increase in women not using contraception may have resulted in more than 500,000 unintended pregnancies and 270,000 abortions in 2010. Although the overall numbers of unintended pregnancies and abortions are dropping, this is due to the increased use of more effective methods like the IUD. In other words, an even more impressive reduction in unintended pregnancies and abortions may have occurred if the number of nonusers had not increased between 1995 and 2010.

So why the increase in nonuse? Access and affordability issues must be considered among the potential explanations for the increase in nonuse of contraception. Since providing family planning services saves public money, it makes good sense to support universal access to family planning services.[3] This is an important part of health care reform that we should all discuss in our communities. At the same time, in our office practices, we should be spreading the word about long-acting reversible contraception, and moving nonusers of contraceptives to use of any method. ■

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Special Feature

How Should You Manage Cervical Cancer Screening in Women with HIV?

By Rebecca H. Allen, MD, MPH

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

Synopsis: *Annual Pap testing is safe for women infected with HIV and longer intervals are appropriate for those with serial negative tests. For women age 30 and older infected with HIV, cotesting with high-risk HPV DNA also could allow for longer intervals between testing.*

Sources: Castle PE, et al. Safety against cervical precancer and cancer following negative human papillomavirus and Papanicolaou test results in human immunodeficiency virus-infected women. *Arch Intern Med* 2012;172:1041-1043.

Keller MJ, et al. Risk of cervical precancer and cancer among HIV-infected women with normal cervical cytology and no evidence of oncogenic HPV infection. *JAMA* 2012;308:362-369.

Massad LS, et al. Negative predictive value of Pap testing: Implications for screening intervals for women with human immunodeficiency virus. *Obstet Gynecol* 2012;120:791-797.

Women with HIV have a higher incidence of cervical intraepithelial neoplasia (CIN) because of the burden and persistence of HPV in that population.[1,2] In our colposcopy clinic, we often see women infected with HIV who struggle with persistent HPV infection and come back year after year for evaluations. Therefore, screening women with HIV for cervical cancer is extremely important. The question of how to handle cervical cancer screening in women infected with HIV has never been explicitly answered by the American Society for Colposcopy and Cervical Pathology (ASCCP) in its guidelines.[3] The United States Preventive Services Task Force states that its cervical cancer screening guidelines do not apply to women who are immunocompromised (e.g., with HIV).[4] Because women with HIV have a higher chance of developing cervical precancer and cancer compared to the general population, the Centers for Disease Control and Prevention has recommended two Pap tests in the first year after HIV diagnosis followed by annual Pap tests provided the results are normal.[5] This recommendation is based on expert opinion because the sensitivity of a single Pap smear was not deemed adequate in this high-risk population. Nevertheless, if the Pap smear result is abnormal, according to ASCCP guidelines, women with HIV are managed the same as women in the general population.[6,7]

To explore the question of cervical cancer screening in women infected with HIV, I reviewed this trio of studies published in 2012. With the new cervical cancer screening guidelines for the general population including lengthening screening intervals,[3] investigators are now looking at screening frequency in the HIV-positive population. Massad et al used data from the Women's Interagency HIV Study, an ongoing U.S. multicenter cohort study of women with and without HIV who are followed to ascertain the development of HIV-related disease. Every 6 months, participants underwent a physical exam including a conventional Pap test. The primary study outcome was cervical precancer defined as a composite of high-grade Pap smears and biopsy results (CIN 2 or worse). The authors excluded women with past abnormal Pap smears, cervical dysplasia, cervical cancer, and hysterectomy. Out of 1225 women with HIV and a baseline Pap test, the au-

thors identified 942 (77%) women with a negative Pap smear. Eight of these women (1%) developed precancer within 15 months and 40 (4%) within 39 months. After three consecutive negative Pap tests, the negative predictive value was 100% at 15 months and 98.1% (95% confidence interval [CI] 97.0-99.3) at 39 months. Additionally, after 10 consecutive negative Pap tests, the negative predictive value was 100% at both 15 and 39 months of follow-up. Therefore, the authors concluded that in HIV-infected women with no history of abnormal Pap cytology or cervical precancer, annual Pap testing is safe and Pap testing every 6 months after diagnosis is unnecessary. Another important finding in this study was that women with HIV with serial negative tests could likely increase their screening interval safely similar to the general population.

In a multivariate analysis during the 15 months of follow-up, Massad et al identified risk factors for precancer in HIV seropositive women were any abnormal cytology (adjusted hazard ratio [HR], 9.9; 95% CI, 7.7-12.6), current smoking (adjusted HR, 1.5; 95% CI, 1.2-2.0), age younger than 31 compared to age older than 45 (adjusted HR 1.5, 95% CI 1.1-2.1), and CD4 count of 200-500 (adjusted HR, 1.8; 95% CI, 1.3-2.3) and < 200 (adjusted HR, 2.2; 95% CI, 1.6-2.9) compared to CD4 > 500, respectively. Use of HAART was not associated with precancer risk. These risk factors make clinical sense and it may be that lengthening screening intervals would be more appropriate for women with normal CD4 counts.

What about incorporating HPV DNA testing for cervical cancer screening in HIV-infected women? Traditionally, HPV DNA testing was not recommended for use in women with HIV because of the higher prevalence of HPV infection and limited evidence for its use in this population.[5] However, in 2003, the Kaiser Permanente Northern California system initiated cotesting with Pap and HPV DNA tests in all women, including those HIV positive, who were 30 years or older. In Castle et al, investigators from Kaiser Permanente Northern California reviewed records on these women in their health plan. The primary outcome was the risk of CIN 2 or worse on biopsy and/or HSIL cytology. Between 2003 and 2010, the authors identified 245 women who had a negative baseline HPV and Pap test and underwent a second cotest. The second cotest was performed at a mean of 24.4 months. Second cotest results were available for 241 women (21 [8.7%] with a positive result) and HPV results for 240 women (27 [11.3%] with a positive result). Of the 236 women with complete follow up, there were no cases of CIN 2 or more (0%; 95% CI, 0.0%, 1.6%) and one case of HSIL cytology (0.4%; 95% CI, 0.0%, 2.3%). Therefore, this small retrospective study showed that HPV DNA testing can be used in conjunction with Pap tests for primary screening in women infected with HIV.

These results are further supported by another analysis of the Women's Interagency HIV Study. Keller et al identified 420 HIV-infected women and compared them to 279 HIV-uninfected women who had normal cervical cytology at baseline. Every 6 months, women underwent Pap testing and cervicovaginal lavage for HPV DNA testing. The primary outcome was the 5-year cumulative incidence of cervical precancer and cancer. Women were censored from the analysis if they had undergone cervical treatment or were lost to follow up. At enrollment, 369 (88%) HIV-infected women and 255 (91%) HIV-uninfected women were high-risk HPV negative. The 5-year cumulative incidence of CIN 2+ was 5% (95% CI, 2%, 8%) in women with HIV and 5% (95% CI, 1%, 8%) in women without HIV. One HIV-infected and one HIV-uninfected woman had CIN 3, but none had cancer. The authors concluded that the risk of precancer and cancer at 5 years was similar in HIV negative and positive women who had negative cotesting. It is important to note the limitations of the Women's Interagency HIV Study in that the results are only generalizable to women with HIV who have undergone regular medical care with long-term follow up.

It may be that more observational or randomized controlled trials on this question will be necessary before organizations change their guidelines for women with HIV. Nevertheless, the results are intriguing and suggest that women with HIV with no past history of abnormal cytology or cervical precancer can be screened with cotesting if they are ≥ 30 years of age and that screening intervals could be lengthened with serial negative Pap tests. This would especially apply to women with normal CD4 counts. Of course, women with HIV who have abnormal Pap smear results should undergo colposcopy and be managed appropriately by current guidelines.[6,7] In addition, one should not forget to perform a visual inspection of the vagina, vulva, and anus at annual exams in HIV-positive patients given the high rate of concurrent HPV disease.[8] ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. **Which of the following is *not* appropriate regarding the efficacy of uterine artery waveforms?**
   a. Uterine arteries do correlate loosely with preeclampsia, overall.
   b. First trimester uterine artery waveform analysis provides more useful information than second trimester uterine artery examination.
   c. Failure of the second wave of trophoblastic invasion is more commonly associated with preeclampsia than surface invasion in the first trimester.
   d. Uterine artery waveforms are better at predicting severe preeclampsia than preeclampsia, overall.

2. **The NICHD network study involved multiparous patients with no high-risk factors for preeclampsia.**
   a. True
   b. False

3. **Which of the following is correct regarding low-dose aspirin?**
   a. It has been shown to prevent preeclampsia if given after 20 weeks of gestation.
   b. It has been shown to cause harm to the fetus in low dosage.
   c. It is most effective if used before 16 weeks.
   d. There are no data to suggest its benefit in patients with abnormal uterine artery waveforms.

4. **Which of the following features was *not* used to establish the diagnosis of uterine papillary serous cancer?**
   a. High nuclear-to-cytoplasmic ratio
   b. Nuclear atypia
   c. High proliferation
   d. P53 protein loss

5. **Comparing the most recent results from the 2006-10 sample of the National Survey of Family Growth to the 1995 survey, there was an increase in the percentage of women reporting:**
   a. condom use as a primary contraceptive method.
   b. non-use of contraception by women at risk for unintended pregnancy.
   c. use of oral contraceptive pills.
   d. use of vaginal methods.

6. **In the study by Massad et al, which was *not* a risk factor for precancer in HIV infected women?**
   a. Smoking
   b. Low CD4 counts
   c. Highly active antiretroviral therapy
   d. Previous abnormal Pap test result

In Future Issues:

Caffeine and Depression Risk

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Menopausal Hormone Therapy and the Risk for VTE, AD

In this issue: Menopausal hormone therapy and risk of VTE and AD; patients' understanding of chemotherapy benefits; and FDA actions.

Hormone therapy and VTE risk

The different drug formulations of menopausal hormone therapy (HT) may determine the risk of venous thromboembolism (VTE), according to a new study. It is known that combined estrogen-progesterone therapy has a higher risk of VTE than estrogen-only therapy, and oral therapy has a higher risk than transdermal therapy. Now, a follow-up study from the Million Women Study with more than 3.3 million patient-years of follow-up looks at the varying risks of different HT combinations. The risk of VTE was again found to be significantly higher for combination estrogen-progesterone therapy compared to estrogen-only therapy (relative risks [RR] = 2.07 [95% confidence intervals (CI) 1.86-2.31] vs 1.42 [1.21-1.66]). Transdermal estrogen-only therapy resulted in no excess risk for VTE (RR 0.82 [0.64-1.06]). Among users of combination estrogen-progesterone, the risk of VTE varied by progestin type with significantly greater risk for preparations containing medroxyprogesterone compared to other progestins (2.67 [2.25-3.16] vs 1.91 [1.69-2.17]; *P* heterogeneity = 0.0007). The risk of VTE was significantly higher (2 times the risk) in the first 2 years after starting combination HT than later years. Five-year risks for pulmonary embolism (PE), both fatal and nonfatal, were calculated as: 1 in 664 for never users of hormone therapy, 1 in 475 for current users of oral estrogen-only, 1 in 390 for users of estrogen-progesterone containing norethisterone/norgestrel, and 1 in 250 for users of estrogen-progestin therapy containing medroxyprogesterone. The authors conclude that VTE risk varies considerably by HT formulation and is greatest in users of oral estrogen-progesterone therapy containing medroxyprogesterone. One case of PE could be avoided for every 1295 current users of oral HT if estrogen-only rather than estrogen-progesterone was used. Among combined HT users, one PE in 700 women could be avoided by use of a progestin other than medroxyprogesterone (*J Thromb Haemost* published online Sept. 10, 2012. doi: 10.1111/j.1538-7836.2012.04919.x). These data follow on the Women's Health Initiative, which also showed a higher risk of breast cancer for combination hormone replacement therapy vs estrogen-only therapy, but this risk is offset by the risk of endometrial cancer in women with an intact uterus on unopposed estrogen. ■

Hormone therapy and AD risk

Does the timing of menopausal HT affect the risk of Alzheimer's disease (AD)? Several studies have suggested the timing of postmenopausal HT is critical, especially during the first 5 years after menopause when hormones appear to be somewhat neuroprotective. The Women's Health Initiative (WHI) study clearly showed that starting HT after age 65 had no effect on cognition and in fact may be harmful. Now a new study confirms that starting HT immediately after menopause may have neuroprotective benefits. In a follow-up from the Cache

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County study, 1768 women provided a detailed history on age at menopause and use of HT between 1995 and 2006. During this interval, 176 women developed AD. Women who used any type of HT within 5 years of menopause were at 30% less risk of AD (95% CI, 0.49-0.99), especially if they used it for 10 years or more. By contrast, woman who started HT 5 or more years after menopause did not have a decreased rate of AD. Confirming the WHI findings, rates of dementia were nearly doubled among those who began combination estrogen-progesterone compounds later in life. The authors conclude that the association of HT and the risk of AD may depend on the timing of use. HT appears to be beneficial during the critical window near menopause, but may be associated with an increased risk if initiated later in life. (*Neurology* 2012;79:1846-1852). An accompanying editorial suggests that AD and coronary heart disease share common risk factors. WHI data show that women assigned to HT close to menopause had a reduction in the risk of coronary heart disease, whereas women given HT later in life had increased risk. The same seems to be true for the risk of AD. Two soon-to-be published studies will provide evidence regarding hormone effects on cognition in younger postmenopausal women (*Neurology* 2012;79:1840-1841). The decision to initiate HT in postmenopausal women is generally based on severity of symptoms, risk of breast cancer, risk of venous thromboembolic disease, and other factors. Benefits on cognition and potential protection against AD may now need to be added to the equation. ■

Chemotherapy often misunderstood

Chemotherapy for metastatic lung or colon cancer may provide palliation and prolongation of life by weeks or months, but a new study shows that most patients with these diseases erroneously think that chemotherapy is curative. Researchers studied nearly 2000 patients in the Cancer Care Outcomes Research and Surveillance study who were alive 4 months after diagnosis of stage IV lung cancer or colorectal cancer. All patients received chemotherapy. Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy "was not at all likely to cure their cancer." This misunderstanding about the benefits of chemotherapy was more prevalent among nonwhite and Hispanic patients as compared to non-Hispanic white patients (odds ratio [OR] for Hispanic patients 2.82, 95% CI, 1.51-5.25; OR black patients 2.93, 95% CI, 1.80-4.78). Patients who rated communication with their physician favorably also had a higher OR (1.90; 95% CI, 1.33-2.72). Educational level, functional status, and the patient's role in decision making were not associated with inaccurate beliefs about chemotherapy. The authors conclude that "many patients receiving chemotherapy for incurable cancers may not understand that chemotherapy is unlikely to be curative." This misunderstanding suggests that patients "have not met the standard for true ongoing informed consent" and may not accept toxic treatment with no reasonable hope of cure. The data also suggest that patients rate their doctors as better communicators if they are more optimistic. The authors suggest that honest communication is "a marker of quality of care" but may cause lower patient ratings (*N Engl J Med* 2012;367:1616-1625). ■

FDA actions

The FDA has approved a new drug for the treatment of chronic myelogenous leukemia (CML). Omacetaxine mepesuccinate is a protein translation inhibitor that was originally identified in the 1970s as a potential treatment for CML as well as other hematologic conditions and even solid tumors. It was eventually dropped from development as the tyrosine kinase inhibitors (TKIs) became the mainstay of therapy. Emerging resistance to imatinib and other TKIs has led to renewed interest in the drug. It was recently approved for chronic, accelerated, or blast-phase Philadelphia-chromosome-positive CML that is resistant or in patients who are intolerant of other therapies including TKIs. Approval was based on a study of patients in chronic or accelerated-phase CML who had been treated with two or more TKIs. Omacetaxine is administered by subcutaneous injection. It is marketed by Teva Pharmaceuticals as Synribo. It joins Pfizer's bosutinib (Bosulif), which also was recently approved for the same indication.

The FDA has approved perampanel as adjunctive treatment for partial onset seizures in patients 12 years of age and older. The drug is the first in its class of noncompetitive AMPA receptor antagonists that are taken orally once daily. Approval was based on data from three Phase 3 studies of nearly 1500 patients with partial-onset seizures which found that perampanel, when used as an adjunctive therapy with other anti-seizure medications, significantly reduced seizure frequency. The drug comes with a boxed warning regarding serious neuropsychiatric events including agitation, aggression, anxiety, paranoia, euphoria, anger, and irritably. Perampanel is marketed by Eisai Inc. as Fycompa. ■