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INSIDE

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Is Desipramine or Lidocaine an Effective Treatment for Vulvodynia?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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Dr. Ling reports no financial relationship to this field of study.

Synopsis: *Topical lidocaine and oral desipramine, either in monotherapy or in combination, were no better than placebo in this randomized controlled trial.*

Source: Foster DC, et al. Oral desipramine and topical lidocaine for vulvodynia. *Obstet Gynecol* 2010;116:583-593.

In the vulvar vestibulitis clinical trial conducted at the University of Rochester between 2002 and 2007, patients with vulvar vestibulitis syndrome (localized provoked vulvodynia) were enrolled in a 12-week randomized, placebo-controlled treatment trial. Each eligible subject was scrutinized for other causes of entry dyspareunia. Once enrolled, each patient was assigned to one of four treatment arms: oral desipramine and topical lidocaine cream; oral desipramine and placebo cream; oral placebo and topical lidocaine cream; or oral placebo and placebo cream. The 25 mg desipramine tablet (or comparable placebo) was increased by 1 tablet each week starting with 1 tablet at bedtime to a target dose of 150 mg by week six. The lidocaine (or placebo) cream was applied four times daily. Multiple measures were used to evaluate pain, but the tampon insertion test was used as the primary outcome to evaluate vaginal insertional pain. All four treatment arms resulted in substantial reduction in pain, with neither desipramine or lidocaine being significantly more effective than placebo. In the 40-week open-label phase of the study following the initial 12-week randomized trial, patients undergoing vestibulectomy were significantly improved when compared to those who chose non-surgical treatment.

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■ COMMENTARY

Whether you realize it or not, this study is an integral part of your practice. Since I've become a regional referral center for patients with difficult vulvar pain problems, the impact is even greater in my personal practice. As a result, I know that these difficult-to-diagnose and even more difficult-to-treat patients with vestibulitis — aka vestibulodynia aka localized provoked vulvodynia — are being seen in every women's health practice. If nothing else, this study and the comments below should make each of us wonder whether the next patient with recurrent vaginitis or entry dyspareunia or recurrent perineal itching actually might be an undiagnosed case of this condition, which for purposes here will be referenced as "VVS," a shortened version of the old term "vulvar vestibulitis syndrome."

First, let's make sure that we understand the implications for the use of medicines used to treat neuropathic pain in general, and VVS in specific. Only one tricyclic antidepressant, desipramine, was studied. We know that several other medications have efficacy in patients with suspected neuropathies. Just because desipramine was not better than placebo in this study does not mean that there is not a role for neuropathic treatment. Was the duration of use long enough? Was the starting dose of 25 mg with weekly increases of 25 mg the right dosing pattern? Would other antidepressants or anticonvulsants have fared better? What about combinations of these drugs?

Second, the use of lidocaine as described may not have been better than placebo, but the way it was used also had limitations. Would 2% have worked better? Would overnight use of lidocaine on a cotton ball as described by Zolnoun et al been better in patients with VVS?[1]

Third, even though this was an extremely well-done study with great implications both for future research as well as daily patient care, we should be cautious about being overly zealous in its interpretation. The authors also bring up several good points in their discussion, some of which are included in the list below. I have included some "tips" that I have found helpful also. Some of the take-home messages from this study include:

1. Each of us needs to be on the lookout for patients who might have VVS. Examples might include those who present with unexplained burning or itching or entry dyspareunia. Vaginal discharge that keeps recurring also could be a symptom of VVS.

2. Patients actually may benefit just by having a diagnosis and explanation of the symptoms. This takes her out of the "it's all in your head" category and gives her something tangible that needs treatment. Showing her the area in question by having her hold a hand mirror to visualize the vestibule as you touch with a cotton tipped swab can be a significant educational tool.

3. Treatment with desipramine (or amitriptyline or nortriptyline) could start at 10 mg with weekly increases of 10 mg for a slower increase of dose with a possible lessening of side effects, e.g., dry mouth, constipation, or morning grogginess.

4. Applying lidocaine with a cotton ball overnight, during the day, before sex, or as needed are all options to how it can be used for VVS.

5. Other medications (including gabapentin, Tegretol, Lyrica, and Cymbalta) have been used successfully for neuropathic pain and have been approved by the FDA.

6. Still other medications (e.g., keppra, gabitril, trileptal, topamax) not approved by the FDA are used for presumptive neuropathic pain.

7. It is unknown in any given case whether VVS symptoms will improve over time, even without treatment.

8. There may well be a positive therapeutic effect provided by the practitioner who shows that he/she believes the patient's symptoms and is trying to help.

9. Looking for other explanations of painful symptoms may include finding endometriosis, interstitial cystitis, fibromyalgia, lichen sclerosus, and other conditions. Patients may well benefit from treatment of multiple diseases.

As you can see, I'm passionate about diagnosing and treating VVS. It is particularly frustrating to see patients who have been misdiagnosed for many years, sometimes being pigeon-holed into more commonly applied categories of yeast infection, bacterial infection, herpes, chronic urinary tract infections, sperm allergy, atrophic vaginitis, or "psychosomatic." Maybe we can all take this first step forward together — one small step for each of us as di-

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Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

agnosticians, but a giant leap for women with VVS. ■

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Nifedipine for Preterm Labor

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Source: Conde-Agudelo A, et al. Nifedipine in the management of preterm labor: A systematic review and meta-analysis. *Am J Obstet Gynecol* 2011;204:134.e1-20.

Over the years, different tocolytics have been in vogue, only to be discarded later because meta-analyses showed that the agent simply did not work. This month's review will focus on nifedipine, a medication that has been in and out of favor for more than 20 years. Conde-Agudelo et al just published a review of nifedipine that may now tip the scales regarding therapy for preterm labor.[1]

The group scoured the literature from 1960, looking for clinical trials involving nifedipine as a tocolytic. They found 26 studies that met their stringent quality criteria. Of the 23 studies evaluating nifedipine as an acute tocolytic, 16 were pitted against beta-adrenergic receptor agonists (BARA) such as ritodrine, terbutaline, or isoxsuprine. Eleven of these studies involved ritrodrine — the only tocolytic approved by the FDA. Five studies involved magnesium sulfate, and one study each compared nifedipine with antosiban and nitric oxide donors. No good studies were available in which nefidipine was compared against a placebo or no treatment for acute tocolysis. There were three additional studies in which nifedipine was used as a maintenance tocolytic against either placebo or no treatment.

Pooled data comparing nifedipine with BARA showed a significant decrease in deliveries occurring within 7 days of treatment (37.1% vs 45, relative risk [RR] = 0.82, 95% confidence interval [CI] 0.70-0.97), with 12 patients needing to be treated to prevent one case of delivery before 7 days. In addition, the use of nifedipine was associated with less chance of delivering before 34 weeks (48.4% vs 62.2%). The greatest differences between the two agents were in maternal adverse events, which occurred in 48.4% with nifedipine and 62% with BARA. In comparing the two agents, there was only a 0.6% need to stop treatment with the nifedipine and 8.8% with BARA. On the neonatal side, nifedipine was associated with statistically significant reductions in respiratory distress syndrome (RR = 0.63), necrotizing enterocolitis (RR = 0.21), and intraventricular hemorrhage (RR = 0.53).

When compared with magnesium sulfate, there were no significant differences in the ability to prolong labor or to prevent immediate neonatal complications. However, there was a significant decrease in maternal adverse events (23.5% vs 35.6%) with the use of nifedipine.

Finally, three trials evaluated the use of nifedipine as a maintenance tocolytic. Although this analysis only contained a total of 215 patients, there were no differences noted in any maternal or fetal outcome compared with either no treatment or placebo, except the ability to prolong pregnancy by an average of 6.3 days with nifedipine.

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To summarize the findings, nifedipine was better at prolonging pregnancy, while decreasing neonatal complications and maternal morbidity, compared with BARA, but it did not seem to be any more effective than magnesium sulfate in prolonging pregnancy. However, significantly fewer maternal side effects were noted with nifedipine. The benefit of maintenance tocolysis with nifedipine only showed up in one, perhaps significant, category — a prolongation of pregnancy by an average of 6 days. Nevertheless, this did not translate into any neonatal benefit.

Virtually every tocolytic that has been used over the last 20 years has been shown by meta-analysis to be ineffective in preventing preterm labor while potentially increasing neonatal or maternal morbidity. If prolonging pregnancy were as simple as stopping contractions, then possibly all tocolytic therapies would be effective. However, in many cases the etiologic process starts long before there is a hint of preterm labor, and attempting tocolysis with any agent is like standing in front of a runaway train with a stop sign. However, if we are going to make an attempt at all, it should be with the safest agent. The current meta-analysis points toward nifedipine as the winner.

The use of nifedipine previously has been questioned because of its potential effect on the heart (reduces cardiac after-load and negative ianotropic effect). This, in turn, may decrease utero-placental perfusion. To the contrary, a very recent study in normotensive pregnant women showed that, despite significant after-load reduction with nifedipine, the compensatory increase in cardiac output maintained blood pressures, resulting in no ill effects on

the utero-placental or fetal circulations.[2]

Finally, I need to comment on an article that was featured in the March 2010 *OB/GYN Clinical Alert* that dealt with a possible relationship between BARA use in pregnancy and autism in the children exposed to this type of medication.[3,4] This month a rather pointed editorial emerged in the *American Journal of Obstetrics and Gynecology* that strongly challenges the previous authors' hypothesis that such a relationship exists.[5] However, as shown in the Conde-Agudelo meta-analysis, there is now enough evidence to indicate that there is now little reason to use BARA. ■

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FRAX – It's Not a Dirty Word

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr. Edelman is a implanon trainer for Schering Plough.

Synopsis: *The U.S. Preventive Services Task Force has updated its guidelines for osteoporosis screening. For women who do not clearly meet eligibility criteria for screening, an easy-to-use and accessible tool is available to aid clinicians in identifying those who need screening.*

Source: U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2011;154:356-364.

This publication is an update on osteoporosis screening from the 2002 U.S. Preventive Services Task Force (USPSTF) recommendation.[1] The USPSTF now recommends that *all* women age 65 and older receive screening for osteoporosis. In women younger than age 65, osteoporosis screening should be performed if their risk is equivalent to a 65-year-old woman. To determine screening eligibility for these women, a free online screening tool called FRAX (see below for more details) is available. The screening test most commonly used in clinical practice and in outcomes research is the dual-energy x-ray absorptiometry (DXA). There remains a lack of evidence regarding the best screening interval for women whose initial test is negative but a minimum of at least 2 years is needed to reliably demonstrate a change in bone mineral density due to the precision capabilities of the DXA. Unlike the recent USPSTF recommendation regarding breast cancer screening, these recommendations are very similar to those of the American Congress of Obstetricians and Gynecologists (ACOG).[2]

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Clinicians and even the public understand that a hip fracture in the elderly is a game changer, if not the "beginning of the end" since more than a quarter will die within 12 months.[3] Less significant fractures also can cause serious morbidity through chronic pain and immobility. Yet, osteoporosis and—more importantly—osteoporotic-related fractures are preventable; very little if no harm is associated with screening and treating. The USPSTF has performed an updated review of the evidence regarding screening.[1] The USPSTF recommendation states that *all* women age 65 and older should receive screening for osteoporosis and women younger than this age should undergo screening if their risk is equivalent to a 65-year-old woman. There is no upper age limit to stop screening, and it is recommended that clinicians individualize to a patient's remaining lifespan and the potential benefit from treatment, which takes approximately 1.5 to 2 years to achieve.[4]

Pray tell, how do you know if a woman under age 65 is at higher risk and needs screening? An online, easy to use, FREE tool is available to help with this question. FRAX or Fracture Risk Assessment[5] (I have no idea where the X comes from) has been designed in collaboration with a number of international entities to help determine a person's 10-year fracture risk using easily available clinical information including: BMI, race, age, parental and personal fracture history, and smoking and alcohol use. Depending on certain risk factors, women as young as 50 might qualify for screening[1] (for example, a 50-year-old woman who smokes, drinks, is thin, and has a parental fracture history, or simply, a 55-year-old woman who has

a parental fracture history). It is important to make sure to use the correct country designation when logging in to the site as the tool is calibrated for certain populations. Try it out at www.shef.ac.uk/FRAX/ and add it to your Internet "favorites" file. There also are apps for smart phones.

Unfortunately, there remain some unanswered questions that the USPSTF cannot address as the evidence is lacking. This includes routine screening for men. I realize that if you are reading this commentary you probably don't care about screening men but you may be male yourself and then it's one less screening test you need to worry about unless you also have a risk similar to a 65-year-old woman! Additionally, there is no clear guidance regarding when to repeat DXA testing in a woman whose initial testing was normal. Data do exist showing that the screening interval with DXA testing should be no less than 2 years as the modality does not have the precision to demonstrate a change in less time, but it may be that the interval should be longer than 2 years.

There may be some of you still grumbling about why the USPSTF recommendations for mammography are so different from ACOG.[6] Take a sigh of relief as the USPSTF update is very similar to what is already recommended by ACOG — to screen women age 65 or older or postmenopausal women younger than age 65 with 1 or more risk factors.[2] ■

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Special Feature

Is it Heresy or Good Medicine? HRT in Survivors of Gynecological Malignancies

By Robert L. Coleman, MD

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

Synopsis: *In most scenarios, hormone replacement therapy is safe in survivors of gynecological malignancies as measured by progression-free and overall survival. There are, however, notable exceptions and cautions, and usage should still follow the principles afforded to women without a gynecologic cancer history.*

Source: Ibeanu O, et al. Hormone replacement therapy in gynecologic cancer survivors: Why not? *Gynecol Oncol* 2011;ePub April.

Although the annual incidence of all gynecological malignancies remains between 75,000 and 80,000, a far greater number of women with this history are survivors. Further, a sizable proportion of this cohort is pre- or peri-menopausal and report significant symptoms of estrogen deprivation either as a result of surgery or following prescribed adjuvant chemotherapy and/or radiotherapy. However, there is significant concern regarding the use of hormonal replacement therapy (HRT) in these women, as it may be intimated that therapy could increase the risk of recurrence or secondary malignancy. This concern is particularly evident in women carrying a germline mutation in BRCA1/BRCA2, women who have a personal history of breast cancer, and women with a history of endometrial cancer. In each of these situations, the foundation of apprehension comes from extrapolation of the results from randomized studies of HRT use in healthy women, where associations of increased risk of malignancy have been documented, as well as the noted impact of estrogen/hormones on new cancer development. Fortunately, a review of available (but limited prospective) data in gynecologic cancer cohorts combined with closer scrutiny of these randomized trials of HRT support the short-term safety of HRT in most patient cohorts who exhibit menopausal symptoms. As with women without a personal history of gynecologic cancer, HRT should be administered

Table. Recommendations for short-term HRT use in various clinical scenarios

Clinical Situation	HRT Acceptable?	Level of Evidence
Endometrial cancer (Type I)	Yes – early-stage, low-risk disease after hysterectomy	Level I-III
Ovarian cancer	Yes – caveat: caution in women with tumors expressing ER/PR	Level I-III
Cervix cancer	Yes	Level II-III
BRCA gene mutation carriers	Yes – after RRSO ± hysterectomy AND no personal history of breast cancer	Level II
BRCA gene mutation carrier with a personal history of hormone-dependent breast cancer	No	Level II
Lynch II syndrome gene mutation carriers	Yes – but no data on safety and best considered if risk-reducing hysterectomy and BSO	None

HRT: hormone replacement therapy; ER/PR: estrogen receptor/progesterone receptor; RRSO: risk-reducing salpingoophorectomy; BSO: bilateral salpingoophorectomy

at the lowest effective dose for the shortest period of time necessary. In addition, symptomatic patients with a personal history of hormone-dependent breast cancer and hormone-expressing ovarian cancers should be managed with non-HRT strategies.

Commentary

Up to 40% of women diagnosed annually with a gynecologic malignancy in the United States will be pre- or peri-menopausal.[1] Since the principle tenet of therapy in most of these situations is to remove or sterilize incumbent disease, a large proportion of these women will be thrust artificially into an estrogen-deprived state, the symptoms of which are exacerbated by the abruptness of hormone fluctuation and the stress in dealing with the new diagnosis. Although HRT is effective in ameliorating symptoms from surgically induced menopause, there has been general concern in using HRT in women with gynecologic malignancy because of the theoretical potential of hastening an unknown natural disease history or stimulating quiescent metastatic disease.[2] This concern was further elevated when initial data from randomized controlled trials of HRT use in healthy women documented increased risks of incident breast and ovarian cancer.[3] Coupled with the well-described epidemiological and molecular relationship of unopposed estrogen use and the risk of endometrial cancer, most clinicians are reluctant to discuss or offer HRT in women with gynecological cancer. Despite further clarification in the type and duration of HRT exposure and these risks, general concern persists, particularly in light of the paucity of data of HRT use in women with a personal history of gynecologic cancers. However, observational and some prospective studies have been conducted in this setting and provide some guidance for clinicians trying to help women achieve the highest quality of life in dealing with their disease. A summary of the clinical scenario, the recommendation for short-term HRT use, and the level of evidence to support this recommendation is outlined in the Table.

Endometrial Cancer

Perhaps the most contentious primary site in regard to this debate is one where a strong relationship between estrogen use and development of cancer already exists. Indeed, years ago, incidence rates of epithelial endometrial cancer appeared to parallel the number of prescriptions written for unopposed conjugated estrogen HRT, highlighting the hormone-dependent nature of this cancer. In addition, progesterone and anti-estrogen therapy for advanced stage and metastatic endometrial cancer are still considered valid treatment options for hormone expressing tumors. So, it is not without merit that concerns for HRT exist for women with a history of endometrial cancer. Fortunately, this is also the disease site that the strongest safety data — particularly in women with early-stage, low-grade disease. More than 25 years ago, Creasman and colleagues reported that HRT use in Stage I endometrial cancer was associated with a significant *decrease* in recurrence (2% vs 15%) compared to placebo in a non-randomized comparison.[4] However, the strongest data stem from a randomized, placebo-controlled, double-blinded trial conducted by the Gynecologic Oncology Group, in which 1236 women with Stage I-II endometrial cancer were randomized to estrogen or placebo for a planned 3 years duration.[5] Unfortunately, publication of the Women's Health Initiative (WHI) greatly influenced the enrollment to this trial, causing it to close prematurely (achieving 60% of its intended accrual). Nevertheless, after a median follow-up of 3 years, recurrence rates (2.3% vs 1.9%), progression-free survival (94.3% vs 95.6%), and overall survival (hazard ratio [HR] 1.27; 80% confidence interval [CI] 0.92-1.77) were all non-significant between the two arms. The ability to infer these results across other stages, histologies, and races is extremely

limited and should only be undertaken with caution; however, it would appear that the risk, if present, is low, and short-term use in early-stage, low-risk patients can be considered.

Ovarian Cancer

The molecular relationship between estrogen and ovarian cancer is complex and dependent upon not only ligand-receptor interaction and subsequent downstream nuclear processes, but also non-genomic intracellular signaling, which incorporates multiple additional pathways to direct the cellular growth response and differentiation. Therefore, it is not surprising that epidemiological evidence of a strong link between HRT use and lifetime risk of ovarian cancer has been mixed, including a recent meta-analysis concluding the absence of an association between the two.[6] However, there are three important considerations in this disease that require further mention: patients with a personal history of ovarian cancer, patients undergoing risk-reducing salpingoophorectomy (RRSO) due to BRCA mutation status, and patients with low-grade serous (or Type I) ovarian cancer.

HRT use in women with a personal history of ovarian cancer has been the subject of several observational and two small randomized controlled trials. In a 1999 report, Guidozzi and colleagues randomized 130 patients with high-grade, advanced stage ovarian cancer to either conjugated estrogen or placebo after surgical debulking and adjuvant chemotherapy.[7] Patients who had taken HRT before their diagnosis were excluded. After a median follow-up of 4 years, there was no apparent increase in risk for recurrence or death due to HRT. Several observational trials have concluded the same, including in cohorts of women with low malignant potential tumors. These observations regarding the latter cohort are relevant as the age of diagnosis is substantially lower. The strength of these data would support the short-term use of HRT in symptomatic patients after appropriate counseling.

As has been discussed in *OB/GYN Alert* previously, women who carry a germline mutation in BRCA1 or BRCA2 are at substantial lifetime risk for the development of ovarian and breast cancer. Many, after appropriate counseling and testing, choose RRSO, as this has been shown to substantially decrease the risk of both cancers. However, most women undergoing the preventive intervention do so before menopause and are likely to exhibit intense menopausal symptoms, which may interfere with their quality of life. In light of the previously established association of HRT use and breast cancer, combined with the heightened lifetime risk of breast cancer due to BRCA mutation, it is not surprising concern exists for HRT use in this population. However, several studies would suggest the practice does not appear to increase this risk. In one prospective cohort study by Rebbeck et al, the reduction in subsequent breast cancer afforded by RRSO (HR 0.40; 95% CI 0.18-0.92) was not negatively influenced by the use of HRT after the procedure.[8] The results, while reassuring, also have a molecular basis as it has been well-documented that BRCA mutation carriers (particularly BRCA1) who subsequently develop breast cancer have a "triple-negative" phenotype.[9] That is, they don't express the estrogen receptor, progesterone receptor, and are Her-2-neu negative. Since data from the WHI suggested the progesterone component of HRT was associated with the risk for subsequent breast cancer, removal of the uterus at the time of RRSO has been endorsed to help simplify the strategy for HRT in these women. Nevertheless, BRCA mutation carrier patients with a personal history of hormone receptor positive breast cancer should not receive HRT as it appears the use is associated with a significantly increased risk of recurrence, contralateral, and metastatic disease.

Finally, it has become increasingly evident that a proportion of serous (and some endometrioid) ovarian cancers are driven by distinctly different molecular pathways (Type I ovarian cancer) relative to high-grade serous cancer, and may be responsive to progesterone and antiestrogen based therapy. This is not unlike the situation for endometrial cancer; however, there are no data to support or refute HRT use in this setting and, as such, should be considered cautiously.

Cervix Cancer

Although an uncommon disease in the United States, cervix cancer is frequently diagnosed in premenopausal women. Those with early-stage disease usually are offered surgical extirpation to allow for ovarian preservation and to avoid long-term effects of radiation on the genital track, which include vaginal shortening, loss of plasticity, vaginal dryness, dyspareunia, and menopausal symptoms. The ovaries are exquisitely radiosensitive and are sterilized at doses far lower than that required for microscopic tumor cell kill. As such, a common practice in women with an unknown or suspected risk for postoperative radiation who wish ovarian preservation is adnexal transposition (moving the ovaries out of the pelvic radiation field). However, for those receiving primary chemoradiation or in whom the ovaries were not transposed or failed following the procedure, HRT remains an important intervention to ameliorate menopausal symptoms and to treat the effects of ionizing radiation on the vaginal tissues. Immunohistological assessment for estrogen and progesterone receptors in squamous and adenocarcinomas of the cervix demonstrate their presence, but prognostically, this expression has not been linked to adverse outcomes. One prospective study followed 120 women with invasive cervix cancer treated with HRT (40 treated with estrogen alone, 40 with

estrogen/progestin) or placebo (n = 40) after primary surgery or radiation.[10] No adverse effect on recurrence or survival was observed with treatment. Although no prospective randomized trials have been conducted in this patient cohort, the risk to benefit ratio appears to favor use and should be considered.

Summary

Quality of life considerations are becoming an increasingly important aspect of survivorship in women with gynecologic malignancies, particularly as the cache of patients increases with effective primary treatment. As can be appreciated in this discussion, HRT use, once considered a contraindication to women with a cancer history, may be carefully considered. As is the case for women without this personal history, the lowest effective dose for the shortest period of time should be exercised in those deemed good candidates after careful consideration and counseling. ■

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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 Questions

6. The USPSTF recommends that all women aged 65 and older undergo screening for osteoporosis.
a. True
b. False

7. What is FRAX?
a. A curse word used on "Star Trek"
b. A clinical tool to determine a woman's 10-year fracture risk
c. A clinical tool to determine the amount of calcium replacement a woman needs if she has osteoporosis

8. Regarding the Conde-Agudelo article, which of the following *DOES NOT* fit with the results? Compared with BARA, nifedipine was associated with:
a. fewer maternal side effects.
b. less respiratory distress syndrome.
c. fewer deliveries within 7 days.
d. less necrotizing enterocolitis.
e. All of the above are correct.

9. Nifedipine was better at prolonging pregnancy than magnesium sulfate.
a. True
b. False

10. Which of the following is most applicable to the findings regarding nifedipine?
a. Nifedipine decreases uterine blood flow.
b. Nifedipine does not cross the placenta.
c. Nifedipine causes an increase in cardiac output which maintains maternal blood pressure.
d. Nifedipine was associated with the same amount of maternal side effects as magnesium sulfate.

11. Which of the following is a *NOT* a true statement?
a. Women with a history of adenocarcinoma of the cervix can be considered for HRT after primary chemoradiation therapy.
b. A woman with no prior cancer history but who relates a strong family history of breast/ovarian cancer should not receive HRT.
c. Risk reducing salpingoophorectomy can significantly reduce the risk of subsequent breast cancer.
d. A premenopausal woman treated for early stage endometrial cancer should not receive HRT.

Answers: 6. a, 7. b, 8. e, 9. b, 10. c, 11. b.

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.*

Women's Health Issue — Adverse Medication Effects

In this issue: Calcium supplements and MI; birth control pills and VTE; ACE inhibitors and breast cancer risk; spending on pharmaceuticals; and FDA actions.

Calcium supplements and MI risk

Do calcium supplements increase the risk of myocardial infarction (MI)? Researchers from New Zealand recently reanalyzed data from the Women's Health Initiative (WHI) in an attempt to answer this question. In 2008 the same group published a randomized, placebo-controlled trial of calcium supplements in nearly 1500 healthy postmenopausal women that showed upward trends in cardiovascular event rates with calcium use (*BMJ* 2008;336:262-266). The same group subsequently carried out a meta-analysis of cardiovascular events in randomized, placebo-controlled trials of women taking calcium supplementation without vitamin D. In that study, calcium supplementation significantly increased the risk of MI by about 30% (*BMJ* 2010;341:c3691). Although these studies garnered some interest, they were also viewed with skepticism, and most physicians, especially in this country, did not change their practice of recommending calcium supplementation for postmenopausal women. The New Zealand group then turned to the WHI data, a rather strange place to look considering that one of the main outcomes of WHI was the finding of no adverse effect of calcium and vitamin D on cardiovascular risk. However, the researchers found one major caveat: WHI did not consider whether women were taking calcium on their own prior to entry into the study. The New Zealand group got access to the original NIH data and were able to tease out women who were not using personal calcium supplements at randomization. They found nearly 17,000 women who fit that category. Women in this subgroup who were randomized to calcium and vitamin D had small but significant increased risk for cardiovascular events with hazard ratios that ranged from 1.13-1.22 ($P = 0.05$ for clinical MI or stroke, $P = 0.04$ for clinical MI or revascularization). When the WHI data were added to the previously done meta-analysis of three placebo-controlled trials, calcium and vitamin D were found to increase the risk of MI (relative risk [RR] 1.21 [95% confidence interval [CI] 1.01-1.44]; $P = 0.04$), stroke (1.20 [CI 1.00-1.43], $P = 0.05$), and the composite of MI or stroke (1.16 [CI 1.02-1.32], $P = 0.02$). Trial level data was available for more than 28,000 women who were randomly assigned to calcium plus vitamin D or placebo. Calcium or calcium plus vitamin D increased the risk of MI (RR 1.24 [CI 1.07-1.45], $P = 0.004$) and a composite of MI or stroke (1.15 [CI 1.03-1.27], $P = 0.009$). The authors conclude that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially MI. They suggest that a reassessment of the role of calcium supplementation in osteoporosis management is warranted (*BMJ* 2011;342:d2040 doi:1136/*BMJ*.d2040, published April 19, 2011). This study has been hotly debated and was even criticized in an editorial in the same issue of *BMJ*. Nonetheless there is a bit of irony in using WHI data, which are largely responsible for millions of women stopping hormone replacement therapy, to show a relationship between calcium and

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cardiovascular disease disease. There is no suggestion in any of these data that dietary calcium leads to adverse events. It is postulated that the rapid increases in calcium that occur with calcium supplementation may somehow play a role in increased cardiovascular risk.

Birth control pills and VTE risk

A progestin commonly used in birth control pills may increase the risk of venous thromboembolism (VTE). A recent report suggests that women taking oral contraceptives containing drospirenone may be at increased risk of VTE compared to women taking contraceptives containing other progestins. Two studies were recently published in *BMJ*. The first was a case-controlled study of U.S. women that showed that women taking drospirenone-containing contraceptives were twice as likely to develop nonfatal VTE compared to women taking levonorgestrel (*BMJ* 2011;342:d2151). The other study, a case-controlled study of British women, showed a three-fold higher rate of VTE with drospirenone-containing contraceptives compared to levonorgestrel (*BMJ* 2011;342:d2139). Oral contraceptives containing drospirenone include Yaz, Yasmin, and Angeliq.

ACE inhibitors and breast cancer risk

Researchers at UCLA and Kaiser Permanente in northern California recently published data suggesting that angiotensin converting enzyme inhibitors (ACEi) may increase the risk of breast cancer recurrence in breast cancer survivors. Using a database of nearly 1800 women with a history of breast cancer, there were 292 recurrences, 174 breast cancer deaths, and 323 total deaths. Twenty-three percent of the women in the study were exposed to either a beta-blocker or an ACEi. ACEi exposure was associated with breast cancer recurrence 1.5 times baseline (HR 1.56, 95% CI 1.02-2.39, $P = 0.04$) but not increased cause-specific or overall mortality. Beta-blocker exposure was associated with lower hazard of recurrence and cause-specific mortality. There was no dose-response with either medication. When a beta-blocker was combined with an ACEi, there was a lower hazard ratio for recurrence than with ACEi alone. The authors suggest that ACEis may be associated with an increased risk of breast cancer recurrence; although beta-blockers may be somewhat protective, more research is needed (*Breast Cancer Res Treat*, published online, DOI: 1007/s10549-011-1503-3). Beta-blockers have been shown to be protective against breast cancer recurrence in other studies, but the ACEi findings were unexpected.

Spending on U.S. pharmaceuticals

Spending on pharmaceuticals in the United States grew at its smallest level in years in 2010, according to a report by the IMS Institute for Healthcare Informatics. Pharmaceutical spending increased 2.3% in 2010 compared to 5.1% in 2009. Generics dominated the pharmaceutical market in 2010 making up 78% of total market share compared to 63% in 2006. Of the top 25 drugs by volume, only three were brand-name products: atorvastatin (Lipitor), clopidogrel (Plavix), and montelukast (Singulair). By spending dollars, however, Lipitor was the top grossing product at $7.2 billion in 2010, down from $7.6 billion in 2009. Esomeprazole (Nexium) was second at $6.3 billion, while Plavix ranked third at $6.1 billion. The domination of generics is of major concern to the pharmaceutical industry since there are few new drugs in the development pipeline and several high-profile drugs are due to lose protection soon. Foremost among these is Pfizer's Lipitor. Pfizer has been battling to maintain its patent protection, but generic manufacturer Watson Pharmaceuticals is expected to introduce the first generic atorvastatin in November of this year. Likewise, Merck's Singulair will likely lose its patent protection next year. The economy also has played a role in the decrease in pharmaceutical spending as the total volume of medicines consumed decreased 0.5% in 2010 along with a decrease in the number of doctor office visits of 4.2%. This extends a decline that began in mid 2009 — likely due to higher unemployment and rising health care costs.

FDA actions

The FDA has approved rituximab (Rituxan) for the expanded indication to treat Wegener's granulomatosis and microscopic polyangiitis, two rare vasculitides. The effectiveness of rituximab was demonstrated in a single control trial in which 197 patients with either condition were randomized to rituximab plus glucocorticoids or oral cyclophosphamide plus glucocorticoids. After 6 months, 64% of the patients treated with rituximab had a complete remission compared to 53% of patients treated with cyclophosphamide. Rituximab is manufactured by Genentech.

The FDA has approved gabapentin enacarbil for the treatment of moderate-to-severe restless leg syndrome. The approval was based on two 12-week clinical trials in adults showing the effectiveness of the drug vs placebo. Gabapentin enacarbil is formulated as a once a day extended-release tablet. It is marketed by GlaxoSmithKline and Xenoport as Horizant. ■