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Fetal Fibronectin

ABSTRACT & COMMENTARY

For good reason, much recent attention has been directed toward diminishing preterm birth, a problem that continues to be the major cause of infant mortality. Although little headway has been made in the treatment of preterm labor (PTL), substantial progress has been gained in the diagnostic component of PTL investigation. Two of the most studied predictors of PTL, fetofibronectin (fFN) and cervical length (CL) have been applied mostly to populations at high risk for PTL. However, recently an article appeared by Iams and colleagues that assessed these diagnostic modalities in a low-risk population.

Data from a subset of 2197 patients enrolled in the now famous Preterm Prediction Study who were either primigravida or had no risk factors for PTL were analyzed. Bishop curves, cervical length by transvaginal ultrasound, and cervical fetal fibronectin were obtained in all of the above patients at 24 weeks' gestation.

Three percent of these low-risk patients delivered spontaneously before 35 weeks, a prevalence rate not unexpected in this low-risk setting. All 3 factors were significantly associated with preterm birth (Bishop score of > 4, relative risk [RR] = 3.6, fFN of > 50 ng/mL, RR = 8.2; cervix of < 2.5 cm, RR = 6.9). However, the sensitivities were low for each of the tests (high Bishop score, 23.4%, positive fFN 23.4%, and short cervix 39.1%). From this study one could conclude that, because of the low sensitivities, a screening program using these diagnostic tests in a population with a low prevalence rate would not be efficacious.

The article was chosen as a springboard for discussion not because of its less than exciting outcomes. It was chosen to simply point out that this study's results should not be extrapolated to a high-risk population where the diagnostic potential of fFN and, in some cases, CL, continues to burn brightly. (Iams JD, et al. *Am J Obstet Gynecol*. 2001;184:652-655.)

COMMENT BY JOHN C. HOBBINS, MD

Fetal fibronectin is a glycoprotein in the interface between the chorion and decidua, which finds its way into the cervix and vagina

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INSIDE

when this interface is unstable. Normally it is found in the cervix until about 20 weeks, after which time the cervix is virtually fibronectin-free until just before labor ensues. For this reason, it has been studied as a predictor of PTL and, recently, as a predictor of successful labor induction.

Most studies have concentrated on the ability of a sample taken from the cervix and vagina at 24 weeks to predict preterm birth (PTB) prior to 35 weeks with the idea that prevention (intervention) be initiated for those at highest risk of PTB. A majority of the studies with large enough numbers to answer this question have been spawned from a large collaborative study sponsored by the National Institutes of Child Health & Human Development (NICHD) involving many centers in the NICHD Network (Preterm Prediction Study).

Another investigative focus with extremely important clinical connotations is the ability of fFN to predict PTB in third trimester patients presenting with preterm contractions. Investigation in this area is composed mostly of studies with relatively small numbers of patients. Both investigative questions have huge public health implications. PTB is perhaps one of the most vexing problems in obstetrics, and if clinicians knew which patients were at highest risk of PTB by the end of the second trimester through yet-to-be-determined preemptive therapeutic strikes, PTB might be averted.

The second question is just as important to answer and, perhaps, has a more reasonable chance of immediate success. Only a small percentage of patients with preterm contractions are truly in PTL, so we have been treating everyone with preterm contractions with tocolytics, antibiotics, etc to potentially affect only the few who really might benefit from this therapy. This shotgun approach is fraught with unnecessary confinement and/or uncomfortable side effects for the majority of patients, and prodigious costs have been generated through unnecessary hospitalizations and medications. Even studies showing negative results with various interventions in patients with preterm contractions have been flawed by an inability to tell who really is in PTL, thereby diluting the difference in results between treatment and controls.

Fetal fibronectin has been on the scene since the early 1990s. However, the assay only recently has been available in hospitals around the country. Prior to this time, the only way results could be obtained was to send the cervical/vaginal specimen to 1 central lab in the United States. By the time the result is returned 1 or 2 days later, the patient had already declared herself, and if the result was "negative," many caregivers were reluctant to believe the results and to stop the therapy.

Now the results are available within hours, allowing clinicians to concentrate potential therapy on those who really need it. However, the true worth of the test is in its negative predictive value, and those not confident in the data in the literature regarding the test's ability to exclude true PTL need not order the test.

Here is the current story on fFN in symptomatic third trimester patients. Perhaps the most instructive study involved 763 patients admitted with symptoms of PTL and cervical dilation of less than 3 cm and intact membranes. If fFN was positive (in 150 patients), 20 (13%) delivered within 7 days, 25 (16.7%) delivered within 14 days, and 67 (44.7%) delivered before 37 weeks. Most important, if the fFN was negative (613 patients), only 3 delivered within 7 days, 5 delivered within 2 weeks, and 95 delivered before 37 weeks. This results in negative-predictive values of 99.5%, 99.2%, and 84.5%, respectively. This simply meant that for patients admitted with the presumed diagnosis of PTL, if their fFN was negative, only 1 in 200 would deliver within 2 weeks of admission.

Using this information clinically to decide which patients with preterm contractions to treat with tocolytics

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and which patients to transfer to a tertiary care center, Joffe in a "before-and-after" type study showed a significant decrease in admissions for PTL, length of stays for those admitted, and decreased use of tocolytics after fFN was introduced as a diagnostic test. In a recent Australian study, Giles et al showed a negative fFN result reduced maternal transport for PTL to a tertiary care hospital by 90% and diminished the need for tocolytics by 64%. They calculated that the cost savings for 58 fFN-negative patients not transferred by fixed wing was $30,000. The cost savings from avoidance of hospitalization were even more startling. So—using fFN wisely can allow clinicians to concentrate on those patients who truly require tocolytic attention. Also, contemporary studies should now be able to better demonstrate the efficacy of various tocolytic methods by excluding most of the patients who are not at risk for PTB.

Let us now turn back to fFN as a second trimester predictor of PTL. The largest and most comprehensive study thus far is the large Preterm Prediction Study, from which the low-risk data cited above were extracted. The fFN bottom line in this study is that any patient with a positive fFN at 22-24 weeks has a 14 times greater chance of delivering a baby at less than 32 weeks (a threshold with the greatest neonatal implications). This and other studies have also suggested that a second trimester positive fFN predisposed patients to a higher risk of having bacterial vaginosis, premature rupture of membranes, and having a short cervix (< 2.5 cm).

A short cervix alone at 22-24 weeks is also a reasonable predictor of PTB or asymptomatic PTL, but like fFN, a single number, above which one can be reassured and below which one should be worried, has been difficult to come by. In the now frequently cited earlier Iams study, a 2.5 cm cervical length by transvaginal sonography seemed to be the best screening end point. However, if a threshold of 1.5 cm was chosen, as published by a British group, the RR of PTB earlier than 33 weeks was 46.2, compared with 8.1 for fFN.

As shown by Goldenberg and colleagues, fFN, cervical length, and a history of PTB have an exponential effect on risk of PTB. For example, if a patient at 24 weeks has neither a positive history, a short cervix (< 2.5 cm), nor a positive fFN, she runs a 0.5% chance of delivering preterm (< 35 weeks). Any 2 of the above risk factors gives a patient a 35-fold increase in likelihood of a PTB, and 3 of 3 factors increases the risk by 100-fold.

Lastly, perhaps even the level of fFN can be fine tuned to better suit the clinical situation. In one study, it was shown through receiver-operating characteristic (ROC) analysis that the original fFN cutoff point of 50 ng/mL was reasonable in a population of mixed risk. However, perhaps this threshold should be adjusted upward or downward depending upon the degree of risk for each patient. The same could also be said for cervical length. Only a few studies have addressed the adjunctive usefulness of the 2 tests, but we will have to wait for these answers to evolve in expanded high-risk studies. In the meantime, it looks like fFN can play an extremely important role in the early prediction of PTL and in those patients presenting in the third trimester with preterm contractions. Enlightened use of this diagnostic test should decrease costs, minimize side effects, and allay patient and caregiver angst. ❖

Suggested Reading

1. Goldenberg RL, et al. *Am J Obstet Gynecol*. 1997;177:8-12.
2. Peaceman AM, et al. *Am J Obstet Gynecol*. 1997;17: 13-18.
3. Joffe GM, et al. *Am J Obstet Gynecol*. 1999;180: 581-586.
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Screening Mammography in Women Younger Than Age 50

ABSTRACT & COMMENTARY

Synopsis: *Screening mammography before age 50 continues to be controversial.*

Source: Ringash J, Canadian Task Force on Preventive Health Care. *Can Med Assoc J*. 2001;164:469-476.

The canadian task force on preventive health care neither recommends the inclusion of screening mammography younger than age 50 nor the exclusion based upon the available evidence. The Canadian Task Force on Preventive Health Care reviewed 68 articles on screening mammography of women age 40-49. Out of this literature they accepted 7 randomized clinical trials and 6 meta-analyses for critical review. They found much to criticize in the literature on this particular subject, especially the statistical power in the studies to

detect a benefit in women younger than 50. Nevertheless, they concluded that the most recent evaluations of the randomized trials indicate approximately an 18% reduction in breast cancer mortality when women age 40-49 are screened with mammography. They appropriately review the effects of an increased number of mammograms in younger women. The 2 major problems include unnecessary biopsies, which range from less than 1% in Sweden to 5-9% in the United States. The second major problem is the psychological stress of being called back for further evaluation. The Task Force finally concludes that the available evidence cannot suggest that mammography should be included in the periodic health examinations of women age 40-49. At the same time, they conclude that the available evidence does not indicate that it should be specifically excluded. Thus, their final recommendation is that women age 40-49 should be informed of the current situation and assisted in their own personal decisions.

COMMENT BY LEON SPEROFF, MD

I have been a strong proponent that screening mammography should begin at age 40 rather than 50. It is well recognized that breast tumors grow faster in younger women compared with older women, and therefore, screening mammography at a frequency less than every year means that more cancers will be detected late in younger women. The earlier randomized clinical trials used the frequency of every 2 years, and it's not surprising that their results failed to demonstrate a striking benefit.

There continues to be national confusion regarding this issue. The National Institute of Health recommends against screening mammography in women younger than age 50. The American Cancer Society and the National Cancer Institute advise screening every 1 to 2 years. The reason for this confusion, as well as the conclusion of the Canadian Task Force on Preventive Health Care, is that conclusions have been based strictly on the randomized clinical trial data. The United States National Institutes of Health Consensus Development Panel in 1997 made a similar recommendation. Neither the Canadian Task Force nor the United States Panel offered any guidance as to how the clinician could assist the patient in individual decision making. This is a good example of the problems we have in this era of emphasis on evidence-based medicine when we try to make our decisions strictly by randomized clinical trial data. Many times such data are not available or the data are too limiting. A case where the data are not available, for example, is smoking and lung cancer. If we waited for data from a randomized clinical trial, we would never advocate cessation of smoking to prevent lung cancer. This situation with mammography under age 50 is an example where the randomized clinical data are too limited. There is a British trial underway randomly assigning women age 40 or 41 to annual mammography or usual care. Results are expected after 2003. Until then, we have to make individual decisions with our patients based on our medical judgment.

In my judgment, annual mammography is indicated for women younger than age 50 despite the problem of an increased number of biopsies and the psychological stress, because this is the only method we have to detect these tumors that are in fact growing faster and would be detected at a later stage with a worse outcome by having mammography later in life. We should also keep in mind that women with a first-degree relative with premenopausal breast cancer should begin annual mammography 5 years before the age of the relative when diagnosed. ❖

Epithelial Disorders Adjacent to Invasive Vulvar Carcinomas

ABSTRACT & COMMENTARY

Synopsis: *Invasive vulvar carcinoma associated with lichen sclerosis or squamous hyperplasia has a poorer prognosis than that associated with HPV infection.*

Source: Rouzier R, et al. *Gyencol Oncol*. 2001;81: 414-419.

Recently, invasive squamous cell carcinoma of the vulva has been subdivided into 2 entities: that associated with vulvar dermatoses such as lichen sclerosus and squamous hyperplasia, and that associated with human papillomavirus (HPV) infection. The HPV-associated type occurs in women who are younger in age.

In order to determine whether the 2 groups of vulvar carcinoma have different survivals, Rouzier and colleagues evaluated 108 patients with invasive squamous cell carcinoma. Most of these patients were treated with wide resection with a 1 cm margin of normal skin at the resection lines. The pathology of each case was reviewed, and all cases were assigned to 2 different categories. In the first, the invasive squamous cancer was associated with some type of vulvar dermatosis. In the second group the cancer was associated with "undifferentiated high

grade vulvar intraepithelial neoplasia." This second type is associated with HPV infection. Rouzier et al did not perform HPV DNA probes on the study material.

Of the patients, 77 of 108 had some type of epithelial abnormality adjacent to the invasive cancer. In 36 cases it was squamous hyperplasia, HPV-associated vulvar carcinoma in situ (VIN III) in 25 cases, and lichen sclerosus in 16 cases. The group of patients that were associated with vulvar dermatoses were statistically significantly older than those associated with HPV. Kaplan-Meier survival analyses showed that survival was poorer for the group of patients associated with a vulvar dermatosis.

Rouzier et al suggest that it is not necessary to perform HPV DNA analysis to separate invasive cancer into subgroups. Those associated with HPV infection exhibit an "undifferentiated VIN" pattern compared to a "differentiated VIN" pattern which is associated with vulvar dermatoses.

COMMENT BY KENNETH L. NOLLER, MD

For some time now it has become clear that not all invasive squamous cancers of the vulva are the same. Those individuals who develop the disease at a younger age seem to do much better than those who develop it at a later age when compared stage for stage. When HPV DNA probes have been used to study these cancers, HPV-positive cases tend to be those that occur in younger women who have a better survival. However, even in younger HPV-positive women there is a significant risk of death.

Rouzier et al introduce terminology that is not commonly used in the United States at the present time: undifferentiated VIN and differentiated VIN. This terminology has recently been accepted by the International Society for the Study of Vulvar Diseases, but has been slow to catch on among pathologists. Whether this terminology will gain favor in the United States or not is yet to be seen. Certainly more studies need to be done to determine whether the undifferentiated type of VIN is truly associated with HVP infection more frequently than the differentiated type.

The current study would have been better had Rouzier et al performed HPV DNA tests on the specimens. While their conclusions probably would not have changed, they would be more believable if supported by HPV DNA evidence. Nonetheless, the results certainly suggest that invasive vulvar cancer is worse if it occurs in a background of lichen sclerosus or squamous cell hyperplasia. ❖

Treatment of Uterine Papillary Serous Carcinoma with Paclitaxel

ABSTRACT & COMMENTARY

Synopsis: *Paclitaxel appears to have excellent activity in the treatment of advanced or recurrent uterine papillary serous carcinoma.*

Source: Ramondetta L, et al. *Gynecol Oncol*. 2001;82: 156-161.

Ramondetta and colleagues treated 20 patients with histologically confirmed advanced or recurrent uterine papillary serous carcinoma (UPSC) with a 24-hour infusion of paclitaxel 200 mg/m^2 every 3 weeks. Patients received from 1 to 11 cycles of therapy. Among 13 women with measurable disease receiving 2 or more cycles of therapy, 4 had a complete clinical response and 6 had a partial response. The objective response rate was 77%. The median time to progression was 7.3 months (range, 2-21 months). The other 3 patients with measurable disease had stable disease for a median of 6 months. The 5 patients without evaluable disease received 5-6 cycles of adjuvant paclitaxel. Three developed recurrence (range, 4-10 months; median, 7.2 months). Neutropenia was the major toxicity. Eleven of the 20 patients required G-CSF support, and 9 were hospitalized for neutropenic fever. At the time of analysis, 13 women had died of disease, 4 were alive with disease, and 2 were disease-free. Both disease-free patients had been treated for nonmeasurable advanced stage disease. Ramondetta et al concluded that paclitaxel appears to have excellent activity in the treatment of advanced or recurrent UPSC, an uncommon but aggressive malignancy.

COMMENT BY DAVID M. GERSHENSON, MD

UPSC remains an aggressive form of endometrial cancer that is associated with a relatively high recurrence rate. Unfortunately, once relapse of UPSC occurs, the disease is essentially incurable. In general, any modality of therapy has been ineffective in achieving an objective response of significantly prolonging survival. Response to platinum-based chemotherapy has generally been reported to be no greater than about 30%. A previous report by Zanotti and colleagues noted a response rate of 89% UPSC patients treated with single-agent paclitaxel or the combination of paclitaxel and a platinum drug;

however, this study included a heterogeneous group of patients, including those with advanced stage primary tumors and those with recurrent tumors.[1] The optimal treatment of metastatic UPSC—either primary advanced or recurrent—remains uncertain. Others have reported the use of whole abdominopelvic radiotherapy in the treatment of metastatic UPSC; however, the numbers of patients studied have been small. The results from the present study and that by Zanotti et al suggest that the combination of paclitaxel and a platinum drug (either carboplatin or cisplatin) is a reasonable choice for patients with metastatic UPSC. Obviously, because of the poor prognosis associated with this disease, we need to continue our search for new effective agents. Hopefully, the new era of "targeted therapies" will produce more active treatments. ❖

Reference

1. Zanotti K, et al. *Gynecol Oncol*. 1999;74:272-277.

Treatment of Inflammatory Cytologic Abnormalities Detected By Pap Smears

ABSTRACT & COMMENTARY

Synopsis: *There appears to be no clinical benefit to treatment of inflammatory cytologic abnormalities.*

Source: Webb J, et al. *Journal of Lower Genital Tract Disease*. 2001;5(2):82-84.

For many years, it has been the practice of many clinicians to prescribe intervaginal or oral antibiotic therapy to patients who have a Pap smear showing inflammatory cytologic abnormalities. The rationale for such therapy has been repeatedly questioned yet the practice persists.

Webb and associates in this pilot study asked all women who had a Pap smear report which showed inflammatory cytologic abnormalities at their institution to participate in this study. Patients who agreed were assigned to 1 of 2 oral metronidazole regimens, vaginal metronidazole, or no therapy.

This study included 159 women. The method of patient assignment did not result in equal sized treatment groups. However, when the data from the 4 groups were compared, Webb et al could not demonstrate a statistically significant difference among the groups. Webb et al conclude that empiric antibiotic treatment of women with inflammatory changes on Pap smears is not clinically indicated.

COMMENT BY KENNETH L. NOLLER, MD

I have always wondered where the practice of treating inflammatory cells on Pap smears with antibiotics came from. The test was not designed to detect infection, and the presence of such cells does not mean an infection is present. The fact that there are some white cells present on the slide does not mean that anything needs to be, or should be treated. Even though cervical cytology can detect the presence of fungal organisms, changes consistent with BV, and trichomonads it is not clear that any of these should be treated unless the patient has symptoms. Indeed, in the revision of the Bethesda terminology that is currently being considered the whole category of "benign cellular changes" is probably going to be eliminated.

While this was not a great study (lack of randomization of treatment arms, nonblinding, inadequate sample size, etc) it did fail to detect any significant difference in Pap smear reports subsequent to antibiotic therapy vs. placebo. There have been prospective, randomized, clinical trials performed and they also have failed to detect any basis for treatment of inflammatory smears with antibiotics. Unfortunately, the practice persists. ❖

Special Feature

Are All Estrogens the Same?

By Sarah L. Berga, MD

For years, it was taught and widely believed that all estrogen products were comparable and, therefore, what should drive choice was cost and convenience. Emerging evidence suggests that this clinical dictum is not true. If it is not true, by what criteria, then, does one chose an estrogen preparation? To address this issue, we need to understand what an estrogen is and what gates estrogen action.

First, what is an estrogen? The liberal answer is that an estrogen is any substance whose binding to an estrogen receptor initiates postreceptor activity. A more conventional answer is that it is an 18-carbon, 4-ring structure derived from a cholesterol backbone. Selective estrogen receptor modulators, SERMs, bind to estrogen receptors, are not derived from a cholesterol backbone, and either block or do not initiate full physiological

postreceptor responses. Phytoestrogens are closer to conventional estrogens in chemical structure, but do not bind as avidly to estrogen receptors. In the same manner as SERMs, they may act as partial agonists or antagonists, depending on the prevailing intracellular hormone soup. Thus, they may antagonize full estrogen action in eumenorrheic women while eliciting partial estrogen action in postmenopausal women. The so-called "cognate" or physiological estrogens (barring pregnancy) are estradiol and estrone. During an ovulatory menstrual cycle, estradiol (E2) ranges from a low of ~30 pg/mL to a high of ~350 pg/mL, with an average of ~110 pg/mL. The ratio of estradiol to estrone (E1) is ~1:1. Common pharmacological estrogen preparations include:

1. those with a saturated B ring (eg, equilin, a constituent of conjugated equine estrogens);
2. conjugated estrogens, the major constituent of which is estrogen sulfate;
3. derivatives such as ethinyl estradiol, which has a ethinyl group added to carbon 17;
4. micronized estradiol, which is designed to be given orally because the micronization process protects the estradiol from being degraded by gastric secretions, and;
5. transdermal estradiol, which diffuses across the skin into the venous circulation and circulates primarily as estradiol.

The most obvious difference between oral from transdermal estradiol administration is the ratio of estradiol:estrone achieved in the circulation. Because of the first-pass hepatic metabolism that accompanies oral administration, the ratio of estradiol:estrone in the circulation is ~3:1. With transdermal or vaginal administration, the ratio of estradiol:estrone is ~1:1, and thus these latter routes of administration lead to more physiological patterns in the circulation. Also with oral administration of estradiol, the level of estrone sulfate is ~10-fold higher than with transdermal administration.[1] There is also a myriad of other differences between oral and transdermal estradiol owing to the hepatic first-pass effect, including increased coagulation and altered metabolism of other substances such as alcohol. Since there are no long-term data comparing clinical outcomes with oral vs. transdermal estradiol, we must depend on biochemical evidence. The biochemical evidence suggests that not all estrogens are the same.

Second, what gates estrogen action? The following is a short list of key determinants:

1. the density of steroid receptors in a given tissue;
2. ratio of occupation of ERa and ERb, which is in turn determined by the mix of estrogens in the circulation impinging upon a given tissue;
3. sulfatase activity in the target tissue (makes sulfated estrogens available to the cell by cleaving off the sulfate group);
4. other enzymatic activities in a given tissue that might convert precursors to estrogens;
5. tissue-specific coregulators, often called tissues-specific chaperones, that guide the dimerized estrogen receptors to key areas in the DNA called estrogen response elements (EREs), and;
6. the other steroids interacting with the cellular machinery.

It is interesting to note that one of the key chaperones, referred to as AP-1, interacts with other steroid-receptor complexes, including that of cortisol. The presence of intracellular cortisol makes AP-1 relatively unavailable to estrogen receptor complexes and, thus, high cortisol levels have the potential to dampen or block estrogen action. There are membrane receptors for estrogen as well, and these seem to be splice variants of classical ERa and ERb. In some cell systems, ERa functions to retard ERb action or availability. Thus, it is critical to balance ERa and ERb occupation to preserve physiological balance in the operation of cellular machinery. What I find fascinating is that ER expression has been reported to be much lower in nonreproductive tissues, thus any estrogenic substance is likely to have a greater effect on reproductive tissues than on nonreproductive tissues.[2] I suspect that this finding indicates that it is unlikely that we will find a SERM that is devoid of estrogen action in the uterus and brain while still eliciting estrogen action in other tissues such as brain and urogenital tract.

So what, you may ask. How might this information alter prescribing practices? Emerging data in endocrinology suggest that physiological replacement engenders better results. This appears to be true for replacement regimens with hypothyroidism and for Addison's disease.[3,4] Available evidence indicates that this may hold for the treatment of menopause as well. The main question that remains in my mind is whether our goal should be to aim for estradiol levels in the physiological range or whether the level should be subphysiological, in the range of 50-70 pg/mL. There are no epidemiological data to guide us in answering this question. At the present, my treatment hypothesis is that subphysiological HRT begun at the time of menopause potentiates the benefits of a healthy lifestyle to retard the onset of age-related deficits. The only reason I can find to not replicate subphysiology is convenience. However, with transdermal estradiol patches, replicating ovarian estradiol secretion is easy. When fertility is not the goal, I am not as sure how much benefit derives from replicating the luteal phase pattern

of progesterone. Since a progesterone patch is not available, our choices here are more limited. In the absence of much data, I lean toward progestin via patch (in combination with estradiol), oral or topical micronized progesterone, or the progestin intrauterine device, Mirena.

There has been a lot of confusion recently regarding the risks and benefits of HRT. I would like to point out that the majority of the studies reporting risks involved women who took an oral estrogen. In particular, the Women's Health Initiative, for all of its virtues, is a study of one estrogen, Premarin. All women who were randomized to receive Premarin got the same dose. Some were overdosed and others underdosed. We do not know if those who suffered ill effects were overdosed because the study was not designed to measure levels achieved. Further, many subjects were postmenopausal for many years prior to enrollment. The initiation of Premarin may have had profound effects on coagulation, but this also was not measured. Contrary to popular opinion, Premarin is not a weak estrogen and since it is sulfated, the tissues that may have received the highest exposure were the breast and the endometrium, because those tissues have high levels of the enzyme sulfatase.[5] I suspect that the increased risks of deep venous thrombosis (DVT) and myocardial infarction (MI) were attributable to the acute effects of oral estrogen upon hepatic stimulation and a subsequent increase in coagulation. Some women may have had pre-exisiting conditions that posed excess risk for DVT or MI. Thus, epidemiological trials in which the main estrogen taken was Premarin do not adequately test the hypothesis that subphysiological estradiol replacement begun at the time of menopause enhances health. I worry that we have oversimplified the art and science of HRT and, in so doing, we have misled our patients and ourselves. Given these considerations, I continue to recommend subphysiological HRT as an adjunct to a healthy lifestyle. I doubt, however, that any estrogen regimen can undo the harm of a lifetime of bad health habits or reverse established disease. ❖

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CME Questions

8. The following statements are true of screening mammography *except*:

a. No reduction in breast cancer mortality has been demonstrated with screening mammography younger than the age of 50.
b. Thus far, randomized clinical trials including women younger than the age of 50 have been underpowered to assess the effect in younger women.
c. A false-positive rate yields an increase in unnecessary biopsies.
d. Medical judgment requires making decisions when you don't have all the facts you need to make a decision.

9. In the study by Ramondetta et al, the objective response rate in patients with uterine papillary serous carcinoma (UPSC) treated with paclitaxel was:

a. 15%.
b. 30%.
c. 52%.
d. 77%.
e. 90%.

10. In the article by Webb et al, antibiotic treatment of patients with inflammatory cytologic changes on Pap smears resulted in:

a. decreased patient symptoms.
b. reduction of the rate of CIN.
c. prevention of the transmission of STDs.
d. None of the above

11. Invasive cancer of the vulva is often associated with other conditions of the vulvar skin. In the article by Rouzier et al, which of the following associated problems resulted in the best prognosis?

a. Lichen sclerosus
b. Squamous cell hyperplasia
c. HPV infection
d. None of the above

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *OB/GYN Clinical Alert*. Send your questions to: Robert Kimball, *OB/GYN Clinical Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *OB/GYN Clinical Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. ❖

In Future Issues:

Pegylated Lipsomal Doxorubicin vs. Topotecan for Ovarian Cancer