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INSIDE

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False Labor

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Patients with preterm contractions, who subsequently were diagnosed to have false labor and discharged, do not have an increased risk for early preterm birth, neonatal mortality, or lower Apgar scores. However, they do have a slightly greater chance of delivering in the late preterm period (34 to 36 weeks).*

Source: Chao TT, et al. The diagnosis and natural history of false preterm labor. *Obstet Gynecol* 2011;118:1301-1308.

A NUMBER OF PREVIOUS REVIEWS IN *OB/GYN CLINICAL ALERT*, INCLUDING a Special Feature, have been devoted to preterm birth (PTB), a problem that has been on the rise in the United States despite significant efforts to curb it. Despite this gloomy trend, a recent report from Parkland Hospital in Dallas actually may provide some reassurance to patients suspected of having preterm labor. Unlike other PTB outcome studies, this study specifically addresses the fate of pregnancies when the diagnosis of false labor is made.

The authors reviewed the records of 843 patients with gestations between 24 weeks 0 days and 33 weeks 6 days who presented to the labor and delivery with persistent preterm contractions (PTC).[1] If the patients had a cervical dilation of 2 cm or greater, they were admitted. If not, they were monitored in a triage area for 2 hours. If the contractions continued at a frequency of more than 1 per 10 minutes and/or if there was a cervical change, they were admitted. However, if the contractions were less frequent, and if there was no change in the cervix by digital examination, they were discharged.

Six hundred ninety (82%) patients were discharged with the diagnosis of false labor. The outcomes of these pregnancies were compared

to the outcomes observed in the overall population during the same 12-month period. The false labor group had a non-significant rate of PTB before 34 weeks of 2% vs 1% in the control group (P = 0.28; NS). However there was a statistically significant, but modest, increase in the rate of late PTB (34 to 36 weeks) compared to the baseline population (5% vs 1%, P = 0.02, respectively). Interestingly, only 1 out of 10 in the false labor group with 1 cm cervical dilatation delivered within 3 weeks of her episode of false labor. Although there were no differences between admissions to the NICU, Apgar scores, or neonatal death compared with controls, there was an increase in respiratory distress syndrome (RDS) in the study population (2% vs 1%; P = 0.001). The authors concluded that patients discharged with false labor between 24 and 34 weeks gestation are at slightly greater risk for late PTB (34-36 weeks), but not for early PTB (< 34 weeks) or neonatal mortality.

■ COMMENTARY

This paper again confirms that about four out of five patients presenting with PTC are not in labor. Yet, because of our heightened awareness of the impact of PTB, and, perhaps, our obsession to prevent it, we often commit patients with PTC to many days in the hospital in an effort to keep an occasional patient from delivering early. Of course, the problem is that once admitted, we are not very good at keeping those with true preterm labor from delivering anyway. In the meantime, these patients, now away from family support, are being housed and fed for up to $3,000 a day while being exposed to institutional food and our own special brand of pathogens.

The study did not include transvaginal cervical length measurements or fetal fibronectin in the diagnostic mix. Recent investigation has shown that the negative predictive value of either of these tests is greater than 90%,[2,3] and one wonders if the few late PTBs in the false labor patients might have been picked up with the addition of these methods.

In the past, the investigative thrust had been to focus on stopping a process that is already underway, which is like trying to detain a runaway truck with a stop sign. Fortunately, most current investigation has been directed toward identifying the causes of PTB so that preemptive measures can be undertaken. Nevertheless, while waiting for new information to evolve, it should be kept in mind that most clusters of PTC are of no consequence, and we need to concentrate on identifying those patients with these contractions who can be safely discharged. The Dallas group was able to send 690 patients with PTC home over the space of 1 year. Let's say there was a policy to observe all of these false labor patients in the hospital for 4 days (at a very conservative cost of $2,000 per day). That represents a total outlay of $1.3 million, with the only downside being that the 5% probability of preventing a late PTB delivery (34-36 weeks).

Cost aside, the data from this and other studies can give patients reasonable reassurance that false labor is really the opposite of "true" labor, and not a reason to panic. ■

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Does HRT Improve Cognitive Function?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *In a cross-sectional sample of postmenopausal women not using hormonal therapy, higher*

serum levels of estrogen were associated with improved semantic memory and verbal episodic memory abilities.

Source: Ryan J, et al. Hormone levels and cognitive function in postmenopausal midlife women. *Neurobiol Aging* 2012;33:617.e611-e622.

To investigate whether gonadal hormones influence cognitive function in postmenopausal women, the authors administered a comprehensive battery of neuropsychological tests on two occasions (2 years apart) to participants enrolled in the population-based, longitudinal Melbourne Women's Midlife Health Project. A total of 148 women (mean age 60 years) who had undergone natural menopause and were not using hormone therapy underwent the neuropsychological testing at year 11 of the study, with 108 completing retesting at year 13. Total and free estradiol, estrone, and testosterone levels were measured at the time of the first testing. The tests included an adaption of the California Verbal Learning Test II, using semantically related words and a 10-item list learning task using unrelated words. Both of these tests assessed immediate and delayed recall. A variety of other tasks related to immediate and delayed recognition, letter-number sequencing, category fluency, and naming also were administered. To reduce the number of cognitive outcomes examined and thus the risk of a Type 1 error, the investigators incorporated a principal-component analysis to identify four groupings of correlated cognitive tests: verbal episodic memory, visual episodic memory, semantic memory (the ability to recall words or names), and executive function–visuospatial skills.

Initial analyses compared the characteristics of women at the time of baseline testing, according to cognitive factor scores, using correlations and t-tests. The change in cognitive function over the 2-year period was calculated by subtracting each baseline test score from the corresponding score 2 years later. Low change scores indicated a decline in cognitive function. Linear regression analysis was used to model the association between individual hormone measures and cognitive function at baseline, and analyses were adjusted a priori for potential confounders (age, education level, depressive symptoms, and age at menopause).

In the multiple linear regression analyses, better semantic memory performance was associated with higher total ($P = 0.02$) and free ($P = 0.03$) estradiol levels and a lower ratio of testosterone to estradiol ($P = 0.007$). There were no statistically significant associations between hormone levels and verbal episodic memory (although this was at the $P = 0.08$ level), verbal episodic memory, visual episodic memory, or executive function–visuospatial skills. The authors concluded that in postmenopausal women, endogenous estradiol and testosterone levels and the testosterone/estradiol ratio are associated with semantic memory and verbal episodic memory abilities.

■ COMMENTARY

Although most of the basic research in nonprimate species and functional studies in nonhuman primates and women support that estrogen has a profound effect on memory and executive function,[1] we lack strong clinical data to support whether postmenopausal women should consider estrogen replacement therapy for cognitive protection. This is unfortunate, as memory complaints are common in midlife, and many women would choose to use a product that would improve or prevent these symptoms if one existed. Although cognitive protection is not a labeling indication for any hormonal product, a number of other interventions designed for healthy brain aging have been accepted by the public, unencumbered by the regulatory burden of evidence of efficacy and with no comprehensive evaluation of risk. *Ginkgo biloba* anyone?

Since the publication of the main results from the Women's Health Initiative (WHI) almost 10 years ago, the public debate on hormone replacement therapy (HRT) has focused primarily on risk. When I talk to young clinicians, I find they have received limited experience counseling women regarding postmenopausal hormone therapy. I think it is important to discuss the very real possibility of benefit with my patients, and put risk in perspective. But how should a clinician counsel a newly menopausal women presenting for HRT for cognitive protection? Is the evidence compelling? What if she has no other menopausal symptoms?

The Women's Health Initiative Memory Study, a planned substudy of the WHI that evaluated the incidence of dementia and mild cognitive impairment in postmenopausal women, concluded that HRT not only failed to protect against cognitive decline, but actually increased the risk of dementia.[2] But we know that the WHI enrolled a group of women with cardiovascular risk factors at an average age of 10 years after menopause. Do these results apply to otherwise young, healthy recently menopausal women? They do not seem to when cardiovascular outcomes are evaluated, and I suspect the brain is the same. For the cardiovascular system, clinical trials and surrogate studies support that timing is critical: protection occurs with early (shortly after onset of menopause) and continued exposure while prolonged estrogen deprivation results in irreversible changes that limit the benefit of estrogens in older initiators.[3]

Similar data exist for the brain, suggesting that early and often applies to HRT initiation if the goal is cognitive protection.[4] The Ryan study puts a slightly different perspective on this, showing that semantic memory (the ability to recall words or names) is correlated with serum

estrogen levels in postmenopausal women not using HRT. A couple of observations: First, the mean estrogen levels were quite low in this study, certainly in the range we expect with menopause. Does this mean that we are measuring an effect that takes many years to develop? Second, testosterone/estrogen levels were inversely related to semantic memory. In other words, as women move to a more androgen-dominant endocrine environment (due to ovarian production of androstenedione and testosterone following the loss of follicular activity and rising luteinizing hormone), their memory declines. This is a red flag for women with intact ovaries in natural menopause; they may be more at risk for memory problems. I would want to hedge my bet with a little exogenous estradiol to move to a more favorable balance.

Brain function is another extremely important potential benefit of hormonal therapy. Although there is some inconsistency in the results of current clinical information, animal studies and functional imaging studies in women suggest benefit. High-quality longitudinal studies will be needed to determine whether the Timing Hypothesis is true with respect to brain function. Women taking estrogen now may be in a position to remember the question when the story is complete! ■

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Check the Stock: Recall Issued for Akrimax OCs

Does your clinic use oral contraceptives (OCs) labeled under the Akrimax Pharmaceuticals brand? If so, you need to check for packs of Lo/Ovral and its generic equivalent, due to a voluntary recall issued in late January.

The recall was announced by Pfizer, the manufacturer of the drug. Akrimax Rx Products of Cranford, NJ, marketed the product under its Akrimax Pharmaceuticals brand. The product was distributed to warehouses, clinics, and retail pharmacies nationwide. The recall includes 14 lots of Lo/Ovral-28 (norgestrel and ethinyl estradiol) tablets and 14 lots of norgestrel and ethinyl estradiol tablets (generic). This recall involves about one million pill packets.

A Pfizer investigation found that some blister packs of the drug might contain an inexact count of inert or active ingredient tablets. Also, the tablets might be out of sequence. The company says the cause of the packaging error has been rectified. "As a result of this packaging error, the daily regimen for these oral contraceptives may be incorrect and could leave women without adequate contraception, and at risk for unintended pregnancy," the company press release states. "These packaging defects do not pose any immediate health risks; however, consumers exposed to affected packaging should begin using a non-hormonal form of contraception immediately."

The company advises patients who have affected product to notify their health care provider and return the product to the pharmacy.

Any adverse events that might be related to the affected product should be reported to Akrimax Medical Information by telephone (877) 509-3935 (8 a.m. to 7 p.m. Central Time, Monday-Friday). Adverse events also may be reported to the FDA's MedWatch Program. Events may be entered online; mailed to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787; or faxed to (800) 332-0178. ■

Prognostic and Practical Implications of Germline BRCA Status

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Women with ovarian cancer who carry germline mutations in BRCA1 or BRCA2 have a better prognosis (overall survival) than those women with ovarian cancer who do not. BRCA2 mutation confers a stronger effect compared to BRCA1. These findings affect treatment decisions and clinical investigation.*

Source: Bolton KL, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA* 2012;307:382-390.

Women who carry a deleterious germline mutation in BRCA1 or BRCA2 have a substantially higher lifetime risk of developing ovarian cancer. Previous reports have suggested that if ovarian cancer develops in these women, their prognosis is better, particularly if they carry a mutation in BRCA2. However, the association has been inconsistent and limited by small series, variable treatments, and identification techniques. To better elucidate the association of BRCA status and outcome, the authors conducted a pooled analysis of 26 observational studies that included data from 1213 ovarian cancer cases with pathogenic germline mutations in BRCA1 (n = 909) or BRCA2 (n = 304) and from 2666 non-carriers. Untested patients with ovarian cancer from families with a documented germline mutation were assumed to carry the same mutation. Patients were recruited and followed between 1987 and 2010. The 5-year overall survival was 36% for non-carriers, 44% for BRCA1 carriers, and 52% for BRCA2 carriers. After adjusting for study and year of diagnosis, BRCA1 and BRCA2 mutation carriers showed a more favorable survival than non-carriers (for BRCA1: hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.68-0.89; $P < 0.001$; and for BRCA2: HR, 0.61; 95% CI, 0.50-0.76; $P < 0.001$). These survival differences remained after additional adjustment for stage, grade, histology, and age at diagnosis. Of interest, this effect was attenuated when the analysis was based on women recruited solely by strong family history (without formal testing). Overall, ovarian cancer patients harboring a germline mutation in BRCA1 or BRCA2 have a significantly improved 5-year overall survival. BRCA2 carriers have the best prognosis.

■ COMMENTARY

The current report provides the most definitive information to date on the prognostic significance of germline BRCA1 and BRCA2 mutations on epithelial ovarian cancer mortality. The data are important because prognostic associations about ovarian cancers that develop in BRCA1 or BRCA2 germline carriers have been inconsistent in previous reports, particularly in BRCA1 carriers. BRCA1 carriers have a higher overall risk, develop cancer at a younger age, and may benefit, to a lesser degree, from prophylactic surgery compared to BRCA2 carriers.[1] The study's diverse population, large sample size, and statistical rigor are its strengths and provide the most convincing data to date that BRCA-associated ovarian cancer (both BRCA1 and BRCA2) has sufficiently different biology compared to wild-type ovarian cancer. This becomes important in making treatment recommendations because the BRCA genes perform many important functions in normal cells, including a major role in high-fidelity DNA damage repair through homologous recombination. Their altered or truncated function in cancer cells leads to augmented cell kill, particularly with agents (chemotherapy and radiation) that cause DNA double-strand injury. Indeed, recent studies have suggested improved ovarian cancer outcomes also may result from aberrations in other genes governing the homologous recombination pathway like EMSY, PTEN, and the Fanconi genes.[2]

A second important implication from this study is that, like age, performance status and debulking result; BRCA status should be included as an important stratification variable when assessing the outcomes of treatment trials. The strength of this effect is not considered in a treatment population (10-15% of participants), it could significantly vary the interpretation of clinical trials involving cytotoxic agents. Since BRCA testing is not universally performed in women with the disease, preinvestigational assessment of homologous recombination deficiency is warranted. Finally, knowledge of BRCA mutation status in this population will help to identify patients likely to benefit from agents targeting DNA repair mechanism "workarounds," such as the poly(ADP)-ribose polymerase inhibitors.[3,4] ■

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Treating CIN 2 in Young Women

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

Synopsis: *Spontaneous regression does occur in women with CIN 2 in this age group.*

Source: McAllum B, et al. Is the treatment of CIN 2 always necessary in women under 25 years old? *Am J Obstet Gynecol* 2011;205:478.e1-7.

In this retrospective study of young women performed in New Zealand between 2005 and 2009, 57% of 452 patients with biopsy-proven cervical intraepithelial neoplasia (CIN) 2 were treated immediately whereas 157 (35%) met the criteria for conservative management. Of these, 62% showed spontaneous regression based upon a median of 8 months follow-up. Persistent disease was identified in 38%. None of the patients had their dysplasia progress to cancer.

■ COMMENTARY

My, my, how times have changed. In the remote past (i.e., during my residency in the late 1970s), we were collectively on a "seek and destroy" mission regarding dysplasia. After all, we wanted to prevent cervical cancer, and the best way to prevent dysplasia from progressing to invasive disease was to treat precursor lesions. We had the relatively new tool of colposcopy, allowing us to perform directed biopsies and, thereby, reducing the need for more invasive cold-knife conizations. Be it conization, cryosurgery, and even hysterectomy, ridding the woman of her dysplasia was on the top of our priority list. Admittedly, we didn't understand the role of human papillomavirus, so our world view was a bit skewed.

Fast forward a couple of decades, and our improved understanding of pathophysiology of the disease allows us to chill a bit. We were able to raise the age at which young women were counseled to be initially screened. We also became far more "hands off" in regard to treating dysplasia in adolescents, recognizing that the body's immune system would resolve cases of CIN 1 which, in the past, were treated with ablation, cryosurgery, and/or excision.

As science progresses, the potential need for us to intervene in many cases of CIN may be decreasing. I say "may" because, as these authors correctly point out, the safety of this approach needs to be validated with larger study. Within this small retrospective group of patients, even though no patients progressed to cancer, there were significant findings in the "immediately treated" group. One patient had microinvasive disease while two patients had adenocarcinoma in situ.

These data emphasize why patient care should not be driven by the outcomes of retrospective studies. The interpretation of data is fraught with a number of limitations. For instance, in this study, definitions were not controlled; conservative management was not outlined; treatment intervals varied; the rationale for immediate treatment or delayed management was not recorded; there was no long-term follow-up plan described; and there was no confirmation of histologic diagnoses, i.e., there was not a second pathologist's interpretation. Perhaps the most telling of the shortcomings, and maybe even a fatal flaw of the study, was the way in which regression of disease was defined. One-third (30.6%) of the patients were reported to show regression of CIN 2 — based only on normalizing of the pap smear and colposcopic appareance. Since both techniques have well-documented false-negative rates, the clinician would do well to cast a critical eye.

On a more positive note, since median follow-up was only 8 months, there are potentially more friendly factors to this management plan. For example, some cases of regression were seen at 18 to 24 months, suggesting that longer follow-up could bring even higher regression rates.

The prospective data collection hopefully will include data points that standardize time intervals, histologic definitions, human papillomavirus typing, and viral load as well as demographic information.

As always, our desire to "first do no harm" is a consideration. If we don't have to intervene on dysplasia and feel comfortable that even CIN 2 can be watched without

jeopardizing a woman's health, that's a good thing. That willingness to keep our hands off must be based on sound scientific information, most of which still remains to be identified. For now, each young patient (under 25 years of age as defined in this article) presents a therapeutic challenge for both patient and physician to weigh the alternatives. Today, there appear to be more options for women in this age group to consider. We should be willing to partner with each one in deciding the path that makes the most sense for her. Even though this article is not "ideal," it will help me with how "I deal" with young patients with CIN 2. ■

Special Feature

Gender Medicine and the Obstetrician-Gynecologist

By Sarah L. Berga, MD

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

IT MIGHT SOUND OBVIOUS TO A REPRODUCTIVE MEDICINE SPECIALIST to say that "every cell has a sex." On the other hand, even an obstetrician-gynecologist might be surprised to know how much of a contribution sex differences make to health and disease. A recent editorial in the *Lancet,* titled "Taking Sex into Account in Medicine," highlighted that gender-diverse teams have higher team IQs and promote innovation, and remarked that "being male or female might be a more important determinant of health, illness, and response to treatment" than is currently known or appreciated.[1] One important biological concept is that sex differences are more than just hormonal in origin. For instance, the transcription factor XIST (X-inactivation-specific transcription) is a long, noncoding RNA that does more than inactivate the "extra" X chromosome. The absence or presence of XIST regulates cellular molecular machinery in ways just now beginning to be defined. Recently, we have witnessed the launch of two new journals — the *Biology of Sex Differences* (2010) and *Gender Medicine* (2006). In January 2012, the Institute of Medicine released a report entitled, "Sex-Specific Reporting of Scientific Research" that advocated the reporting of the sex of cells and animals used in biomedical science.[2] The report also called for studies, particularly clinical trials, to determine the presence or absence of sex differences. To which specialists does the field of women's health and gender medicine belong? And what is the role of the obstetrician-gynecologist in ushering in this new era in which we seek to discover how sex modifies disease presentation, diagnosis, and treatment?

I would suspect that most obstetrician-gynecologists consider their core expertise to be in conditions that are unique to women such as pregnancy, endometriosis, anovulation, and cervical dysplasia. Recently it was reported that XY neurons die by a caspase-independent pathway and XX neurons by a caspase-dependent pathway.[3] Does this mean that we need to treat men and women who experience a stroke with different interventions or medications? Does this explain why acute and chronic sequelae of stroke differ in men and women? Clearly, the treatment of stroke is outside the typical practice pattern of an obstetrician-gynecologist. On the other hand, who is going to ensure that the neurologist knows that the neurons of men and women die by different pathways and thus necessitate different treatment approaches? To help address the knowledge deficit, the National Institutes of Health recently released a RFA soliciting applications to elucidate the neurobiology of sex differences.[4] But what about sex differences in other tissues and organs? And who is going to raise awareness about the need to specify the effects of sex when treating patients? I hasten to add that it is important to recognize that both men and women will benefit from this expanded knowledge-based and focused treatment approach. It seems to me that obstetrician-gynecologists will play a role in determining sex-appropriate interventions and that our role will be as a member of an investigative or clinical team.

Allow me to share another molecular nugget. The genes expressed by cells of male and female rats exposed to glucocorticoids vary by sex. In female rats, glucocorticoids lead to a much greater expression of genes that regulate inflammation than in male rats. Further, when exposed to an infectious challenge, male rats given glucocorticoids survived while female rats died because of an exuberant inflammatory response. Think of the many conditions for which we prescribe glucocorticoids without any consideration that there may be sex-specific effects. Indeed, glucocorticoids could well exacerbate rheumatological conditions in women and suppress them in men. Clearly, we must understand sex-specific responses to interventions to optimize health for men and women. The bottom line is that we need to understand conditions found only in women, conditions more common in one sex over the other, conditions that present differently in men and women, and how sex modifies treatment responses.

These are early days in the field of the biology of sex differences. But what of gender medicine? First, we must

get our nomenclature straight. Sex is commonly understood as a biological quality based on genetics or morphology. Gender is a sociocultural process or behavioral expectation associated with one's perceived sex. Thus, the field of obstetrics and gynecology has evolved from one in which only the conditions unique to women were the focus to one that serves to advocate for better health for women and men. Obstetrician-gynecologists are logical partners for multidisciplinary teams that aim to evolve best practices according to both sex and gender. ■

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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.
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CME Questions

1. **Which statement does *not* fit regarding the Dallas protocol for triaging patients with preterm contractions?**
   a. Patients who had cervices of 2 cm or more were admitted.
   b. Patients with cervices of 1 cm or less were observed for 2 hours.
   c. Patients who had contractions greater than one every 5 minutes would be discharged.
   d. Patients who had a cervical change during the 2-hour observation period were admitted.
   e. All of the above are correct.

2. **In patients with preterm contractions, ultrasound cervical length and fetal fibronectin can rule out preterm birth with more than 90% accuracy.**
   a. True
   b. False

3. **Which of the following is correct regarding outcomes in patients who were discharged with the diagnosis of false labor, compared with controls?**
   a. There was no difference in late preterm birth (34 to 36 weeks).
   b. There was a significant difference in preterm birth at less than 34 weeks.
   c. There was a significant difference in Apgar scores.
   d. There was no difference in neonatal mortality.
   e. There was a difference in additions to the newborn special care unit.

4. **Over 2 years, decline in semantic memory in postmenopausal women not using hormonal therapy was associated with:**
   a. higher free estradiol levels.
   b. a low testosterone to estradiol ratio.
   c. early onset of Alzheimer's disease.
   d. lower levels of free and total estradiol.
   e. increased alcohol use.

5. **In the study by Bolton et al, BRCA1 or BRCA2 mutation |was assessed by which of the following?**
   a. Family history alone
   b. Mutation sequencing
   c. Both family history and mutation sequencing
   d. Tumor biopsy

In Future Issues: **Osteoporosis Screening**

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.*

Dutasteride and Low-Risk Prostate Cancer

In this issue: New treatment for prostate cancer; avastin and breast cancer; new CMS disclosure rule; and FDA actions.

Adjunct to active surveillance?

Low-risk prostate cancers are nonpalpable, low-grade tumors associated with prostate-specific antigen (PSA) levels less than 10 ng/mL. For these patients, active surveillance is an option, allowing a period of observation to help decide who should be treated or not treated. Generally, this involves repeated biopsy sampling with the option to treat more aggressively if higher grade tumors are found. Active surveillance is more frequently utilized in Europe and Canada than in the United States, where more aggressive treatment is the norm. A new study from the U.S. and Canada investigates the safety and efficacy of the 5α-reductase inhibitor dutasteride on prostate cancer progression in men with low-risk disease. A total of 302 men ages 48-82 with low-volume Gleason score 5-6 prostate cancer were randomized to dutasteride 0.5 mg per day or placebo. Patients were followed for 3 years with prostate biopsies done at 18 months and 3 years with the primary endpoint being time to prostate cancer progression. After 3 years, 38% of men in the dutasteride group and 48% of men in the control group had prostate cancer progression (hazard ratio 0.62; 95% confidence interval [CI], 0.43-0.9; $P = 0.009$). Dutasteride was not associated with an increase in adverse events. There were no prostate cancer-related deaths and no incidence of metastatic disease in either group. The authors conclude that "dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer" (*Lancet* published online January 23, 2012). An accompanying editorial points out the appeal of a safe oral drug that can prevent prostate cancer progression, but the author cannot recommend the drug based on this study due to several limitations — short duration, no evidence of mortality difference, and, most importantly, the risk that 5α-reductase inhibitors may decrease the volume of low-grade, but not high-grade, cancers. (*Lancet* published online January 23, 2012). This study comes at a time when physicians are actively debating the pros and cons of screening for prostate cancer. The recently published PLCO trial showed that PSA screening does not lower the risk for death from prostate cancer while there is evidence of harm (*J Natl Cancer Inst* 2012;104:125-132). Some would argue that rather than treating low-grade prostate cancers, it may be better not to diagnose it at all. This issue is sure to be a topic of discussion at the FDA if GlaxoSmithKline requests approval for dutasteride (Avodart) for the management of low-risk prostate cancer. ■

More to the avastin/breast cancer story?

In November 2011, the FDA revoked the approval of Genentech's bevacizumab (Avastin) for the treatment of breast cancer. The somewhat controversial decision was based on lack of evidence of improved survival with the drug, even though several studies have shown improvement in progression-free survival. This has sparked a debate regarding surrogate clinical endpoints, such

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as progression-free survival or pathological complete response, which is the endpoint used in two new studies recently published in the *New England Journal of Medicine*. The first study from Germany randomly assigned 1948 women with medium-sized tumors to receive neoadjuvant epirubicin and cyclophosphamide, followed by doxetaxel with or without bevacizumab, in patients with HER2-negative breast cancers. Rates of pathological complete response were 14.9% without bevacizumab and 18.4% with the drug (odds ratio 1.29; 95% CI, 1.02 to 1.65; $P = 0.04$). Patients with hormone receptor-negative ("triple negative") tumors did better while patients with hormone receptor-positive tumors saw no improvement (*N Engl J Med* 2012;366:299-309). The other study, supported by the National Cancer Institute, looked at about 1200 patients with operable HER2-negative breast cancer. Patients were given neoadjuvant therapy with docetaxel plus capecitabine or paclitaxel plus gemcitabine followed by doxorubicin-cyclophosphamide. They were further randomized to receive bevacizumab for the first six cycles. Adding capecitabine or gemcitabine to docetaxel had no effect and increased toxicity; however, adding bevacizumab increased the rate of pathological complete reponse (28.2% without bevacizumab vs the 34.5% with bevacizumab, $P = 0.02$). Bevacizumab increased the rates of hypertension, left ventricular systolic dysfunction, hand-foot syndrome, and mucositis. The authors conclude that bevacizumab significantly increased the rate of pathological complete response (*N Engl J Med* 2012;366:310-320). An accompanying editorial points out that the ongoing controversy regarding bevacizumab for the treatment of breast cancer revolves around the issue of using surrogate endpoints in clinical trials as well as broader economic issues in the treatment of cancer. Although the study showed improvement in the surrogate endpoint of pathological complete response (defined as absence of residual tumor in the breast and nodes in the European study and a less stringent criteria of absence of residual tumor in the breast only in the American study), neither study was powered to show differences in survival — the criteria the FDA used to withdraw the approval for bevacizumab (*N Engl J Med* 2012;366:374-375). It is unlikely that either of these studies will influence the FDA to change its decision until more definitive survival data are available. ■

Disclosure rule open for comments

The Centers for Medicare and Medicaid Services is requesting comments on a proposed rule that would require drug and device companies to report all financial relationships with physicians. The new rule is part of the Affordable Care Act. It would require disclosure of payments for food, entertainment, gifts, consulting fees, honoraria, research funding for grants, education or conference funding, royalties or licenses, and insurable contributions. Physicians would also need to disclose stock ownership in pharmaceutical and device companies, with all this information provided on a public website. Failure to disclose this information would mean substantial fines for physicians. Comments will be accepted until mid-February with the final rule expected later in 2012. ■

FDA actions

Responding to concerns about increasing antibiotic resistance, the FDA has issued an order that prohibits the use of cephalosporins in cattle, swine, chickens, and turkeys effective April 15, 2012. This rule is intended to limit the indiscriminate use of cephalosporins and preserve the effectiveness of the drugs in humans.

The FDA has approved a once-weekly, extended-release formulation of exenatide for treatment of type 2 diabetes. The drug is a glucagon-like peptide-1 receptor agonist and is indicated as an adjunct to diet and exercise for improved glycemic control. It is the first once-weekly diabetes drug to be approved. The approval was based on the DURATION-5 trial, which compared once-weekly exenatide with twice-daily exenatide injection. Exenatide extended-release is approved with a Risk Evaluation and Medication Strategy (REMS) because of concerns regarding acute pancreatitis and the potential risk for medullary thyroid cancer, as well as concerns about QT prolongation and cardiovascular risk. Exenatide extended-release will be marketed by Amylin Pharmaceuticals and Alkermes plc as Bydureon.

The FDA has approved vismodegib to treat adult patients with advanced basal cell carcinoma who are not candidates for surgery or radiation, and for patients with metastatic disease. The drug was approved under the agency's priority review program and is the first approved drug for metastatic basal cell carcinoma. The once-a-day oral pill inhibits the Hedgehog pathway, a molecular pathway found in basal cell carcinomas but few other normal tissues. The approval was based on a single, multicenter trial of 96 patients in which 30% of patients with metastatic disease experienced a partial response and 43% patients with locally advanced disease experienced a complete or partial response. Vismodegib is marketed by Genentech as Erivedge. ■