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Loop Electrosurgical Excision Procedure and Cesarean Section Rate

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: A recent study comparing patients having had loop electrosurgical excision procedures with those who had punch biopsies alone or Pap smears only has shown no differences in cesarean rates between groups.

Source: Frey HA, et al. Risk of cesarean delivery after loop electrosurgical excision procedure. *Obstet Gynecol* 2013;121:39-45.

LOOP ELECTROSURGICAL EXCISION PROCEDURE (LEEP) HAS PLAYED AN important role in the diagnosis and treatment of cervical cancer. However, since the cervix is so intimately involved in the conduct of labor, obvious questions emerge regarding whether removing tissue from the cervix will have an adverse effect on subsequent pregnancies.

In an effort to see if LEEP affected the cesarean section rate (CSR), researchers from St. Louis reviewed their records over a 10-year period (1996-2006).¹ Five hundred ninety-eight women were identified who had LEPPs prior to their next pregnancies. Data also were collected on another 522 matched controls, all of whom had had cervical biopsies, as well as another 588 patients who had had Pap smears alone prior to pregnancy. The investigators then focused on decisions and events occurring during these patients' next pregnancies, such as CSR, reasons for the cesarean sections, and indications for induction of labor. They also tried to correlate these delivery variables with the size of the LEEP specimens obtained and the time interval between the procedures and the deliveries.

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After adjusting for age, parity, prior cesarean delivery, body mass index, and birth weight, there were no differences in the CSRs in those with LEEPs compared with the Pap smear group if delivery occurred at term (28.5% vs 26.3%; relative risk [RR], 1.08; 95% confidence interval [CI], 0.88-1.33) or if preterm (45% vs 46%; RR, 0.98; CI, 0.72-1.33). Also, there were no differences in CSR in term patients with LEEPs compared with punch biopsy patients at term (26.1% vs 26.5%; RR, 1.08; CI, 0.88-1.33) or preterm (45.4% vs 41.8%; RR, 0.98; CI 0.72-1.33).

Importantly, when "failure to progress" or "arrest of labor" were used as a reason for cesarean delivery, there were no differences between groups, nor were there differences in the percentages of inductions. Last, the length of time between the LEEP and delivery and the amount of cervical tissue removed at the time of the LEEP had no bearing on the route of delivery. Specifically, the average LEEP tissue sample measured 1.8 cm³ for those having a cesarean section vs 1.7 cm³ for those having a vaginal delivery ($P = 0.71$).

■ COMMENTARY

The concept that cervical scarring post-LEEP may affect the dynamics of labor and, therefore, the route of delivery is worth studying, and this paper certainly seems to put that concern to rest. LEEPs did not increase the rate of cesarean delivery, in general, nor increase the rate of arrested of labor, in particular. Neither was there a greater need for induction of labor in these patients. The size of

the tissue sample did not have an effect on the ability of the cervix to dilate.

What about the opposite effect of LEEP on cervical tissue integrity? Is it possible that removal of cervical tissue weakens the cervix to the point of causing preterm labor? This answer is not so clear. For example, a study from Finland involving 624 patients suggested that LEEP is associated with a doubling of preterm birth (PTB) when compared with controls (12% vs 6.5%).² Furthermore, a repeat LEEP increased the rate of PTB five-fold.

Counterpoint information has emerged from Parkland Hospital in Dallas where investigators studied 511 patients who had LEEPs and found no increase in the rate of PTB over controls (no LEEPs).³

If there really is a risk of PTB with LEEPs, then there are two possible reasons: 1) The stability of the cervix is simply weakened by the removal of tissue or 2) The distance between the ectocervix and the amniotic cavity is shortened, thus providing bacteria with a shorter pathway to the membranes.

First, little stability is provided by the last few millimeters of the cervix, and prior to preterm labor the cervix shortens from the inside, not the outside. Second, although not yet borne out by solid data, our anecdotal impression is that patients who are many months post-LEEP do not have shorter cervices in the second trimester.

So ... until further data have emerged to further confuse or clarify the issue, we can tell our LEEP patients that their risk of delivering by cesarean section is no greater than anyone not having the procedure. However, it still is unclear if LEEP predisposes them to preterm labor. Although I have been inclined to be very optimistic about their chances for a term delivery, I have been suggesting that an ultrasound cervical length (CL) assessment be accomplished at 18 to 24 weeks. If the measurement is > 3 cm and they do not have a history of PTB, the risk of preterm labor is very low. If the CL is 2.5-3.0, then they should return in 10 days for a repeat examination. If there is no change, then they can be reassured, and no further testing is necessary. If the CL is < 2.5 cm, then they should be considered at some risk for PTB and managed according to the provider's protocol du jour. ■

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Prevention of Cardiovascular Disease with Mediterranean Diet

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: A Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events in a large, multicenter, randomized study of high-risk women and men conducted in Spain.

Source: Estruch R, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279-1290.

WITH THE BACKGROUND OF SEVERAL OBSERVATIONAL cohort studies and a secondary prevention trial that demonstrate a reduction of adverse cardiovascular outcomes among adults adherent to a Mediterranean diet, the authors designed the PREDIMED (Prevención con Dieta Mediterránea) trial, a parallel-group, multicenter, randomized study conducted in Spain. Beginning in 2003, they recruited and enrolled men and women with no cardiovascular disease (CVD) at enrollment, but who were identified to be at high risk for developing CVD on the basis of having either type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature coronary heart disease. Subjects were randomly assigned to one of three dietary intervention groups: a Mediterranean diet supplemented with extra-virgin olive oil (approximately 1 liter per week), a Mediterranean diet supplemented with nuts (30 g of mixed nuts per day [15 g of walnuts, 7.5 g of hazelnuts, and 7.5 g of almonds]), or a control diet (advice to reduce dietary fat).

Participants received baseline dietary counseling and quarterly individual and group educational sessions. Depending on group assignment, subjects also received either free provision of extra-virgin olive oil, the mixed nuts, or small nonfood gifts (control diet group). Biomarkers of compliance, including urinary hydroxytyrosol levels (to confirm compliance in the group receiving extra-virgin olive oil) and plasma alpha-linolenic acid levels (to confirm compliance in the group receiving mixed nuts), were measured in random subsamples of participants at 1, 3, and 5 years.

The primary endpoint was the rate of major cardio-

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vascular events (myocardial infarction, stroke, or death from cardiovascular causes). On the basis of the results of an interim analysis, the trial was stopped after a median follow-up of 4.8 years after a total of 7447 persons were enrolled (age range, 55-80 years). More than half (57%) of the subjects were women. A reduction in the risk of CVD was seen with both Mediterranean diet groups; the multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54-0.92) for the group assigned to a Mediterranean diet with extra-virgin olive oil and 0.72 (95% CI, 0.54-0.96) for the group assigned to a Mediterranean diet with nuts. No diet-related adverse effects were reported. The two Mediterranean diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses.

The authors concluded that the evidence from this randomized, controlled trial demonstrates that a Mediterranean diet supplemented with extra-virgin olive oil or nuts can reduce the incidence of major cardiovascular events in high-risk adults.

■ COMMENTARY

Although this elegant study received only limited press, the implications for our patients are profound. While there has been much written about obesity, lack of exercise, and other factors associated with cardiovascular risk, we have had little to offer high-risk women for risk reduction other than general advice about diet and exercise and statins. In too many primary care practices, the typical approach is to abandon dietary change early, and proceed directly to statin therapy. Many patients seem to like this approach, as it requires no major lifestyle modification.

While substantial evidence¹ supports the use of statins to reduce the risk of CVD, the results of the PREDIMED trial should reinforce our counseling of diet changes as the cornerstone of prevention. About 40% of subjects in each of the diet cohorts in this study were statin users; the supplemented Mediterranean diet groups still enjoyed a 30% reduction in CVD. While this study enrolled both

men and women, more than half were women, and a subgroup analysis showed no differences in outcomes.

But can we study a Mediterranean diet in Spain? Contrary to cultural expectation, fewer than 9% of subjects were eating a Mediterranean diet, according to results of the baseline dietary screening (perhaps those who did were healthy and not part of the screening population). This was a high-risk group, with almost 50% using ACE inhibitors and almost one-third on oral hypoglycemic agents.

Importantly, subjects in this study overall were compliant with the dietary intervention. By 3 years, they significantly increased weekly servings of fish (by 0.3 servings) and legumes (by 0.4 servings) in comparison with those in the control group. They also increased their consumption of either extra virgin olive oil (to 50 g and 32 g per day, respectively) or nuts (to 0.9 and 6 servings per week) according to their assigned groups. These main nutrient changes were associated with reductions of other fats. For this reason, the incorporation of olive oil or nuts is the key. Notably, there were no significant differences in physical activity between the three groups.

Talking about weight loss and exercise can be difficult, and vague recommendations are not helpful. Evidence from the PREDIMED trial should be presented to encourage women to eat better, not less. There are a number of heart-healthy Mediterranean style cookbooks available. The recipe options are delicious, and go well with an Oregon pinot noir! ■

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Influenza Vaccination in Pregnancy

ABSTRACT & COMMENTARY

By **Rebecca H. Allen, MD, MPH**

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

Synopsis: In this randomized, controlled trial, text messages regarding the importance of influenza vaccination in pregnancy did not increase vaccine uptake in a low-income population receiving prenatal care.

Source: Moniz MH, et al. Improving influenza vaccination rates in pregnancy through text messaging: A randomized controlled trial. *Obstet Gynecol* 2013;121:734-740.

THE AUTHORS PERFORMED A RANDOMIZED, CONTROLLED trial at the Magee Women's Hospital outpatient clinic in Pittsburgh, Pennsylvania, over two consecutive influenza seasons (2010-2011 and 2011-2012). Participants were randomized to one of two text messaging groups: 1) a control group that received information regarding general preventive health in pregnancy and 2) an intervention group that received information regarding general preventive health and the importance of influenza vaccination in pregnancy. The participants received 12 weekly text messages, and inclusion criteria were age 15-40 years, English-speaking, less than 28 weeks pregnant, and possession of a personal cell phone with text-messaging capability. Women were excluded if they had already received the influenza vaccine that season, desired vaccination on the day of enrollment, had been a previous participant in the study, or had contraindications to the vaccine. Both groups received routine prenatal care and there was no cost to receive vaccines in the clinic. The participants completed anonymous surveys before and after the intervention to evaluate beliefs, attitudes, and behaviors toward preventive health care and text messaging. The study was powered to detect an increase in influenza uptake in the intervention arm from an anticipated background rate of 45-70%.

The authors enrolled 204 women out of 2100 women who visited the clinic for prenatal appointments. The intention-to-treat analysis examined 100 women in the control group and 104 women in the intervention group. Of these, 18 women in the control group and 28 in the flu group were considered unevaluable due to pregnancy termination, failure to receive text messaging, or loss to follow up, leaving 82 and 76, respectively, for the per-protocol analysis. The study population was of low socio-economic status with more than 90% having a high school education or less and 88% utilizing public insurance. The rate of vaccination among study participants was 32% with no difference between the groups (control 31% vs intervention 33%; difference 1.7%; 95% confidence interval -11% to 14.5%). There was no difference between the groups in the per-protocol analysis either. The interval from study enrollment to vaccine administration was no different between the two groups. The overall background influenza immunization rate in the clinic was 37% during the study period. Not surprisingly, vaccinated women were more likely to report that influenza vaccine in pregnancy was somewhat to very important on the baseline survey compared to non-vaccinated women (63% vs 26%, $P < 0.001$). The text messages made no difference in this initial opinion. Unvaccinated participants reported the

following reasons for not choosing to receive the vaccine: They did not like shots (15%), they were afraid of vaccine side effects (23%), and they had a bad experience with the flu vaccine in the past (15%). Despite the lack of effect on vaccination rates, the majority of participants in both groups reported that they liked receiving text messages as part of their prenatal care and found them helpful.

■ COMMENTARY

Influenza affects approximately 11% of pregnant women, and pregnant women are more vulnerable to serious morbidity and even mortality compared to the non-pregnant population.¹ In addition, influenza infection during pregnancy can cause adverse fetal outcomes. The American College of Obstetricians and Gynecologists (ACOG) recommends that all pregnant women receive the influenza vaccination yearly regardless of gestational age.² The vaccine is safe in pregnancy, but it is estimated that only about 50% of pregnant women receive the vaccine.³ This study attempted to evaluate whether text messages focused on the importance of influenza vaccine in pregnancy could increase vaccine uptake among women who initially did not desire the vaccine. The authors conducted the study in a low-income, urban prenatal clinic and did not find any effect from the intervention. Whether these findings are generalizable to other pregnant populations is unknown. Other studies of text messaging attempts to influence health behavior have been mixed. Given the participants' concerns regarding vaccine safety and fear of needles, the authors acknowledged that more direct text messages addressing these patient-specific barriers to vaccination may have made more of a difference.

Studies have shown that many factors affect whether women choose to receive the influenza vaccine.^{2,4} The health care provider's encouragement has been shown to increase vaccine uptake.^{2,3} Indeed, even in this study, participants stated they would be more likely to receive the vaccine if their health care provider directly recommended it. In addition, ancillary health care workers also have an effect on creating an environment encouraging or discouraging to influenza vaccination.⁵ Another study published in the same issue of *Obstetrics and Gynecology* evaluated predictors of influenza vaccination in a pregnant population.⁴ The authors in this study used the Health Belief Model, which identifies five factors predictive of health behavior change: perceived susceptibility (personal assessment of the risk of getting ill), perceived severity (assessment of the seriousness or consequences of getting ill), perceived barriers (assessment of negative influences related to implementation of the health behavior), perceived benefits (assessment of positive consequences of implementing the health behavior), and cues to action (external influences promoting health behavior). Completely consistent with this model, the authors found

that women who perceived they were susceptible to influenza, that they were at risk of getting seriously ill from influenza, and that they would regret not getting vaccinated, and who trusted recommended guidelines about influenza vaccination during pregnancy were more likely to get vaccinated. In contrast, women who were concerned about vaccine side effects were less likely to get vaccinated.

Clearly, we need better strategies to encourage women to obtain the influenza vaccine in pregnancy. A supportive office environment and modeling by health care staff is important.¹ Specifically informing patients that pregnant women are at increased risk for influenza and its serious sequelae and reassuring them about the side effects of the vaccine are key.⁴ In the end, nothing really substitutes for the provider-patient relationship in encouraging vaccine uptake. ■

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Special Feature

The Right Care, the Right Time, the Right Doc: Only Part of the Story...

By Robert L. Coleman, MD

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

Synopsis: Clinically significant disparities exist in the quality of ovarian cancer care delivered and in overall

survival along both racial and socioeconomic status. These effects appear to persist despite adherence to National Comprehensive Cancer Network guidelines; however, deviation in guideline adherence is common and further impacts survivorship and represents key opportunities for further investigation and study.

Source: Bristow RE, et al. Disparities in ovarian cancer care quality and survival according to race and socioeconomic status. *J Natl Cancer Inst* 2013 Apr 4; [Epub ahead of print].

THE RELATIONSHIP BETWEEN RACIAL AND SOCIOECONOMIC status (SES) disparities and the quality of epithelial ovarian cancer care have been evaluated in previous studies but were limited by small cohort numbers and lack of a quality control benchmarks, such as guideline adherence or overall outcomes. The current population-based analysis of National Cancer Data Base (NCDB) records evaluated these factors in invasive primary epithelial ovarian cancer patients diagnosed between 1998 and 2002. Adherence to National Comprehensive Cancer Network (NCCN) guidelines was defined by stage-appropriate surgical procedures and outlined standards for adjuvant chemotherapy. The primary outcome endpoints were NCCN guideline adherence and overall survival. The context in which these outcomes were considered were race, SES, insurance payer status, household income, age, stage, histology, center where care was delivered, and education. A total of 47,160 patients (white = 43,995; black = 3165) were identified. Factors associated with inferior overall survival were non-NCCN-guideline-adherent care, black race, and Medicaid and non-insurance payer status. Tumor-specific factors, such as stage, grade, and subtype as well as hospital case volume of ovarian cancer cases, also were significantly associated with overall survival in a multilevel survival analysis. Demographic characteristics independently associated with a higher likelihood of not receiving NCCN guideline-adherent care were black race (odds ratio [OR] = 1.36, 95% confidence interval [CI] = 1.25-1.48), Medicare payer status (OR = 1.20, 95% CI = 1.12-1.28), and not insured payer status (OR = 1.33, 95% CI = 1.19-1.49). After controlling for disease- and treatment-related variables, independent racial and SES predictors of survival were black race (hazard ratio [HR], 1.29; 95% CI, 1.22-1.36), Medicaid payer status (HR, 1.29; 95% CI, 1.20-1.38), not insured payer status (HR, 1.32; 95% CI, 1.20-1.44), and median household income < \$35,000 (HR, 1.06; 95% CI, 1.02-1.11). These data highlight statistically and clinically significant disparities in the quality of ovarian cancer care and overall survival, exist independent of NCCN guideline adherence, and divide along racial and SES parameters. More work is necessary to define at-risk populations and strategies to ameliorate factors leading to these observed disparities,

as well as further biological characteristics that may also impact cohort survivorship.

■ COMMENTARY

“Study Criticizes Care in Cancer of the Ovaries...Experienced Surgeons Can Extend Lives,” was a front-page headline in the *New York Times* on March 12, 2013. The piece covered a scientific presentation made at the 2013 annual meeting of the Society of Gynecologic Oncology by gynecologic oncologist, Robert E. Bristow, MD, from the University of California, Irvine, who profiled survivorship in California ovarian cancer patients who were treated either in or out of compliance with established publicly available guidelines to care. This included access to gynecologic oncologists for accurate staging and primary debulking procedures, and optimized use of effective adjuvant treatment strategies, such as dose-dense or intraperitoneal chemotherapy. The NCCN guidelines are established by a committee of disease-specific experts and generally outline sequential decision-making practices under a variety of clinical scenarios (<http://www.nccn.org>). Although they don’t dictate practice, the guidelines provide acceptable considerations at multiple steps in care of patients. In addition, they are reported with the degree of consensus and strength of evidence-based science for these practice recommendations. Some of these algorithms are controversial, particularly when limited or poor quality data are available in the literature. However, strong consensus frequently follows level I evidence (randomized clinical trials) or from repeated historical support.^{1,2} The data presented by Dr. Bristow were provocative because they demonstrated that these guidelines for ovarian cancer management were also prognostic, that is, compliance was associated with significantly better survival.

In some ways, this is not unexpected; it is clear that optimal cytoreduction (no visible residual) and use of the best chemotherapy agents, under optimal infusion schedules and modalities (all supported by positive Phase 3 trials), should provide a patient with the best that we have to offer.³ Deviation from these approaches should (like the control arms of the Phase 3 trials) provide inferior outcomes. However, the adherence or non-adherence to guideline-directed therapy does not consider specific patient factors, underlying nuances that might add to or detract from individual therapeutic modalities, or decisions made in concert with an individual patient’s desire. For example, we know that germline BRCA mutation carriers (BRCA-mt) have improved outcomes relative to those whom are BRCA-wild type (BRCA-wt).⁴ However, there are differential outcomes seen *within* the BRCA-mt cohort relative to the modality of chemotherapy delivery. Indeed, while ovarian cancer patients appeared to have improved overall survival with intraperitoneal (IP) de-

livery of cisplatin and paclitaxel, the BRCA-mt patients appeared to benefit substantially better than their cohorts receiving intravenous infusion of the same agents.⁵ This kind of nuance, like an audited surgical cytoreduction success variable, is not easily captured in the database from which these data were gathered. Thus, the impact, which might be only captured well by a (an unethical) trial where women were randomized to guideline-directed care vs guideline-avoided care, will not be easily sleuthed.

Added to this are the provocative results presented in the current study by the same study team. In this report, a much larger cohort of ovarian cancer patients were examined in an audited clinical database (NCDB), which reports the outcomes of about 70% of newly diagnosed cancers in the United States. They only included epithelial ovarian cancers and examined several putative prognostic factors of survival such as age, race, stage of disease, grade, payer status, median household income, education, hospital case volume, and care practices adhering to NCCN guidelines. They also looked at how these factors related to the delivery of NCCN-based care. Several striking relationships were found in the analysis. The first was that the overall 5-year survival for ovarian cancer care initiated more than a decade ago is well below 50%. Since this time, many new agents have become available; however, their widespread use is limited by lack of FDA approval and none have affected overall survival. This has greatly reduced the pace of survivorship gains over the last decade compared with the previous two. Next, putative benefit from guideline-adherent care was confirmed. Somewhat surprisingly, there was a strong relationship in survival by race stratification. Indeed, white patients fared far better than blacks in both care categories (adherent or non-adherent care). Black patients also were far less likely to get NCCN guideline-adherent care. Of interest, payer status was strongly associated with overall survival, even when controlled for adherence to guideline care. However, black patients were significantly more likely to be classified as having no insurance/self pay or on Medicare or Medicaid, which were three of the lowest performing cohorts in outcomes among patients getting guideline-adherent care. Several factors could explain these findings, such as imbalanced degree of surgical cytoreduction, access to high-volume surgeons, intensity of chemotherapy, and different treatment strategies for management of recurrent disease. However, it also intimates that there may be intrinsic differences in patient populations, as exemplified by the data from BRCA-mt carrier status. Of interest, racial factors have been recently linked to response to novel targeted agents in other malignancies and to tolerance of chemotherapy.⁶ This describes an emerging field of science called pharmacogenomics.

These data, although not definitive, are important con-

siderations in the current climate of the Affordable Care Act. Since socioeconomic status factors have been linked to survival in ways being addressed by access to care, some of the complex issues underlying health care disparities may be engaged anew with the focus on improved outcomes to care. The expectation already has been realized in screening and prevention campaigns, where results have crossed all races and socioeconomic levels. However, much more work needs to be done on a population-based scale to understand the intricacies of how these aspects of, and to, health care can be leveraged to optimize treatment outcomes of cancer patients. ■

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CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

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

CME Questions

1. Which of the following does *not* fit the results of the featured St. Louis study? Those with loop electrosurgical excision procedure (LEEPs):
 - a. had the same cesarean section rate (CSR) as those with punch biopsies.
 - b. had the same CSR as those with Pap smear alone.
 - c. had a higher rate of cesarean section for failure to progress.
 - d. did not have a higher CSR if the next pregnancy ended in a preterm birth.
2. There is no relationship between the size of the LEEP sample and the chances later for a cesarean section.
 - a. True
 - b. False
3. Which of the following is true concerning the present knowledge about the relationship between LEEP procedures and preterm birth (PTB)?
 - a. There is uniform evidence to link LEEPs with PTB.
 - b. There is conflicting evidence regarding a relationship between LEEP and PTB.
 - c. LEEP has been shown to cause premature rupture of the membranes.
 - d. The mechanism for preterm labor after LEEP procedures is that there is a gradual cervical shortening inward from the site of the cone.
4. In the PREDIMED trial, a reduction in cardiovascular disease with a Mediterranean diet supplemented with either extra virgin olive oil or nuts was seen:
 - a. only in men with a body mass index > 30.
 - b. among all subgroups compared to the control diet.
 - c. among women who also began a moderate exercise program.
 - d. only in women and men with pre-existing Type 2 diabetes.
5. In the study by Moniz et al, which of the following is *not* a reason that participants did not choose to receive the influenza vaccine during pregnancy?
 - a. Fear of vaccine side effects
 - b. Previous adverse experience with the influenza vaccine
 - c. Cost of the vaccine
 - d. Did not like needles or shots
6. Which of the following associations were *not* described as different between black and white ovarian cancer patients?
 - a. Survival
 - b. Stage at presentation
 - c. Payer status
 - d. Procedural volume of ovarian cancer cases in hospitals
 - e. Age

In Future Issues:

Targeted Therapy for Low-grade Serous Ovarian Cancer

Clinical Briefs in Primary CareTM

The essential monthly primary care update

By Louis Kuritzky, MD

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

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JUNE 2013

Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer

Source: Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816.

THE PREVAILING 5-YEAR TAMOXIFEN REGIMEN for breast cancer has been shown to reduce breast cancer mortality by as much as one-third over a 15-year interval; a comparison with a shorter regimen (1-2 year) found the longer duration to be superior. Would even longer tamoxifen administration (i.e., > 5 years) provide even greater risk reduction of breast cancer and its consequences, and if so, would longer regimens induce greater toxicity to other non-targeted tissues (e.g., induction of endometrial cancer)?

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized women with estrogen receptor-positive breast cancer (B-CA) to either 5 years ($n = 3418$) or 10 years ($n = 3428$) of tamoxifen. Follow-up continued for 5 years after conclusion of the 10-year tamoxifen course. The estrogen-receptor positive B-CA group actually represents only about half of all of the women enrolled in ATLAS; the estrogen-receptor negative population of ATLAS demonstrated no risk reduction through longer tamoxifen administration.

Numerous outcomes favored 10-year tamoxifen over 5 years and were statistically significant: B-CA recurrence (617 vs 711 cases), B-CA mortality (639 vs 722 deaths), and ischemic heart disease death

or hospitalization (127 vs 163 cases). On the negative side of the equation, all-cause mortality was not impacted by the longer tamoxifen regimen, and there was a significant increase in pulmonary embolism (41 vs 21 cases) as well as endometrial cancers (116 cases vs 63 cases).

These results were apparently sufficiently impressive enough to make the cover story in the *Lancet*. Your reviewer, however, takes pause at the fact that — similar to the situation with results for prostate cancer screening, which has recently been diminished by convincing evidence that screening may reduce prostate cancer mortality but not total mortality — a 10-year tamoxifen regimen reduces B-CA mortality but not total mortality, and has not-insubstantial adverse effects as well as costs. ■

Is There More Pro than Con in Probiotics in Critically Ill Adults?

Source: Barraud D, et al. Impact of the administration of probiotics on mortality in critically ill adult patients. *Chest* 2013; 143:646-655.

THE TECHNICAL DEFINITION OF PROBIOTIC offered by the World Health Organization and the Food and Agriculture Organization sounds promising enough: "viable microorganisms that, when ingested in a sufficient amount, can be beneficial for health." Unfortunately, the existing literature on the benefits of probiotics is not quite so convincing.

Barraud et al performed a meta-analysis of randomized, controlled trials published between 1950-2012 in which probiotics were used in the intensive care unit (ICU)

setting, ultimately netting 13 clinical trials, all published after 2002 ($n = 1439$). The probiotic used in each of these trials was in the *Lactobacillus* family, and although some trials used only one *Lactobacillus* strain, several trials used mixed strains of *Lactobacilli*. Endpoints included ICU mortality, hospital mortality, ICU infections, incidence of diarrhea, and duration of mechanical ventilation.

Of the above-mentioned endpoints, a statistically significant favorable odds ratio was seen only for the incidence of ICU-acquired pneumonia, even though the overall larger category of ICU-acquired infections was not statistically significantly improved. Although the failure to achieve significance to numerous endpoints is disconcerting, the authors point out that since probiotic administration is generally safe, the favorable impact on ICU-acquired pneumonia (a reduction of approximately 40%) might prompt consideration for use in patients known to be particularly at risk for this consequence. ■

Are OSA Outcomes Better in the Hands of Sleep Specialists than Primary Care Clinicians?

Source: Chai-Coetzer CL, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: A randomized trial. *JAMA* 2013;309:997-1004.

THE RECOGNITION OF OBSTRUCTIVE SLEEP apnea (OSA) as a health burden of compelling epidemiologic presence with significant impact on both quality of life

and cardiovascular health has been recognized by health care providers of essentially all disciplines. Increasingly, sophisticated sleep laboratory monitoring devices allow ever more detailed (and usually more costly) understanding of sleep dysregulation. At the same time, awareness of the frequency and consequences of OSA among diverse disciplines of medicine has resulted in a sufficiently burgeoning population of individuals who merit screening that sleep labs are often unable to keep pace with the increasing demand.

A proliferation of simpler, home-based tools for the identification and potential management of OSA that can be used by sleep specialists and primary care clinicians alike has prompted the question of whether outcomes for OSA patients attended by sleep specialists (who are usually not primary care clinicians), typically with complex sleep analysis tools (which are most commonly employed in a specific sleep laboratory), are superior to outcomes for patients attended by primary care clinicians with less sophisticated home-based tools.

The authors report on a randomized, controlled, non-inferiority trial of patients with OSA identified and treated either in a university sleep laboratory by sleep specialists or by community primary care practices. The primary outcome was improvement in the Epworth Sleepiness Scale, a commonly used and validated scoring system for monitoring sleepiness associated with OSA.

At the end of the 6-month trial, scores on the Epworth Sleepiness Scales were identical in both groups, and outcomes in the primary care group were determined to be non-inferior to sleep specialist care. Hopefully, primary care clinicians will become more involved in the identification and management of OSA, since equally salutary outcomes are seen in their hands as in the hands of sleep specialists. ■

Inhaled Steroids Increase Risk of TB in COPD Patients

Source: Kim J, et al. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143:1018-1024.

REACTIVATION OF TUBERCULOSIS (TB) IS AN ongoing concern among patients who receive immunosuppressive agents such as TNF-alpha agents for rheumatoid arthritis. Similarly, long-term use of systemic steroids (i.e., ≥ 30 days) in amounts as small as 7.5 mg/day of prednisone increases the risk of TB. Inhaled corticosteroids (ICS) have been associated with systemic effects such as growth retardation (in asthma), reduced bone mineral density, and increased risk of pneumonia (in chronic obstructive pulmonary disease [COPD]). Whether ICS might also be associated with risk for development or reactivation of TB has not been fully clarified.

Kim et al performed a retrospective analysis of COPD patients ($n = 620$) in a university hospital in South Korea (where the background prevalence of TB is substantially greater than many other nations) to compare the rate of TB activation in persons who had received ICS with controls. To eliminate the confounding factor of systemic steroid use, COPD patients who had received ≥ 7.5 mg for 1 month or more were excluded from the analysis.

There was a substantially greater and statistically significant risk for development of active TB among COPD patients who had been treated with ICS (hazard ratio = 9). In patients whose baseline chest x-ray showed evidence of prior (but quiescent) TB, the hazard ratio for activation of TB was 25!

Although the prevalence of TB is much greater in Korea than in the United States,

these data suggest greater vigilance for TB activation in patients chronically using ICS, especially if their x-rays indicate evidence of prior TB. ■

The ASH Position Paper on Orthostatic Hypotension

Source: Shibao C, et al. ASH position paper: Evaluation and treatment of orthostatic hypotension. *J Clin Hypertens* 2013;15:147-153.

STANDING FROM A SEATED OR SUPINE POSITION is normally associated with minimal, if any, blood pressure (BP) change, thanks to homeostatic mechanisms that alter splanchnic and peripheral blood compartments by selective intravascular redistribution and vascular tone. When BP change upon standing exceeds 20/10 mmHg, a diagnosis of orthostatic hypotension (OH) is established. Although tilt-table testing is often suggested for formal diagnosis, simple office measurement of BP 1-3 minutes after standing suffices.

Although sometimes OH produces minor distracting symptoms of dizziness that may be diminished by standing slowly, leg crossing, maintenance of good fluid balance, etc., it can also be a cause of falls, with anticipatable subsequent catastrophes such as hip fracture. Additionally, OH epidemiological data have noted an association between OH and stroke.

A variety of commonly used medications can precipitate or exacerbate OH, including alpha blockers, diuretics, vasodilators, dopamine agonists, and tricyclic antidepressants, modulation of which may improve symptoms. Pharmacologic treatments for OH include fludrocortisone (to increase intravascular volume), midodrine (a short-acting vasopressor agent), and other sympathomimetic agents.

OH is also seen in several primary neurologic disorders such as Parkinson's disease, multiple system atrophy, and Lewy body dementia.

Clinicians should suspect OH particularly in patients who report dizziness, unexplained falls, or syncope, although even symptoms such as blurred vision or neck/shoulder pain ("coat hanger" distribution pain) may reflect OH. Fortunately, a variety of lifestyle and pharmacologic treatments can be helpful. ■

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Do Perioperative Beta-Blockers Reduce Mortality?

In this issue: Beta-blockers and noncardiac surgery; prenatal medication exposure and risk of autism; reasons for statin discontinuations; and FDA actions.

Perioperative beta-blockers

The use of perioperative beta-blockers has been debated for decades. Now, a large study from the U.S. Department of Veterans Affairs (VA) suggests that the drugs may be of benefit in selected patients. In a retrospective cohort analysis, exposure to beta-blockers on the day of or the day following noncardiac surgery was evaluated among a population-based sample of nearly 137,000 patients from 104 VA medical centers. The main outcome was all-cause 30-day mortality and cardiac morbidity. Overall, 55,138 patients (40%) were exposed to beta-blockers, although the rate was nearly 68% in those undergoing vascular surgery. Exposure increased with increased cardiac risk factors. Death occurred in just over 1% of patients and cardiac morbidity occurred in just under 1%. Overall, exposure to beta-blockers was associated with a lower mortality (relative risk [RR] 0.73%; 95% confidence interval [CI], 0.65-0.83; $P < 0.001$; number needed to treat [NNT], 241). The effect was greater in patients with higher cardiac risk factors, which include high-risk surgery, cerebrovascular disease, ischemic heart disease, heart failure, diabetes, and renal insufficiency. When stratified by the revised Cardiac Risk Index variables, patients with two or more cardiac risk factors had a RR of 0.63 (95% CI, 0.50-0.80; $P < 0.001$; NNT, 105), with three risk factors the RR was 0.54 (95% CI, 0.39-0.73; $P < 0.001$; NNT, 41), and with four or more risk factors the RR was 0.40 (95% CI, 0.25-0.73; $P < 0.001$; NNT, 18). This effect was limited

to patients undergoing nonvascular surgery. Beta-blocker exposure also significantly reduced the rate of nonfatal Q-wave infarction or cardiac arrest by 37%. The authors conclude that in patients undergoing noncardiac, nonvascular surgery, perioperative beta-blockers significantly reduced 30-day all-cause mortality in patients with two or more cardiac risk factors and support the use of the drugs in these patients. They also suggest a multicenter randomized trial to assess the benefit in patients with low-to-intermediate risk. The authors were unable to find a benefit in stroke risk or in patients undergoing vascular surgery. They were also unable to determine if various beta-blockers (such as metoprolol vs atenolol) were of benefit or if the benefit was from various dosing regimens. (*JAMA* 2013; 309:1704-1713). ■

Medication use and pregnancy

Two studies suggest that certain medications used during pregnancy may increase the risk of autism in offspring. In the first, which looked at antidepressants in pregnancy, researchers from Sweden reviewed the records of 4429 children with autism spectrum disorder (ASD) as well as 43,000 age- and sex-matched controls. A history of maternal, but not paternal, depression was associated with an increased risk of ASD and the association was confined to women reporting anti-

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depressant use during pregnancy (adjusted odds ratio 3.34; 95% CI, 1.50-7.47; $P = 0.003$). This association was irrespective of whether serotonin reuptake inhibitors or non-selective monoamine reuptake inhibitors (tricyclic antidepressants) were used. The association was confined to autism without intellectual disability. Still, the use of antidepressants accounted for only 0.6% of cases of ASD during the study, so the drugs were “unlikely to have contributed significantly towards the dramatic increased prevalence of autism spectrum disorders” (*BMJ* 2013;346:f2059). In the other study, researchers from Denmark reviewed the records of children exposed in utero to valproate (used to treat seizures and other neuropsychological disorders in mothers). Of more than 655,000 children born between 1996 and 2006, 5437 identified with ASD, including 2067 with childhood autism. The overall risk of autism in all children was 1.53%, but of the 508 children exposed to valproate, the absolute risk was 4.42% (95% CI, 2.59-7.46%) for ASD and 2.50% (95% CI, 1.30-4.81%) for childhood autism (adjusted hazard ratio, 5.2). The risk was similar regardless of the indication for use of valproate in the mother. These findings suggest that maternal use of valproate significantly increases the risk for ASD and childhood autism in offspring. The authors suggest that a risk-benefit analysis should be considered for women on valproate in their childbearing years (*JAMA* 2013;309:1696-1703). ■

Discontinuation of statins

Most patients who stop statins due to side effects will tolerate the drugs if rechallenged, according to the findings of a new study. In a retrospective cohort study using data from two Boston hospitals, researchers reviewed the records of nearly 108,000 patients on statins and found statin-related events such as muscle pain documented in 18,778 (17.4%). Of those patients, 11,124 stopped the drugs at least temporarily and 6579 were restarted within the subsequent 12 months. The vast majority of patients restarted on a statin tolerated the drug (92.2%), although about half were eventually switched to a different statin. The authors conclude that statin-related side effects are common and often lead to discontinuation; however, most patients who are rechallenged can tolerate statins long-term. They suggest that “statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class” (*Ann Intern Med* 2013;158:526-534). ■

FDA actions

The FDA has updated labeling of the new tamper-proof oxycodone (OxyContin), while at the same time denying approval of generic forms of the original formulation of oxycodone. The new labeling indicates that the product “has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting).” The agency’s refusal to approve generic forms of the original formulation was based on the increased risk of abuse inherent in the non-tamper proof form leading to the risk of serious adverse events including overdose and death. Because of this, the agency has determined that the benefits of the original OxyContin and its generics no longer outweigh its risks and it has been withdrawn from sales. The new tamper-proof formulation is more difficult to crush, break, or dissolve. If tampered with, it forms a viscous hydrogel that cannot be easily injected or snorted. Oral abuse is still possible.

The FDA has approved a fixed combination of doxylamine succinate and pyridoxine for the treatment of nausea and vomiting due to pregnancy. This is a reintroduction of a product widely used between 1956 and 1983. Then marketed as Bendectin, the product was voluntarily withdrawn by the manufacturer due to lawsuits related to birth defects, although evidence of risk was not supported by scientific evidence. The reapproval was based on a study of 261 women experiencing nausea and vomiting due to pregnancy in which the drug was more effective than placebo in relieving symptoms. Since the 1980s, observational studies have shown that doxylamine and pyridoxine do not pose an increased risk of harm to the fetus. The recommended starting dose is two tablets taken at bedtime on an empty stomach. The combination is marketed by Duchesnay Inc. as Diclegis.

The FDA has approved prothrombin complex concentrate for the rapid reversal of anticoagulation by warfarin and other vitamin K antagonists. Plasma is the only other option for this use currently available, and prothrombin complex can be given at significantly lower volume than plasma. The product is made from pooled plasma of healthy donors that is processed to minimize the risk of viral and other diseases. The approval was based on a study of 216 patients who were anticoagulated and had major bleeding. Plasma complex concentrate was found to be similar to plasma in its ability to stop major bleeding. Plasma complex concentrate is marketed by CSL Behring as Kcentra. ■