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INSIDE

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Prediction of Intra-amniotic Inflammation

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado Health Sciences Center, Denver

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

Synopsis: *With a formula using maternal WBC, cervical length, and gestational age, it is possible to roughly assess the risk of intrauterine inflammation in patients with preterm labor, allowing clinicians to identify which patients could benefit most (and least) from amniocentesis.*

Source: Jung HJ, et al. Non-invasive prediction of intra-amniotic inflammation in women with preterm labor. *Ultrasound Obstet Gynecol* 2011;37:82-87.

ALTHOUGH THE RELATIONSHIP BETWEEN INTRAUTERINE INFECTION AND preterm labor (PTL) has been addressed in previous *OB/GYN Clinical Alerts*, I cannot pass up the opportunity to review a recent paper that sheds new light on a rational approach to PTL.

In an attempt to find a non-invasive way to determine which patients with PTL have intrauterine infection and/or inflammation, a team of investigators from South Korea studied patients who were admitted between 21 and 35 weeks with the diagnosis of PTL (by the presence of regular contractions and cervical change). The dependant variables studied included ultrasound cervical length, maternal white blood cell count (WBC), C-reactive protein (CRP), and cervical dilation by digital examination. Intrauterine infection and intrauterine inflammation were defined by positive cultures or significant presence of interleukin-6 (Il-6), respectively, in amniotic fluid, obtained by amniocentesis after admission.

The results involved 153 patients; 7.2% (11/153) had positive amniotic fluid cultures and 19.6% (30/153) had cytokine evidence of

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inflammation (Il-6 > 2.6 ng/mL). Of the 11 with positive amniotic fluid cultures, eight had both *Ureaplasma urealyticum* and *Mycoplasma hominis*, and the remaining three had only one of these two types of bacteria present. All 11 of the intrauterine infection cases also had evidence of inflammation. Neither digital exam nor CRP was statistically associated with intrauterine infection or inflammation.

The authors tried inserting the various non-invasive variables into formulas that would best predict the endpoints of amniotic inflammation or infection. They found that a combination of gestational age, cervical length, and maternal WBC worked best. In fact, if this formula predicted a probability of inflammation (risk score ratio) of 0.20, the sensitivity was 67%, specificity was 71.5%, positive predictive value (PPV) was 36.4%, and the negative predictive value (NPV) was 90%. This means that using the above risk score ratio, one would be missing only 10% of those with intrauterine inflammation and negating the need for amniocentesis in 90% of cases.

■ COMMENTARY

The literature shows that for every three patients with PTL, intrauterine inflammation is responsible for at least one of these PTLs. Actually, the above study had a somewhat lower incidence at 1 in 5. The current thinking is that the inflammatory process occurs in a stepwise fashion. First, bacteria ascend from the vagina to an extramembranous intrauterine site, setting off a maternal inflammatory response involving cytokines. This, in turn, stimulates contractions, while softening and shortening the cervix. In phase 2 of the process, the bacteria gain access to the amniotic cavity, initiating a fetal cytokine response, sometimes affecting the fetal brain along the way (periventricular leukomalacia and, eventually, cerebral palsy). The fact that IL-6 was positive in all those with positive cultures, but not vice versa, adds credence to this concept. In view of this progression, many have advocated doing amniocentesis in all patients with PTL to document the presence of bacteria and/or inflammation. Then, based on these findings, a management plan could be fashioned.

Unfortunately, amniocentesis is not without risk or discomfort, and, therefore, there has been a push to study non-invasive techniques to identify only those at greatest risk for inflammation/infection. A recent study concentrating on an extensive panel of various inflammatory proteins in cervical secretions has shown promise (sensitivity 73%, specificity 88%, PPV 55%, NPV 94%),[1] but at the moment this type of combination testing is only within the reach of a few centers. So, in the meantime, every component of the above formula is available to the majority of clinicians (cervical length by transvaginal ultrasound, WBC, and documentation of gestational age). The formula that the authors used (obviously available in the original paper) allows the reader to quantify the risk of inflammation. However, a stripped-down version of the concept could be used to roughly assess risk by using these variables separately. For example, if the cervical length were > 2.5 cm, the WBC < 10,000, and the patient were > 32 weeks, the likelihood of infection/inflammation would be quite low, and probably would not be worth the risk of amniocentesis. On the other hand, if all of the above variables were on the other side of these thresholds, the yield could be worth doing an amniocentesis. Again, if one wishes to quantify the risk by the published formula, 90% of the time an amniocentesis would not be needed and tocolytics (calcium channel blockers or prostaglandin synthase inhibitors) could be tried. Since approximately 10% of patients will have a false-negative risk score ratio (< 0.20), any change in the patient's condition could trigger an amniocentesis or delivery at that time.

Knowing whether inflammation is the cause of PTL is crucial in arriving upon a way to solve the "darned if you do, darned if you don't" dilemma every clinician faces when dealing with PTL, especially in very preterm pregnancies. ■

Reference

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Questions & Comments
Call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468.

A New Clinical Entity for Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Professor, University of Texas;
M.D. Anderson Cancer Center, Houston

Dr. Coleman received honoraria from Johnson & Johnson (study sponsor) for consultant work on a scientific advisory board.

Synopsis: *Trabectedin, administered in combination with pegylated liposomal doxorubicin, led to improved progression-free (PFS) and overall survival (OS) in women with partially chemosensitive recurrent ovarian cancer, with a manageable safety profile.*

Source: Poveda A, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: Outcomes in the partially platinum-sensitive (platinum-free interval 6-12 months) subpopulation of OVA-301 phase III randomized trial. *Ann Oncol* 2011;22:39-48.

OVA-301 WAS A LARGE (N = 672), OPEN-LABEL PHASE III TRIAL comparing pegylated liposomal doxorubicin (PLD) to combination PLD and trabectedin (PT) in women with recurrent ovarian cancer. The trial's overall population was previously reported and demonstrated a significant impact on PFS, without a significant improvement in OS. Stratification analysis revealed the impact of benefit was not present in platinum-resistant (treatment-free interval [TFI], < 6 months) patients. Since there is bias to reinstitution of platinum-based therapies in platinum-sensitive patients, the authors conducted the current study to look at the performance of PT in patients with intermediate chemosensitivity (TFI, 6-12 month). The study population was approximately one-third of the overall population and had similar entry characteristics. As anticipated from the previous analysis, PFS was significantly improved (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.45-0.92; $P = 0.0152$), resulting in a median improvement of 2 months (7.4 months vs 5.5 months). However, OS also was improved (HR, 0.59; 95% CI, 0.43-0.82; $P = 0.0015$), resulting in a median improvement of nearly 6 months (23.0 months vs 17.1 months). The safety profile for this cohort was similar to that observed in the overall trial, with the combination arm demonstrating more transient neutropenia and liver function test abnormalities, but with reduced hand-foot syndrome and stomatitis. Interestingly, the authors opined that the significantly longer delay to reinstitution of platinum-based subsequent therapy may have contributed to this effect on OS. An ancillary updated OS analysis from the original trial also was presented with approximately one-third more events, demonstrating a persistent, but nonsignificant, improvement in OS. The authors acknowledge this hypothesis-generating analysis demonstrates superior performance to the new non-platinum doublet in partially platinum-sensitive recurrent ovarian cancer.

■ COMMENTARY

Trabectedin is a marine-derived (*Ecteinascidia turbiata*) anti-neoplastic agent that exerts its effect by covalently binding to DNA, and therefore disrupting transcription. This leads to cell cycle arrest and apoptosis. It was studied in ovarian cancer as a single agent with modest activity, but was noted to have synergy in vitro with PLD. This led to the phase III study in recurrent ovarian cancer detailed above. The data were strong enough to lead the combination to registration in the European Union, but because of lack of OS and inconsistency in assessment of the primary endpoint and toxicity concerns, the combination was not approved in the United States. As the survival data mature, this may be reconsidered. However, the dataset of this well-conducted trial continue to be mined for important therapeutic opportunities. The current report is one example. This is particularly provocative because, while the treatment standards for platinum-resistant and platinum-sensitive patients are well outlined, the cohort with TFIs between 6 and 12 months from primary completion are more controversial. Surveys of oncologists around the United States will split on reintroducing a platinum compound with a non-platinum compound. Usually toxicity, schedule, and tolerance drive the choice. Here we have a new therapeutic combination, which uses a commonly used drug in this setting, PLD, and demonstrates a large benefit, not only in PFS but also in OS. Another recent report has demonstrated that the addition of carboplatin to PLD also is active in this same cohort. This has served as the primary foundation of a new phase III trial comparing PT vs PLD and carboplatin in women defined with intermediate chemosensitive recurrent disease. ■

Additional Reading

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2. Monk BJ, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. *J Clin Oncol* 2010;28:3107-3114.
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cinoma after treatment with platinum and taxanes fails. *J Clin Oncol* 2005;23:1867-1874.

Shoulder Dystocia

ABSTRACT & COMMENTARY

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

Synopsis: *A recent study shows that in shoulder dystocia, if delivery occurs within 5 minutes, the rate of acidosis and hypoxic asphyxic encephalopathy is < 1%.*

Source: Leung TY, et al. Head-to-body delivery interval and risk of fetal acidosis and hypoxic ischaemic encephalopathy in shoulder dystocia: A retrospective review. *BJOG* 2010 Dec 24; Epub ahead of print; doi:10.1111/j.1471-0528.2010.02834.x.

Despite the important progress that has been made in obstetrics, in general, over the last 20 years, shoulder dystocia remains an enigma. Given the rising rate of maternal obesity and gestational diabetes, it is unlikely that the rate of this dangerous complication will be lowered in the near future. It has been difficult enough to nail down cause and effect when dealing with the occasional morbidity associated with shoulder dystocia, but one aspect that has received some investigative attention in the past is the time that it takes after delivery of the head to get the rest of the baby out — the head to body delivery interval (HBDI).

A paper recently appeared in the *British Journal of Obstetrics and Gynecology* in which the authors reviewed birth records from a Hong Kong University Hospital between 1995 and 2009. Of the 62,300 deliveries occurring during this time period, they found 210 cases (0.34%) that fit their liberal criteria for shoulder dystocia (the need for maneuvers other than downward traction of the head or a HBDI of > 1 minute). In 200 of these cases data were available on cord gases, Apgar scores, fetal heart rate patterns, and the presence of hypoxic, ischemic encephalopathy (HIE).

They found that "pathological" fetal heart rate patterns were associated independently with cord arterial pH, but not with base excess (BE). The length of HBDI, however, did correlate with the BE, and there was an inverse relationship with arterial pH, resulting in a drop in pH of 0.011 for every minute of HBDI. This represents a slope that is less steep than had been previously reported.[1] Most importantly, the incidence of severe acidosis (pH < 7.0) and HIE were only 0.5% and 0.5%, respectively, if HBDI was < 5 minutes, and 5.9% and 23.5% if HBDI was ≥ 5 minutes.

The ancillary data also were interesting. The Asian population studied had an incidence of macrosomia (> 4000 g) of 31% when shoulder dystocia was encountered, vs the reported 44%-64% in the same subset of women in Western populations.[2] However, as the authors point out, since the baseline incidence of macrosomia in Asian populations is about 4%, compared with 6%-15% in Western populations, the chance of shoulder dystocia in both populations remains basically the same. In essence, this provides further credence to the seemingly obvious concept that shoulder dystocia results from a mismatch between the size of the baby and the size of the pelvis of the mother.

■ COMMENTARY

The authors' take away message is that cord pH drops with the length of HBDI, "but the rate of acidosis and encephalopathy is very low if the elapsed time is less than 5 minutes." Avoiding morbidity in shoulder dystocia does represent a race against time, and every minute seems like an hour. However, after recording the start time, and asking (shouting?) for help from the most experienced individuals available, one still has more time than was previously believed. Now the clinician can effectively navigate the shoulder dystocia "fire drill" in a controlled fashion. Hopefully, this approach will trump an instinctive reaction to move immediately to an adrenaline-infused hasty, and sometimes forceful, solution to this scary situation. ■

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Will Ovarian Cancer Screening Really Impact Mortality?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Despite the marked survival differences between early and advanced stage ovarian cancer and the promise of "stage migration" with general population screening, modeling suggests the impact will be only modest due to identification of low-risk disease.*

Source: Havrilesky, et al., Development of an ovarian cancer screening decision model that incorporates disease heterogeneity. *Cancer* 2011;117:545-553.

Recent investigation into the molecular pathogenesis of epithelial ovarian cancer has implicated two dominant phenotypes. One manifests by late presentation, advanced stage, and an aggressive clinical course (Type I), and one with a more indolent nature, which, despite an innate chemo-resistance, is associated with long survival (Type II). By studying the natural history of ovarian cancer (Type I vs Type II), the authors sought to evaluate the impact of screening on mortality. They considered both a 1-phenotype and a 2-phenotype model, the latter including the assumptions on outcome based on the contribution of Type II cancers. To calibrate their data, they used stage distribution and survivorship data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database. They also assumed their "screening model" would perform in line with the multimodal screening algorithm (MMS) used in the recently reported U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study, and they adjusted the SEER prevalence ovarian cancer rate to match that reported in the UKCTOCS study. The authors showed that their validation test of screening performance would increase the number of stage I/II cancers (to about 41%), in line with that reported from the UKCTOCS study. Positive predictive value also was close (26%-27% vs 35%). Overall survival for ovarian cancer predicted based on the 1-phenotype and 2-phenotype model was very similar to that expected from the SEER data. Surprisingly, the impact on mortality from an implemented postmenopausal annual screening program resulted in only an 11% (2-phenotype model) to 15% (1-phenotype model) reduction in mortality. Modeling different screening characteristics (sensitivity and specificity) and frequencies adjusted these measures only slightly, with the exception of the screening frequencies, which had its greatest impact with every-3-month evaluation. The authors conclude that screening, such as that used in the UKCTOCS study, will likely have only a modest impact on survival, due largely to the more efficient discovery of indolent malignancy.

■ COMMENTARY

This is a provocative report and tempers some of the enthusiasm that surrounds the anticipated results (2014) from the impressive effort being conducted in the United Kingdom. Initial data from their prevalence study *(see* OB/GYN Alert *July 2009)* has raised hopes that stage migration of high-grade ovarian cancer would translate into notable survival gains. The current study draws attention to a basic tenet of successful and effective cancer screening: An identifiable pre-invasive or early invasive state, which, if identified, is associated with improved outcome. What the study suggests is that the more indolent cancer (which is associated with a better survival) will be more often found through annual screening — largely due to its growth rate. However, the proportion of diagnosed indolent cancer is small relative to typical high-grade cancer. While a 10%-15% reduction in mortality is modest, it would be welcomed in any clinical trial evaluating a pharmaceutical agent, especially in recurrent disease.

While modeling in this fashion is helpful to address potential impact on population dynamics, it is limited by our assumptions. This study is no exception. Many pieces of data needed to be included and the sources for those data, as well as the magnitude for each of the variables, are quite subjective and could be inaccurate. For instance, problems with the SEER registry are notorious because of lack of validation and central review. However, potentially even more problematic was the author's inclusion of clear cell and mucinous cancers into the indolent phenotype. Our understanding of the biology driving these tumors, as well as low grade serous tumors, is quite different than high-grade serous; however, expected mortality from advanced stage clear cell and mucinous tumors are significantly higher than their "aggressive phenotype" and even more so relative to the low-grade serous tumors. Adjusting for anticipated stage at presentation made this cohort perform better in the analysis. Ultimately, the debate will be settled with the UKCTOCS survival analysis due in 2014. At that time we'll be able to determine whether ovarian cancer screening is wishful thinking or a new reality. ■

Additional Readings

1. Menon U, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: Results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;10:327-340.
2. Menon U, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. *J Clin Oncol* 2005;23:7919-7926.
3. Mackay HJ, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. *Int J Gynecol Cancer* 2010;20:945-952.

Special Feature

Oral Contraceptive Use in Obese Women

By Jeffrey T. Jensen, MD, MPH, Editor

Obesity is a growing problem in the United States. The pun would be funny were it not for the adverse influence that the obesity epidemic has had on health care outcomes. Obesity affects every aspect of health, including contraception. The National Institutes of Health has recognized that our understanding of the interactions between obesity and hormonal contraception is inadequate. To address this knowledge gap, NICHD convened a workshop in November 2010 to bring together experts in the field to discuss the state of the science and to plan a research agenda.[1]

Alan Guttmacher, MD, (nephew of the Alan Guttmacher of the Guttmacher Institute), the new Director of NICHD, started out the meeting noting that it is imperative that the institute examine the intersection of obesity and contraception, because part of the Institute's mission is "to ensure that every person is born healthy and wanted" and "that women suffer no harmful effects from reproductive processes." Guttmacher issued a strong statement of support for research in this area, recognizing that there are few other funding entities engaged in this field and asking: "If NICHD doesn't do it, who will?"

Contraceptive Use

Bliss Kaneshiro, MD (University of Hawaii), reviewed data from two nationally representative surveys, the National Survey of Family Growth (NSFG) and the Behavioral Risk Factor Surveillance System (BRFSS).[2,3] Analyses of these data have demonstrated that there is no significant difference in contraceptive non-use among women of different BMIs. Patterns of use are less clear; the cycle 6 NSFG data showed that the patterns of methods used by obese and normal weight women do not differ, whereas the BRFSS survey showed that normal weight women tend to use hormonal methods of contraception, while overweight and obese women tend to use procedural methods (like surgical sterilization). Approximately 20% of American women use oral contraceptives (OC) for birth control, and use of the pill does not seem to differ by BMI group. Data from the NSFG also demonstrated no differences in most measures of sexual behavior, except that overweight and obese women are more likely than normal weight women to report an "ever" history of coitus. Since sexual behavior does not seem to differ, what about efficacy? While data from cycle 6 of the NSFG showed no association between unintended pregnancy and BMI, the Pregnancy Risk Assessment Monitoring System (PRAMS) has detected more unintended pregnancies in obese and overweight women using contraception. However, surveys using self report to evaluate pregnancy intention suffer from bias due to social acceptability.

What about when obese women become pregnant? Catherine Spong, MD (NICHD), emphasized the danger of pregnancy for obese women, beginning with the effect of obesity on pregnancy physiology; increased blood volume and reduced pulmonary compliance can lead to a greater risk of ischemia, infarct, and heart or respiratory failure. Obesity has a multiplicative effect on the risk of venous thrombosis already increased by pregnancy. Obesity also increases insulin resistance and induces changes in inflammatory processes.[4] Maternal obesity makes it more difficult for obstetricians to assess maternal weight gain and detect fetal anomalies with ultrasound. The risk of miscarriage and stillbirth are both increased. It also makes labor more complicated for the mother and infant. Consequently, the risk of cesarean section is increased and with this the risk of maternal complications due to anesthesia.

Efficacy

Having established that pregnancy is risky, what about the effects of hormonal contraception? Data on the effect of obesity on OC efficacy is controversial. The original reports suggesting a difference were from health care databases.[5] More reliable data have come from the large phase IV studies recently commissioned in the United States and Europe. Jürgen Dinger, MD, presented data from the European Active Surveillance (EURAS) and International Active Surveillance (INAS) studies. Results from the latter study were published in January 2011 in *Obstetrics & Gynecology*.[6] Women requesting oral contraception (switch or new start) that participated in the INAS study received a prescription from their usual health care provider and were followed prospectively with outcomes validated and adjudicated. Two interesting findings emerged from this large prospective study based on an analysis of 1634 unintended pregnancies during 73,269 woman-years of oral contraceptive pills exposure. The most significant finding was that women that received a 24-day regimen of drospirenone and ethinyl estradiol had the lowest failure rate (2.1% at 1 year). The adjusted hazard ratio (HR) for failure was 0.7 (95% confidence interval [CI], 0.6-0.8) compared to all 21-day regimens. The large sample of prospectively accumulated data also permitted for an analysis of the effect of BMI. This demonstrated an elevation in the adjusted HR of 1.5 (95% CI, 1.3-1.8) for contraceptive failure in women with a BMI ≥ 35 compared with < 35. These data are consistent with the

effect noted in epidemiologic studies of oral contraceptive failures from a large closed health plan presented by Victoria Holt, PhD (University of Washington).[5] An increase in failure associated with obesity also has been seen in prospective studies of emergency contraception. A 2010 meta-analysis in *Lancet* of two randomized clinical trials with similar study designs demonstrated that the risk of emergency contraceptive failure increases with BMI.[7] This increased risk is more pronounced with levonorgestrel than ulipristal acetate and the difference in efficacy between the two drugs widens for obese women compared to merely overweight women.

If obesity is associated with an increased risk for OC failure, what are the mechanisms? Frank Stanczyk, PhD (University of Southern California), gave an overview of steroid hormone metabolism. Some pathways favor increased steroid hormone metabolism, while others favor increased bioavailability. Other important considerations include comorbidities (such as hypertension and diabetes) and use of other medications that might interfere with metabolism. Recently published studies by Alison Edelman, MD (Oregon Health & Science University), and Carolyn Westhoff, MD (Columbia University), have investigated pharmacokinetics of OCs in obese women.[8,9] The consistent findings from both studies are a delay in the time needed for contraceptive steroids to reach steady state. The vulnerable interval appears to be during the reinitiation of the pill after the hormone-free interval (HFI); failure to achieve an inhibitory level would theoretically increase the risk of development of a dominant follicle, ovulation, and conception. The prospective pregnancy data from INAS showing a reduction in failure by shortening the HFI to 4 days supports this hypothesis. However, there are no clinical trials of extended cycles or continuous use in obese women.

Behavior may matter more. Westhoff reported that in her studies, obesity was associated with a three-fold increase in the risk for total noncompliance in OC use, even when controlling for race/ethnicity. However, she was cautious to suggest that this is related to obesity, as obesity is linked with low socioeconomic status, and the latter may be a predictor of poor compliance. The bottom line for clinicians is the same. Whether an increase in failure is related to altered metabolism or poor compliance, moving to long-acting methods may reduce failure.

Safety

The flip side of efficacy is safety. Contraceptive steroids influence the clotting mechanism in complex ways, and the effect on a number of prothrombotic and anticoagulation proteins can be measured. However, there is no one surrogate marker or panel of markers that reliably predicts thrombosis risk with a product. It is fair to say that the risk is related to estrogen dose, and modulated by the progestin in a combination pill (the more androgenic, the lower the risk). While epidemiologic studies have suggested that levonorgestrel pills have the lowest incidence of venous thromboembolism (VTE), large scale prospective studies do not support these findings.[10] Furthermore, levonorgestrel is a potent androgenic progestin capable of causing insulin resistance and may not be appropriate for obese women at risk for diabetes. Lowering the dose of ethinyl estradiol reduces the risk of VTE, but does this increase the risk of unscheduled bleeding and compound the problem of noncompliance and failure? Will the new estradiol pills be safer? Keep in mind that oral estradiol still influences hepatic globulins and, although E2 is less potent than ethinyl estradiol, much higher oral doses are needed. Results from an active surveillance study of this new product will be years away.

What about eliminating estrogen all together? Progestin-only pills are available, but we know that they are less forgiving of noncompliance and must be dosed on a 24-hour schedule to maintain contraceptive activity through the inhibition of cervical mucus. The compliance problem linked to obesity makes this a potential concern. Also, irregular bleeding may make them less acceptable. Are long-acting methods like implants and IUDs acceptable to obese women? We still have a lot of unanswered questions.

Summary

The goal of the conference was to determine if more research is needed (Answer: It is), and discussions are underway to develop a large-scale randomized trial to address questions of efficacy, acceptability, and safety. The question of safety will need to be resolved through prospective cohort studies like EURAS and INAS with the even larger sample sizes sufficient to address these outcomes with sufficient power.

Pending these results, clinicians must continue to make decisions about OC use in obese women. All obese women need to understand that BMI has a direct and independent correlation with VTE risk that multiplies the risk of OC use. For young, otherwise healthy, obese women, this risk may be acceptable. For sedentary obese women with other risk factors, probably not. However, in all cases, the risk associated with pregnancy will be higher. Using a long-acting, estrogen-free method such as an implant or IUD will always be the safest choice, but this may not be acceptable to all patients. For women choosing to use an OC, use the lowest estrogen dose, and consider extended (e.g., 24-day) cycle or continuous use. ■

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and Need to Know?" Rockville, MD: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); Nov. 9-10, 2010.
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9. Edelman AB, et al. Impact of obesity on oral contraceptive pharmacokinetics and hypothalamic-pituitary-ovarian activity. *Contraception* 2009;80:119-127.
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CME Objectives

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

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

CME Questions

38. Which of the following variables was *not* helpful in identifying patients at greatest risk for intrauterine inflammation?
a. Maternal WBC
b. Maternal CRP
c. Gestational age
d. Cervical length
e. None of the above

39. Which of the following does *not* fit with the results of the HBDI study?
a. The HBDI is inversely proportional to the level of the cord arterial pH.
b. "Pathological" fetal heart rate patterns were independently correlated with pH, but not base excess.
c. HBDI was correlated with pH and base excess.
d. HBDI did correlate with encephalopathy.
e. All of the above are correct.

40. If HBDI is < 5 minutes, the rate of acidosis and encephalopathy is < 1%.
a. True
b. False

41. Which answer best reflects current knowledge regarding shoulder dystocia?
a. The incidence of shoulder dystocia is likely to increase.
b. Asian women seem to have less shoulder dystocia than Western populations.
c. Everything should be done to effect complete delivery before the HBDI has reached 2 minutes.
d. The rate of encephalopathy does not even double after an HBDI of 5 minutes.

42. The INAS study demonstrated which of the following?
a. Obesity did not affect OC efficacy.
b. OC failure is lower with 24 days of active pills compared to 21-day cycles.
c. The most effect pill is a 30 mcg levonorgestrel pill.
d. All of the above

Answers: 38. b, 39. e, 40. a, 41. a, 42. b.

PHARMACOLOGY WATCH

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

Escitalopram for Menopausal Hot Flashes

In this issue: Escitalopram for menopausal hot flashes, rifaximin for IBS without constipation, herpes zoster vaccination, antiepileptics drugs and fracture risk, and FDA Actions.

Escitalopram for hot flashes

Since the Women's Health Initiative was published in 2003, the use of hormone therapy for the treatment of postmenopausal hot flashes has dropped dramatically. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been studied to relieve postmenopausal symptoms, but no agent has been conclusively shown to be effective. A new study suggests that escitalopram (Lexapro™) may offer some relief.

In a study recently published in the *Journal of the American Medical Association*, 205 menopausal women were randomized to 10-20 mg per day of escitalopram or matching placebo for 8 weeks. The primary outcome was the frequency and severity of hot flashes with the average hot flash frequency at nearly 10 per day at baseline. Escitalopram resulted in 1.41 fewer hot flashes per day compared to placebo ($P < 0.001$), although both the active drug group and placebo groups noted reductions. Escitalopram also reduced hot flash severity. There was no difference among women of different races, and the discontinuation rate was small. The authors concluded that escitalopram 10-20 mg per day compared with placebo resulted in fewer and less severe menopausal hot flashes at 8 weeks (*JAMA* 2011;305:267-274). Whether the same effect can be expected with racemic citalopram (Celexa™) is unknown. ■

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Rifaximin for IBS without constipation

Rifaximin, an oral, nonsystemic (poorly absorbed) broad-spectrum antibiotic, may help relieve symptoms of irritable bowel syndrome according to two identically designed studies published in the *New England Journal of Medicine*. A total of 1060 patients who had IBS without constipation were randomized to rifaximin 550 mg three times daily for 2 weeks or matching placebo. The primary endpoint was a proportion of patients with adequate relief of global IBS symptoms; the secondary endpoint was relief of bloating. Significantly more patients in the rifaximin group had adequate relief of IBS symptoms during the first 4 weeks of treatment (40.7% vs 31.7%; $P < 0.001$), as well as improvement in bloating (40.2% vs 30.3%; $P < 0.001$). The incidence of adverse events was similar in the two groups. The authors concluded that among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of the IBS symptoms of bloating, abdominal pain, and loose or watery stools (*N Engl J Med* 2011;364:22-32).

An accompanying editorial points out that the benefit from rifaximin was sustained over 10 weeks after a short 2-week treatment course, but also points out that benefit of the drug was a mere 9%-12% improvement over placebo, barely clinically relevant. Still, for patients who have IBS without constipation who have not responded to other therapies, a single treatment

cycle could be tried (*N Engl J Med* 2011;364: 81-82). ■

Herpes zoster vaccination rates and incidence of shingles

The herpes zoster vaccine cuts the rate of shingles by 55% in the elderly population according to a new report in the *Journal of the American Medical Association*. Researchers at Kaiser Permanente in Southern California performed a retrospective cohort study of health plan members, 75,000 of whom were vaccinated against shingles (age 60 and older) and 225,000 age-matched controls who did not receive vaccine. The rate of herpes zoster was 6.4/1000 person-years in the vaccinated group and 13.0/1000 person-years in the unvaccinated group (hazard ratio, 0.45; 95% confidence interval, 0.42-0.48). Reduction in herpes zoster occurred in all age groups and among individuals with chronic disease. The rate of ophthalmic herpes zoster and hospitalizations for herpes zoster were also significantly reduced.

The authors of the study concluded that among immunocompetent community-dwelling adults age 60 and older, receipt of the herpes zoster vaccine was associated with a lower incidence of herpes zoster (*JAMA* 2011;305:160-166). The study is important because only 10% of those aged 60 and older received the shingles vaccine in 2009, whereas nearly one of three people in the United States will develop shingles in their lifetime. ■

Fracture risk with antiepileptic drugs

Most antiepileptic drugs (AEDs) are associated with an increased risk of nontraumatic fracture according to a retrospective match cohort study. Nearly 16,000 patients with a history of prior AED use (carphenazine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrogine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, or vigabatrin) were compared to up to three matched controls each. Rates of fractures of the wrist, hip, and vertebrae were measured between 1996 and 2004. A significant increase in fracture risk was found for most AEDs, with an adjusted odds ratio of 1.24 for clonazepam to 1.91 for phenytoin. The only AED not associated with increased fracture risk was valproic acid.

The authors concluded that most AEDs are associated with an increased risk of nontraumatic fractures in individuals age 50 or older. They suggested that the risk of fracture with newer AEDs needs to be determined, as well as the effect of bone protective medications in this population (*Arch Neurol* 2011;68:107-112). The mechanism of increased fracture risk in patients using AEDs is unknown, but may be related to accelerated vitamin D catabolism, calcium absorption, or an effect on osteoblasts. ■

FDA Actions

The FDA has approved vilazodone hydrochloride for the treatment of depression in adults. The drug is a selective serotonin reuptake inhibitor as well as a partial agonist of the 5HT 1a receptor. The drug was approved in dosages of 10 mg, 20 mg, and 40 mg for major depressive disorder or major depression. Vilazodone is touted as having fewer sexual side effects than other antidepressants. It carries the same boxed warning as other antidepressant regarding suicidal thinking and behavior in children, adolescents, and young adults. Vilazodone will be marketed by Clinical Data Inc. as Viibryd™.

The FDA is limiting the amount of acetaminophen in combination prescription pain medications. The new requirement limits the amount of acetaminophen to 325 mg in each tablet or capsule. Common medications that will be affected include codeine (acetaminophen with codeine), oxycodone (Percocet®), and hydrocodone (Vicodin®). Over-the-counter acetaminophen products are not affected. This action is being taken to limit acetaminophen-related liver failure. It is felt that lowering the amount of acetaminophen in these products will have minimal effect on efficacy for treating pain. The change will be phased in over 3 years.

The FDA has approved a new transmucosal form of fentanyl for the treatment of breakthrough pain for adults with cancer. The drug is indicated for the management of breakthrough pain in patients with cancer ages 18 and older, who use opiate pain medication around the clock. Breakthrough pain is defined as pain that comes on suddenly for short periods of time and is not alleviated by the patient's normal pain management plan. Patients must be opioid-tolerant to qualify for use with transmucosal fentanyl. The drug is available only through a Risk Evaluation and Mitigation Strategy (REMS) program, which is intended to minimize risk of misuse, abuse, addiction, and overdose. Fentanyl sublingual tablets are available as 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg strengths. Fentanyl sublingual tablets are marketed by ProStrakan Inc. under the trade name Abstral®. ■