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INSIDE

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Antibiotic Use during Pregnancy and Risk of Birth Defects

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, Editor

Synopsis: *First trimester exposure to nitrofurantoin and sulfonamides was associated with an increase in the risk of several birth defects including cleft lip and palate in the National Birth Defects Prevention Study.*

Source: Crider KS, et al. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. *Arch Pediatr Adolesc Med* 2009;163:978-985.

THE PURPOSE OF THIS STUDY WAS TO ESTIMATE THE ASSOCIATION BETWEEN antibacterial medications and selected birth defects. The authors conducted a population-based, multisite, case-control study of women who had pregnancies affected by 1 of more than 30 eligible major birth defects identified via birth defect surveillance programs. The study population included 13,155 cases of women with affected pregnancies and 4941 control women with unaffected pregnancies randomly selected from the same geographical regions (10 states). The main exposure was reported maternal use of antibacterials (1 month before pregnancy through the end of the first trimester), and odds ratios (ORs) measuring the association between antibacterial use and selected birth defects were constructed and adjusted for potential confounders. The reported use of antibacterials increased during pregnancy, peaking during the third month.

Sulfonamides were associated with anencephaly (adjusted OR [AOR] = 3.4; 95% confidence interval [CI], 1.3-8.8), hypoplastic left heart syndrome (AOR = 3.2; 95% CI, 1.3-7.6), coarctation of the aorta (AOR = 2.7; 95% CI, 1.3-5.6), choanal atresia (AOR = 8.0; 95% CI, 2.7-23.5), transverse limb deficiency (AOR = 2.5; 95% CI, 1.0-5.9), and diaphragmatic hernia (AOR = 2.4; 95% CI, 1.1-5.4).

Nitrofurantoins were associated with anophthalmia or microphthalmos (AOR = 3.7; 95% CI, 1.1-12.2), hypoplastic left heart syndrome

(AOR = 4.2; 95% CI, 1.9-9.1), atrial septal defects (AOR = 1.9; 95% CI, 1.1-3.4), and cleft lip with cleft palate (AOR = 2.1; 95% CI, 1.2-3.9).

Other antibacterial agents were not associated with a significant increase in the AOR of these birth defects. The authors concluded that sulfonamides and nitrofurantoins were associated with several birth defects, indicating a need for additional scrutiny. In contrast, penicillins, erythromycins, and cephalosporins appeared to be safer alternatives.

■ COMMENTARY

The National Birth Defects Prevention Study (NBPS) is conducted by investigators at the Centers for Disease Control and Prevention. This large representative multistate database is about as good as we get in the current United States health care system to assess exposure and rare outcomes in a large population-based classic case-control study. While case-control studies cannot demonstrate a causal relationship, they can suggest important relationships worthy of additional consideration. For the assessment of rare outcomes where prospective randomized studies are impractical, they provide the best evidence for clinical guidance.

This study published last fall in the *Archives of Pediatric and Adolescent Medicine* has received little press in the obstetric literature. As I discovered recently that nurses and residents at my institution were not aware of these results, I felt it was important to bring them to the attention of readers of *OB/GYN Clinical Alert*.

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Questions & Comments
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Case-control studies are always subject to confounding. Common events like urinary tract infections (UTIs) will lead to multiple exposures, and common drugs will be widely used. Recall bias further complicates studies of exposure, as those women that experience an abnormal pregnancy may have a greater tendency to report exposure or to recall the drug they were treated with.

More than 2% of women in this study were treated for a UTI in the first trimester. The authors designed their assessment to critical exposure during the period of early fetal development. Still, many of the abnormalities are restricted to an even more limited time of exposure, with most structural anomalies occurring before 6 weeks of gestation.[1] The majority of subjects in the NBPS were treated between 8-13 weeks, well after the expected developmental critical windows for the listed anomalies.

However, the most commonly used antibiotics — penicillins, erythromycins, and cephalosporins (all FDA pregnancy category B) — were not associated with an increased risk of anomalies in this study, while both nitrofurantoin and sulfonamides were associated with significant increased AOR of risk for a variety of anomalies. Sulfonamides (FDA pregnancy category C or D) have been shown to be teratogenic in animal studies, although it is unclear whether sulfonamides without trimethoprim pose a significant risk.[2] The two drugs act synergistically to block two steps in the biosynthesis of reduced folates, and other case-control studies have demonstrated an increased risk of anomalies with first trimester exposure.[3] These drugs can also affect bilirubin metabolism and should not be used in the third trimester and while breast feeding. The observed increase in risk with nitrofurantoin (Category B) is more surprising. The drug primarily concentrates in the urinary tract and has not previously been associated with fetal harm. It is well tolerated, easy to take, and highly effective against most pathogens.

Taken together, the results from this study are far from conclusive. Still, this information will be available on the internet and your patients will be searching that source as soon as they leave the office with your prescription. To avoid a call from your patient (or maybe from her lawyer), it makes sense to provide counseling on your antibiotic choice. Since there are alternatives to use of nitrofurantoins and sulfa/trimethoprim in the first trimester, it is wise to do so even if the evidence is limited. Avoid sulfonamides in the third trimester to avoid the known association with hyperbilirubinemia.

A more important consideration is the reproductive age non-pregnant patient that presents or calls with UTI symptoms. Is it safe to use nitrofurantoin or sulfa drugs in these women? In contrast to the patient at 8 weeks, these are exactly the individuals in whom an early fetal exposure is possible. Consider carefully the drug resistance

patterns in your community, and the contraceptive status of your patient when considering therapy. If she is at high risk for pregnancy, best to avoid these drugs. ■

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Hyperglycemia and Adverse Pregnancy Outcome

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics,
University of Colorado Health Sciences Center, Denver

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

Synopsis: *A recent report may put a new spin on screening for gestational diabetes.*

Source: International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676-682.

This spring a consensus opinion appears in the journal *Diabetes Care*, which represented a summary of deliberations of the International Association of Diabetes in Pregnancy Study Groups (IADPSG), a collaboration of 225 experts in the field from 40 countries, who gathered in Pasadena, CA, in June 2008. Since the current screening protocol for gestational diabetes (GDM) is about 40 years old, the group's goal was to make recommendations based on the best up-to-date information.

The screening guidelines that are in place now were based on the likelihood of a pregnant woman eventually becoming overtly diabetic. Instead, the aim of this group was to arrive upon screening guidelines that best correlated with adverse pregnancy outcomes, and they weighed heavily the results from an investigation published in the *New England Journal of Medicine* in May 2008 — the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study.[1] This study included data from 25,500 patients in 15 centers around the world that were accumulated over a 6-year period. Primary outcomes included large-for-gestational (LGA) infants, primary cesarean section, and neonatal hypoglycemia. Secondary outcomes were preterm birth, shoulder dystocia, need for NICA care, neonatal hyperbilirubinemia, and preeclampsia.

The HAPO screening protocol called for a 75 g glucose load to be given to patients at 24-32 weeks gestation, and fasting 1- and 2-hour plasma glucose levels were evaluated (in essence, a 2-hour glucose tolerance test [GTT]). The managing physicians were blinded to the screening results, except in patients with fasting levels > 105 mg/dL and/or 2-hour levels > 200 mg/dL. They were considered to be overt diabetics and, therefore, were excluded from the analysis.

Not surprisingly, the HAPO study results (attaining statistical significant) showed rising odds ratios for the primary and secondary adverse outcomes with increasing glucose levels in the GTT. However, the authors indicated that "there were no obvious thresholds at which risks increased." To the contrary, the IADPSG Consensus Panel used unpublished data from the HAPO study itself, along with information from other studies, to make some important observations and recommendations regarding thresholds.

The group suggests that all patients with a historical predisposition for diabetes be evaluated on their first visit. If the fasting plasma sugars were > 126 mg/dL, a random plasma sugar exceeds 200 mg/dL, or the HbA1C levels were > 6.5%, these patients should be labeled as overt diabetics. If the fasting plasma sugar is > 6.5%, these patients should be labeled as overt diabetics. If the fasting plasma sugar is > 92 mg/dL, but < 126 mg/dL, they should be considered gestational diabetics. If the results are negative, then all patients should have a 75 g oral 2-hour GTT later, at 24-28 weeks, using the screening thresholds noted below. GDM is diagnosed if any of the three thresholds is equaled or exceeded.

■ COMMENTARY

Although these recommendations will have to pass through a vetting processing by various colleagues and organizations before being officially approved, they are gaining momentum, while being fueled by an alarming increase in obesity and maternal and childhood diabetes.[2] The proposed aggressive screening protocol does represent extra effort, but the good news is that very few undiagnosed GDMs will slip through. The bad news is that the total amount of screen positives will be 18% (based on HAPO data).

For years, the concept of screening every patient for gestational diabetes has not been uniformly supported.

The detractors have maintained that knowing a patient's glucose status (excluding insulin-requiring diabetics) had not been shown convincingly to affect outcome. Also, labeling a patient as having GDM stigmatized her to a point where she might encounter difficulty in getting insurance coverage (something that should be rectified soon by recent legislation). The proponents say that there has been an explosion of childhood diabetes, perhaps catalyzed by a seeming epidemic of obesity in the United States — 60% of Americans are overweight (BMI 25-30 kg/m^2) and 40% are obese (BMI > 30 kg/m^2). The HAPO study shows that GDM is associated with adverse outcomes, but, although there are data to suggest that adjustment of management for these patients is cost-effective,[3] the remaining doubters may have to be convinced by prospective intervention studies using the new guidelines.

So, in summary, here is what the IADPSG suggests:

1. With a liberal suspicion for diabetes, appropriate patients should be evaluated at the time of their first visit. As stated above, if the fasting plasma is > 126 mg/dL, a random glucose is > 200 mg/dL, or the HbA1C exceed 6.5%, then the patient will be considered to be an overt diabetic.

2. If the fasting plasma sugars are 92-126 mg/dL, these patients should be considered to have GDM.

3. All others should empirically have a 75 g 2-hour GTT at 24-28 weeks using the following thresholds:

a. Fasting — 92 mg/dL

b. 1 hour — 180 mg/dL

c. 2 hour — 153 mg/dL

This means that we substitute the above protocol for the standard 1-hour glucose screen, modify the standard GTT to include a 75 g glucose load, and delete the 3-hour blood draw. Although it is tempting to round off the above thresholds to values that are easier to remember (for example, to use 90 mg/dL instead of 92 mg/dL, and 150 mg/dL instead of 153 mg/dL), the group found that it would diminish the efficacy of the screening strategy. Frankly, it is even more tempting to bag the 2-hour blood draw, since, by itself, it was responsible for only 2% of the screen-positive patients.

It should be pointed out that these guidelines have yet to be endorsed by various official bodies, but, despite the confusion they may generate, it appears that they are on a fast track for approval. I am simply reporting on what is on the horizon, so please do not shoot the messenger. ■

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Hormone Therapy and Risk of Lung Cancer

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *An increase in the risk of lung cancer diagnosis was seen in users of combined estrogen-progestogen hormone replacement therapy. The risk increased with duration of use, and became significant after 10 years of exposure. The association was not seen with estrogen-only therapy.*

Source: Slatore CG, et al. Lung cancer and hormone replacement therapy: Association in the vitamins and lifestyle study. *J Clin Oncol* 2010;28:1540-1546.

Lung cancer is the leading cause of cancer-related mortality among women. To investigate the potential role of hormone replacement therapy (HRT) in lung cancer development, the authors evaluated a prospective cohort of 36,588 peri- and postmenopausal women aged 50-76 years from Washington State recruited in 2000-2002 as part of the Vitamins and Lifestyle (VITAL) Study. The cohort was established from a mailing to 168,953 women aged 50-76 years who lived in the area covered by the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) registry. After exclusion for a variety of factors, the subjects tended to be more educated and less likely to be current smokers, but were similar in body mass index (BMI) to the general population. Deaths were ascertained by linkage to Washington State death files, and moves out of the area from the National Change of Address System. Participants with a previous diagnosis of lung cancer, or those with lung cancer identified only on a death certificate were excluded. Only perimenopausal (defined as having menses in the past year that were not regular) and postmenopausal (defined as no periods in the year before baseline, ever use of HRT, bilateral oophorectomy, or age ≥ 60 years) were studied. Exposure to HRT was obtained by self report and categorized by use status (never, former, current) and years of use (< 1, 1-4, 5-9, 10-14, or ≥ 15 years). Years of estrogen plus progestin (EP) use and years of estrogen-only use were computed separately. The reference group was users of neither type of HRT. The outcome, lung cancer, was identified through

the SEER cancer registry during 6 years of follow-up. Hazard ratios (HRs) associated with use and duration of specific HRT formulations were calculated for total incident lung cancer, specific morphologies, and cancer by stage at diagnosis.

A total of 344 cases of lung cancer were identified. After adjusting for smoking, age, and other potential confounders, there was an increased risk of incident lung cancer associated with increasing duration of combined EP use (HR, 1.27; 95% confidence interval [CI], 0.91-1.78 for 1-9 years; and HR, 1.48; 95% CI, 1.03-2.12 for ≥ 10 years; *P* for trend = 0.03). There was also a significant trend toward a more advanced stage at diagnosis associated with increasing exposure to EP therapy. In contrast, use of unopposed estrogen was not associated with an increased risk of lung cancer diagnosis.

The authors concluded that use of combined HRT increases the risk of developing lung cancer in a duration-dependent manner, with an approximate 50% increased risk for use of 10 years or longer.

■ COMMENTARY

I had planned to write this month about the North American Menopause Society's (NAMS) 2010 Position statement on estrogen and progestogen use in postmenopausal women.[1] The revised NAMS statement does not contain any new information or surprises for careful readers of *OB/GYN Clinical Alert*, but nonetheless these public statements are welcome. Controversy and confusion remains prevalent in many published guidelines for postmenopausal HRT, most of which reflect an undue influence of the Women's Health Initiative initial reports. This has led to an overly conservative approach to therapy by many providers. Consequently, large numbers of postmenopausal women do not receive adequate counseling on the benefits and risks of HRT from their providers, while others are misinformed by overly pessimistic reports in the media.

The North American Menopause Society is a nonprofit scientific organization dedicated to the advancement of women's health through the study of menopause. NAMS published an initial position statement on the role of menopausal HRT in October 2002 in response to the first WHI report, and has issued updated statements in September 2003, October 2004, March 2007, and July 2008 to clarify the benefit-risk ratio of HRT for both treatment of menopause-related symptoms and disease prevention at various times through menopause and beyond. The current report provided updates to all the existing sections, and added new information on ovarian and lung cancer.

The 2010 statement reiterated the previous position that estrogen therapy (ET) is the most effective treatment for vasomotor symptoms, and for moderate-to-severe vulvar or vaginal atrophy. The major proven systemic benefit of HRT is a reduction in fracture risk (principally hip fracture). Cardiovascular disease is the No. 1 killer of postmenopausal women. The 2010 Position Statement recognizes that the primary difference between observational studies (that show a benefit of systemic HRT in reducing the risk of CHD) and RCTs (that show no benefit or harm) is timing of initiation of therapy. In general, starting HRT before age 55 or within 5 years of onset of menopause is associated with benefit, while later initiation is associated with increasing risk. The principle risk of HRT is the alteration in hepatic globulins that increases blood clotting. This manifests as a small increase in the risk of ischemic stroke (but no difference in hemorrhagic stroke), and an approximately 2-fold increase in risk of venous thromboembolism (VTE) that is observed across both observational and randomized studies using oral estrogen. More recent evidence from case-control studies suggests that the increase in risk of VTE is observed with oral administration, but not transdermal delivery of estradiol.[2] In addition, the important interaction of obesity with VTE risk (3-fold increase) has recently become more widely recognized.[3]

However, in the office, many discussions of HRT center almost exclusively on cancer risk. A growing body of evidence suggests that HRT may promote the growth of pre-existing breast cancers, with small increases in the risk of breast cancer diagnosis seen in the WHI study among women using combined HRT, but no increase in risk in women using conjugated estrogens alone.[4] A small increase in the risk of ovarian and lung cancer has also been observed. The lung cancer issue is the newest and most important data, as lung cancer is the No. 1 cause of cancer death in women.

The present report by Slatore et al has the standard biases of database studies. It relies heavily on self-report of exposure, and is not representative of the true population with respect to smoking history. Women using estrogen-only therapy were significantly younger and more likely to have undergone hysterectomy with removal of both ovaries. Nonetheless, the association with combined HRT (but not E alone) and breast cancer actually strengthened with adjustment for potential confounders such as smoking and BMI, and the HR increased with duration of use.

To put this into perspective, we need to consider consistency of effect, biologic plausibility, and absolute risk. A similar magnitude of risk for lung cancer was observed for EP therapy in the randomized Heart and Estrogen/Progestin Replacement Study (HERS) trial, although the finding was not statistically significant (HR, 1.39; 95% CI, 0.84-2.28).[5] The same nonsignificant increase was observed in the WHI (HR, 1.23; 95% CI, 0.92-1.63).[6]

The incidence of lung cancer is higher among women than men, suggesting an important gender difference that

hints to biologic plausibility.[7] Both estrogen receptors and aromatase, the enzyme that synthesizes 17β-estradiol (E2), are expressed by lung tumors, suggesting a role for female steroid hormones in lung cancer growth.[8] A number of basic research and clinical studies support a role for local production of estrogen and expression of ERs in lung tumors that arise in men as well as in women. GPR30, a novel protein expressed in lung tumors at high levels, binds E2 and may be a proliferation factor.[8] Still, if estrogen is the whole story, why is the increase in lung cancer not observed in women using unopposed estrogen?

So how do we counsel our patients? This leads us to the discussion of absolute risk. In the United States lung cancer deaths in women now surpass those caused by breast, ovarian, and cervical cancers combined.[9] However, the incidence of lung cancer in nonsmoking women is only about 15-20/100,000 person-years for women ages 40-79 years. For female smokers this increases to between 149-263/100,000 person-years. Assuming a 48% increase in risk with EP therapy, this would translate to an additional 7-9 cases of lung cancer per 100,000 nonsmokers, and 70-120 cases among smokers. Thus, for nonsmokers the number of lung cancer cases attributable to HRT is negligible, while for smokers the risk is similar in magnitude to that observed for breast cancer among EP users (approximately 8-11 additional cancers diagnosed). However, it is important to keep in mind that the survival for women with lung cancer is much lower than with breast cancer.

Taken together, the powerful increase in lung cancer risk attributable to smoking outweighs any other factor, and we should redouble our efforts to help our patients quit. While female smokers are at an increase risk of lung cancer, and combined HRT appears to significantly magnify the risk, women who smoke are also at higher risk for osteoporosis and fracture. A thorough discussion of risks and benefits needs to occur and should address all of these competing interests. Clinicians should document in the medical record the discussion of lung cancer risk and HRT in a similar way they describe breast cancer risk. As noted in the NAMS position paper, for most healthy recently menopausal women, the benefits of HRT will outweigh the risks. ■

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Adding Another Standard to Platinum-sensitive Recurrent Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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M.D. Anderson Cancer Center, Houston

Dr. Coleman serves on the scientific/advisory board of Centocor.

Synopsis: *Combination pegylated liposomal doxorubicin and carboplatin was found to be superior to paclitaxel and carboplatin in platinum-sensitive recurrent ovarian cancer and with a better therapeutic index*

Source: Pujade-Lauraine E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol* 2010 May 24; Epub ahead of print.

To assess the efficacy and toxicity of combination pegylated liposomal doxorubicin (PLD) and carboplatin against industry-standard paclitaxel and carboplatin, patients with histologically proven ovarian cancer with recurrence more than 6 months after first- or second-line

platinum- and taxane-based therapies were randomly assigned by stratified blocks to CD (carboplatin area under the curve [AUC] 5 plus PLD 30 mg/m^2) every 4 weeks or CP (carboplatin AUC 5 plus paclitaxel 175 mg/m^2) every 3 weeks for at least 6 cycles. The primary endpoint was progression-free survival (PFS); secondary endpoints were toxicity, quality of life, and overall survival. Overall, 976 patients were recruited. With median follow-up of 22 months, PFS for the CD arm was statistically superior to the CP arm (hazard ratio, 0.821; 95% confidence interval [CI], 0.72-0.94; $P < 0.005$); median PFS was 11.3 vs 9.4 months, respectively. Severe non-hematologic toxicity (36.8% vs 28.4%; $P < 0.01$) leading to early discontinuation (15% vs 6%; $P < 0.001$) occurred more frequently in the CP arm. More frequent grade 2 or greater alopecia (83.6% vs 7%), hypersensitivity reactions (18.8% vs 5.6%), and sensory neuropathy (26.9% vs 4.9%) were observed in the CP arm; more hand-foot syndrome (grade 2-3, 12.0% vs 2.2%), nausea (35.2% vs 24.2%), and mucositis (grade 2-3, 13.9% vs 7%) in the CD arm. The authors conclude that the new combination has clinical efficacy and a better toxicity profile than paclitaxel and carboplatin.

■ COMMENTARY

This study represents an important advance in our approach for women with recurrent platinum-sensitive ovarian cancer because it is one of the few trials not only adequately powered to address the question of non-inferiority, but also one conducted in a patient population that is reflective of patients we see day to day. These distinctions are important to realize because they stand in contrast to the other trials conducted in platinum-sensitive recurrent ovarian cancer patients where the control arm is predominately a single-agent platinum or a non-platinum agent, and in a population that has not universally been previously exposed to a taxane. These two features have limited the interpretation and exportability of results in previous efforts. The issue of non-inferiority is also one not to be overlooked. Such trial designs are unpopular for many reasons; they are usually larger, more time-consuming, and expensive, only to conclude that the experimental regimen is no worse that a treatment standard. Indeed, in a negative trial powered only for superiority, we are often left to make the erroneous interpretation that the treatment arms are "likely" not different. This trial helped to answer both: non-inferiority of the new arm and superiority. Unfortunately, the short-term metric, progression-free survival, in an open-label study may be influenced by many factors other than treatment effect, which has tempered the enthusiasm of our regulatory agencies (e.g., FDA) in using this outcome to approve new clinical entities. Nevertheless, as the survival data mature in the current study, we are encouraged by the rigor with which this study was undertaken, its outcomes for survival and toxicity, and that availability of the agents, which allows our patients to have another option in the treatment of their disease. ■

Additional Readings

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News Brief

Check Your Approach in Taking Sexual History

Learn to be more specific in your sexual health history taking. Results of a new study from the Kinsey Institute for Research in Sex, Gender and Reproduction at Indiana University in Bloomington indicate that no uniform consensus exists when the term "had sex" is used.[1]

The study examines the responses from 486 Indiana residents, ages 18-96, who took part in a telephone survey conducted by the university's Center for Survey Research. Participants, most of whom were heterosexual, were asked, "Would you say you 'had sex' with someone if the most intimate behavior you engaged in was ...," followed by 14 behaviorally specific items.

In evaluating the responses from the 204 men and 292 women, researchers found that replies did not differ significantly overall between the two genders. An overview of the complete findings shows:

• 95% of respondents considered penile-vaginal intercourse as having had sex, yet only 89% did so if there was no ejaculation.

• 81% saw penile-anal intercourse as having had sex, with the rate dropping to 77% for men in the youngest age group (18-29), 50% for men in the oldest age group (65 and older), and 67% for women in the oldest age group.

• 71% and 73% considered oral contact with a partner's genitals, performing or receiving, as having had sex.

• Men in the youngest and oldest age groups were less likely to answer "yes" compared with the middle two age groups for when they performed oral-genital sex.[1]

"These findings highlight the need to use behavior-specific terminology in sexual history taking, sex research, sexual health promotion, and sex education," state the researchers. "Researchers, educators, and medical practitioners should exercise caution and not assume that their own definitions of having 'had sex' are shared by their research participants or patients."

Specificity is important when clinicians are taking a sexual health history, says **William Yarber**, HSD, professor in the departments of applied health science and gender studies at Indiana University and senior research fellow at the Kinsey Institute. Clinicians might ask how many sexual partners a patient has had; however, the number will differ according to the patient's definition of sex, he observes.

Don't be hesitant

Some health care providers might be hesitant to bring up specific sexual behaviors such as anal sex because they sense that it might be embarrassing to a patient and might influence the level of trust the provider has worked to develop, says Yarber, a co-author of the current study. However, for the health of the individual, specificity is important, he notes.

When initiating a sexual history, use such wording as "Tell me about your sexual activity" and "Do you have any concerns about your sexual life that you would like to discuss?" The elements of a sexual history can include such questions as "Are you currently sexually active?" "Do you have a sexual partner?" and "Do you have sex with men, women, or both?"[2]

Researchers with the current study now plan to look at how cultural differences might impact the definitions of "had sex," says **Brandon Hill**, research associate at the Kinsey Institute and a researcher in the university's Department of Gender Studies. The scientists have conducted similar surveys in the United Kingdom and are comparing responses to those in the United States to determine the influence of cultural differences, Hill says. ■

References

1. Sanders SA, et al. Misclassification bias: Diversity in conceptualisations about having 'had sex'. *Sex Health* 2010;7:31-34.
2. Jones KP. Helping patients communicate about sexuality issues: The power of good sexual health history taking. Presented at the 2003 Contraceptive Technology conference. San Francisco; March 2003.

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

9. Which of the following regarding maternal screening guidelines is *not* appropriate?
   a. Patients not diagnosed to have glucose intolerance in the first trimester will have an oral GTT between 24 and 28 weeks.
   b. A 75 g glucose load will be administered.
   c. Rounding off of threshold values is appropriate.
   d. The three-hour blood sugar portion of the GTT will be abandoned.

10. Lung cancer incidence rates are:
   a. higher in female nonsmokers than in male nonsmokers.
   b. higher in female smokers than in male smokers.
   c. increased in women using postmenopausal combined hormone replacement therapy.
   d. All of the above

11. Which of the following toxicities was increased in the pegylated doxorubicin arm relative to the control arm?
   a. Alopecia
   b. Hand-foot syndrome
   c. Neurotoxicity
   d. Hypersensitivity reactions

Answers: 9. c, 10. d, 11. b.

PHARMACOLOGY WATCH

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

PPIs, *Clostridium difficile*, and Bone Fractures

In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

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Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■