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INSIDE

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Weight Gain with Contraception

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 prospective cohort study, perceived weight gain was found to be an adequate predictor of actual weight gain. Depot medroxyprogesterone acetate and the contraceptive implant were associated with more weight gain than the copper IUD.*

Source: Nault AM, et al. Validity of perceived weight gain in women using long-acting reversible contraception and depot medroxyprogesterone acetate. *Am J Obstet Gynecol* 2013;208:48.e1-8.

The authors performed a two-part analysis of the Contraceptive CHOICE Project, a prospective cohort study in which women in the St. Louis, Missouri, region received a reversible contraceptive method of their choice for up to 3 years at no cost. First, body mass index (BMI) was calculated at enrollment and women were asked at 3-, 6-, and 12-month telephone interviews whether their weight had changed by 5 pounds or more. This perceived weight change was categorized as weight gain, no change, or weight loss. Second, a smaller cohort of women from the main study then were asked to return at 12 months for an objective weight measurement. They had to have been using the levonorgestrel IUS (LNG IUS), copper T380A IUD (Cu-IUD), contraceptive implant, or depot medroxyprogesterone acetate (DMPA) for at least the prior 11 months. Participants were classified as having had weight gain if the calculated weight change was 5 pounds or greater, no change if the calculated weight was less than a 5 pound difference in either direction, or weight loss if the calculated weight change was a loss of 5 or more pounds.

A total of 4133 women met inclusion criteria for the first part of the

study and 281 of those had an objective weight measurement at 12 months. Women who perceived weight gain were more likely to be African American, parous, uninsured, and less educated. Forty-six percent of DMPA users, 41% of implant users, 34% of LNG IUS users, 29% of copper IUD users, and 26% of pill/path/ring users reported a perceived weight gain. The mean weight change for the 281 women with objective measurements was a 2.2 pound increase. Women who perceived weight gain experienced a mean of 10.3 pounds gained. Women who perceived no change to their weight experienced a mean of 1.5 pounds gained. Women who perceived weight loss experienced a mean of 9.5 pounds lost. The sensitivity and specificity of perceived weight gain was 74.6% and 84.4%, respectively, and the positive predictive value was 77%. Having established that perceived weight gain was reasonably predictive of actual weight gain, the authors then used the larger cohort to perform a multivariable analysis. After adjusting for race, the implant (relative risk [RR] 1.29; 95% confidence interval [CI], 1.10-1.51) and DMPA (RR 1.37; 95% CI, 1.14-1.64) users were significantly more likely to perceive weight gain compared with copper IUD users.

■ COMMENTARY

Long-acting reversible contraception (LARC), due to its high efficacy and continuation rates, is considered to be in the top tier of contraceptive efficacy. We should encourage more women who need long-term contraception to choose IUDs and implants. The Contraceptive CHOICE Project investigators have previously reported continuation rates at 12 months of 88% for the LNG IUS 84% for the Cu-IUD, and 83% for the subdermal implant.[1] Satisfaction rates also were higher for LARC methods compared to other methods of contraception such as oral contraceptives and DMPA. One component of contraceptive continuation and satisfaction is weight gain, whether actual or perceived. Clinically, we see many women requesting to change contraceptive methods because of perceived weight gain, although whether the weight gain is due to the method or changes in diet and activity is often not known. This is an important conversation to have with your patient. This study assigns an overall average 2.2 pound potential weight gain across all methods. Although most women are adverse to ANY weight gain, the benefit of LARC and security against pregnancy may be worth the gamble, especially since pregnancy is associated with weight gain that often persists into the postpartum. Therefore, switching women from a highly effective contraceptive will likely increase their risk of pregnancy at the cost of a few pounds. The choice is highly personal and worth the discussion.

This particular study examined the validity of perceived weight gain among women using LARC methods and DMPA against actual weight gain — a highly practical outcome for our population. It has long been known that DMPA use can be associated with weight gain, especially in women who are already obese.[2,3] In the trials for the contraceptive implant, however, mean weight gain in U.S. users was 2.8 pounds in the first year and 3.7 pounds after 2 years. Additionally, only 2.3% of the study population requested that the implant be removed due to weight gain.[4] Interestingly, the authors found that more women using both implants and DMPA, compared to IUDs and the pill/patch/ring, reported perceived weight gain. Perceived weight gain with the contraceptive implant has not been described previously. Although perceived weight gain was not a perfect measure of actual objective weight gain, it was a reasonable approximation associated with decent sensitivity, specificity, and predictive value. Nevertheless, the authors did not report the actual weight gain with each method among the 281 women, which would have been helpful information. In addition, there is no information on diet and exercise habits in the participants.

The investigators propose that providers caring for women using these contraceptives should ask them about weight gain and that perceived weight gain can be just as concerning to women as actual weight gain. They suggest interventions, such as weight loss counseling and screening for diseases associated with obesity including hypertension or diabetes. They do not mention any strategies for changing the contraceptive method or at what weight gain threshold it should be changed. Because of the known association, women on DMPA are likely already moni-

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Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

tored closely for weight gain. In our clinic, all patients on DMPA have their weight and blood pressure checked at each injection visit. Implant users typically present only for their annual gynecologic exams after implant insertion unless side effects are bothersome. Changes in weight are already addressed as part of an annual exam evaluation, but this study may make us pay more attention in contraceptive implant users. ■

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'Off-target' Effects? The Role of Statins in Cancer Biology

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Statin use among cancer patients with diverse malignancies is associated with reduced cancer-related mortality. The mechanism is plausible since statins inhibit cholesterol synthesis, which reduces the pool of compounds necessary in cellular proliferation and maintenance of critical cellular functions, such as membrane integrity, signaling, protein synthesis, and cell cycle progression. Prospective clinical trials are warranted.*

Source: Nielsen SF, et al. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;367:1792-1802.

Cholesterol-reducing statin agents have been associated preclinically with cancer cell growth inhibition and metastases prevention. Given the ubiquitous use of statins in the general population for reduction in cardiovascular risk, the authors evaluated statin use in cancer patients for effects on cancer-specific mortality. They assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007, accompanied by a minimum follow-up of 2 years. Among patients 40 years of age or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins. Multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, were 0.85 (95% confidence interval [CI], 0.83-0.87) for death from any cause and 0.85 (95% CI, 0.82-0.87) for death from cancer. Adjusted hazard ratios for death from any cause according to the defined daily statin dose (the assumed average maintenance dose per day) were 0.82 (95% CI, 0.81-0.85) for a "low" dose (0.01-0.75 defined daily dose per day), 0.87 (95% CI, 0.83-0.89) for "average" dose (0.76-1.50 defined daily dose per day), and 0.87 (95% CI, 0.81-0.91) for "high" dose (> 1.50 defined daily dose per day); the corresponding hazard ratios for death from cancer were 0.83 (95% CI, 0.81-0.86), 0.87 (95% CI, 0.83-0.91), and 0.87 (95% CI, 0.81-0.92), respectively. The reduced cancer-related mortality among statin users as compared with those who had never used statins was observed for each of 13 cancer types. A nested case-control study matched statin cancer patients to three non-statin using cancer patients to control for changes in staging and cancer treatment. The effects were similar to the larger general population analysis. The authors concluded that statin use in patients with cancer is associated with reduced cancer-related mortality. Further study of mechanism and effect in prospective studies is warranted.

■ COMMENTARY

As a complement to last issue's commentary on the use of metformin and its effect on ovarian cancer mortality, we have this provocative report of statin use. To summarize, statin use was associated with reduced cancer-specific mortality across 13 different malignancies. The data were derived from a unique resource, the enviable National Registry of Patients, which has nearly unbelievable quality control within the Danish health care system. Lending credibility to the study's conclusions are the 98% capture of index cancers associated with nearly 100% complete follow-up and prescriptive practices over a 13-year period among the entire Danish population. Also, to confront changes in the cancer classifications, staging, and treatment over the study period, a nested 1:3 matched case-control study was also conducted. In that analysis, statin users with cancer were matched to three non-statin users with cancer controlling for cancer type, gender, age at diagnosis, and year of diagnosis. The consistency of

effect in "all-cause" death and "cancer-specific" death in the two analyses provide legitimacy to the hypothesis that statin use in patients developing cancer may provide up to a 15% reduction in the cumulative risk of these events. This is bolstered by a credible link to the mechanism of action of the statins, which is to perturb cholesterol synthesis. As is recognized, cholesterol is a fundamental structural component of mammalian cell membranes and structures. It is also critical to many cellular processes that govern proliferation, and in cancer cells, processes that are involved in tumor growth, invasion, and metastases.[1,2] In particular, the mevalonate pathway (cholesterol synthesis pathway) is up-regulated in P53 mutated cancers, where cholesterol metabolites serve as important signaling substrates promoting the malignant phenotype.[3] Statin use in preclinical experiments has been shown to inhibit cellular growth and metastases. There is also evidence that statins can block the P-glycoprotein pump, which serves as a mechanism of resistance to some chemotherapeutics.[4]

Since the sample is so large and homogeneous, the clinical impact may be trivial in some cancers and not easily extrapolated to other ethnic groups. In addition, the combination of statins (which are metabolized via intestinal and hepatic cytochrome P450 oxygenases) with chemotherapy needs to be carefully considered, as they may compete for metabolic clearance. Further, there are gaps in the analysis, such as the consideration of important cofactors (tobacco use, balance of screening/early detection practices, cholesterol levels) and the observed lack of a dose effect, which may suggest a minimal dose could be just as important to mortality reduction but with fewer side effects. Nevertheless, the results are thought-provoking and support more definitive clinical investigation into the role of statins in cancer therapy and their effect on long-term survival. ■

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Risk of Uterine Rupture or Placenta Previa after Previous Myomectomy or Classical Cesarean

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 shows that having a previous myomectomy or classical cesarean section does not convey a significantly greater risk of uterine rupture or placenta previa during a subsequent pregnancy, when compared with a low transverse section.*

Source: Gyamfi-Bannerman C, et al. Risk of uterine rupture and placenta accreta with prior uterine surgery outside of the lower segment. *Obstet Gynecol* 2012;120:1332-1337.

Conventional wisdom in obstetrics implies that women with previous uterine surgery outside the lower uterine segment — whether myomectomy or classical cesarean section — incrue an unacceptable risk for uterine rupture during pregnancy. Recently, members of the NICHD perinatal network revisited this concept — this time with enough numbers to question this thinking.[1]

The group compared outcomes from three groups: 1) 167 women who had had prior myomectomies (PMM), 2) 455 pregnant women who had prior "classical" cesarean sections (PC), and 3) 1373 patients who had prior low transverse cesarean sections (LTCS). The dependent variables were uterine rupture (through the myometrium and uterine serosa) and documentation of placenta accreta.

The average gestational ages at delivery were: 35.8 weeks for PMM, 37.3 weeks for PC, and 38.5 weeks for LTCS. The uterine rupture incidence was 0% for the PM group, 0.88% for the PC group, and 0.41% for the LTCS patients. None of these differences were statistically significant. Placenta accreta occurred in none of the PMM, in 0.88% of the PC, and in 0.19% of the LTCS groups. The risk of accreta rose appreciably in patients who had placenta previa, but if present, there was little difference in the frequency of accreta between PC (13.6%) and the LTCS group (11.1%).

■ **COMMENTARY**

The take-home points from this study are:

1. Previous myomectomy has a very low risk of uterine rupture — at least up until 36 weeks.

2. A previous classical cesarean section also conveys a very low risk of uterine rupture, but there was a trend toward a higher rate of placenta accreta (0.88% vs 0.19% in LTCS).

3. In all groups, the risk of rupture and accreta (in those without placenta previa) was very low (< 1%).

One limitation of the study was that the authors could not retrieve data regarding how often the uterine cavity was entered during the myomectomies or the number and location of the myomas. Another interesting deficiency was that the myomectomy pregnancies all were delivered by cesarean section at an average gestational age of 35.8 weeks and, since only 20% of these patients were reported to have had regular uterine contractions, we do not know what would have happened if these pregnancies had continued to term.

It is surprising that the term "classical" cesarean section was not specifically defined in the methods section. The original description of a classical cesarean section pertained to those that were done years ago when the uterine incision involved the upper segment and fundus. Since there were so many PC patients included in the study, it is probably safe to assume that the term "classical" was synonymous simply with a vertical incision somewhere in the uterus.

Other than a few case reports, it is unclear why a history of a PMM has been stigmatized to a point where clinicians automatically default to an early term "prophylactic" cesarean section. This study showed a 0% chance of rupture in these patients, and these results are consistent with another study involving 1225 pregnant women with previous myomectomies who had a rupture rate of only 0.24%.[2]

Prior vertical incisions also have been treated with great caution, another stigma that may be undeserved. For example, in this study only 5.9% in the PC group delivered vaginally (compared with 44% in the LTCS group), strongly suggesting a reluctance to take these patients to term or even to let them labor. Yet, the uterine rupture rate in this group was not statistically different than that of the LTCS group, with both being < 1%. The somewhat greater risk of accreta in the PC group could simply mean that an anterior placenta covers more scar surface than it would with a LTCS scar, especially if there was no evidence of placenta previa.

The findings of this study should send a message that the idea of "prophylactic" early-term cesarean section in patients who simply have a history of a previous myomectomy needs rethinking. If not immediately abandoned, this method should at least be studied in comparison with expectant management. ■

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Special Feature

Testosterone — It's Not the Magic Bullet

By Catherine Leclair, MD

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

1998 WAS A LANDMARK YEAR FOR MEN'S SEXUALITY. THE FDA approved sildenafil (Viagra®), a medication that now has household name familiarity. Viagra and its longer-acting cousins not only revolutionized the treatment of erectile dysfunction (ED) for men, but the PDE5 inhibitors are now used recreationally to enhance the sexual encounters for many couples without ED. Although Viagra proved to be a major advancement for the common and troublesome male sexual symptom of ED, no comparable breakthrough has been achieved in women's sexuality. Despite initial curiosity by some providers to try Viagra in women, in most cases, the problem doesn't match the solution. That's because the PDE5 inhibitors primarily address sexual arousal. Although epidemiologic studies reveal that up to 42%[1,2] of women have concerns about their sexuality, the most common complaint is low libido. The clinician who treats female sexual dysfunction simplistically as a category rather than a spectrum of disorders rarely will achieve therapeutic success.

Female sexual function has a major influence on quality of life. When problems arise, the multidimensional and multifactorial determinants do not facilitate a quick fix in a 15-minute office encounter. In 2000, a consensus team of experts in the field of women's sexuality convened to define women's sexual dysfunction as an initial step to improve clinical care and research in the field of women's sexuality.[3] The definitions give credence to both the psy-

chological and physiological influences on these common problems with diagnoses included in four categories: 1) sexual desire disorders (hypoactive sexual desire disorder [HSDD] and sexual aversion disorder); 2) sexual arousal disorder (AD), 3) orgasmic disorder, and 4) sexual pain disorders (dyspareunia, vaginismus, and noncoital sexual pain disorder). New to these diagnoses was the element of "personal distress," which accounts for the vital role of the human psyche in sexual expression. Viagra, as a PDE5 inhibitor, is indicated for arousal dysfunction by inducing vasodilation of the genital tissue. Unfortunately, arousal disorder as a pure abnormality is rare in women, and it is challenging to distinguish AD from HSDD — a more complex problem rooted in the psychosocial dynamic. It's no wonder Viagra doesn't work in the majority of women.

In an effort to find that magic bullet for HSDD, the spotlight continues to focus on testosterone. Testosterone is a potent androgen produced in the adrenal gland, the ovary, and through peripheral conversion of steroid precursors from both glands. Testosterone is almost exclusively bound to either sex hormone binding globulin (SHBG) or albumin and peaks mid-cycle in premenopausal women. Therefore, any product (e.g., oral contraceptive pills) that impacts the concentration of SHBG will affect the amount of bound testosterone. Over a woman's lifetime, testosterone levels wane, but unlike the rapid drop in estrogen seen at menopause, the decline in testosterone production is modest. Testosterone normograms are challenging to interpret since many have been modeled after scales for men and vary based on age and menstrual phase and fail to provide guidance on free hormone levels — factors that contribute to the confusion and misunderstanding generated by obtaining testosterone levels. However, since the decreased sexual desire and impaired sexual response exhibited by hypogonadal men improve with physiologic levels of testosterone replacement, many investigators have presumed that testosterone plays a central role in female sexuality and sexual behavior.

To date, studies in women suggest a complex relationship between testosterone and sexual function and support that supplementation may have a limited role in select populations of women. Although several routes of supplementation — e.g., oral, transdermal (patch), subcutaneously injected (pellet), and topical (gel or cream) — have been studied, the route most associated with significant results in postmenopausal (PMP) women has been the patch. Mind you, doses studied induced levels considered supra-physiologic for women. On the plus side, the transdermal testosterone patch has been shown to improve the number of "sexually satisfying events" (SSE) in PMP women, as well as several other secondary sexual outcome measures. The most robust data come from several randomized trials comparing a 300 mcg or 150 mcg transdermal testosterone patch to a sham patch over 12-24 weeks.[4-9] One important caveat is all participants in these studies received concomitant estrogen therapy. There is a strong role for estrogen alone in sexuality, as it treats symptoms of vaginal dryness, vulvovaginal atrophy, and vasomotor symptoms — all of which are important in normal sexual function in the PMP woman.[10,11] In a population of surgically menopausal (hysterectomy/oophorectomy) women, Shifren showed that use of a 300 mcg testosterone patch was associated with a significant increase in SSE, pleasure-orgasm, well-being, masturbation, and sexual fantasies compared to a 150 mcg testosterone or placebo patch over 12 weeks.[4] The number of sexually satisfying events increased from a baseline of one time per month to two to three times per month. In the INTIMATE Surgically Menopause-1 study published in 2005, Simon corroborated these findings in a larger group of PMP estrogen-replete women over 24 weeks.[5] The follow-up INTIMATE Naturally Menopausal-1 study published in 2006 also supported the use of a 300 mcg patch in women taking a stable dose of estrogen-progesterone replacement.[6] Women reported less sexual distress while enjoying more sexual desire and SSE. In the last patch study, Braustein demonstrated that increasing the dose of the testosterone patch to 450 mcg did not result in additional benefit.[7] To tease out the effect estrogen may play in healthy sexuality in PMP women, Davis evaluated the transdermal testosterone patch in PMP women who were *not* replaced with estrogen.[8] Again, a number of important sexual outcomes including the number of SSE, sexual desire, and frequency improved in women using the 300 mcg patch. As the primary outcome, the number of SSE increased from a baseline of 0.7/4 weeks to 2.1/4 weeks in women using the higher dosed patch. These changes were not seen in the group receiving the 150 mcg or control patch. However, breast cancer was diagnosed in four women receiving the testosterone patch (compared to none in the placebo group) — all of whom had a normal screening mammogram within 12 months of enrollment (recall that androgens are aromatized to estrogens in many tissues). This is the major reason why the patch has not received FDA approval.

The role of testosterone in premenopausal women has been less well studied and is more controversial. Theoretically, this population should have normal testosterone levels since ovarian function has not ceased. Still, many women seeking a medical explanation for low libido insist on having a level checked (often ordered by a naturopath or primary care doctor, but brought to you to "fix"). Since testosterone levels are subject to menstrual phase changes, defining a true low can be challenging. Additionally, sexual outcomes have not consistently been correlated with testosterone levels so the prognostic implication of any level is questionable. There is one well-designed, randomized, placebo-controlled trial in premenopausal

women worth mentioning. In this study, Davis randomized 261 otherwise healthy women aged 35-46 years to one of four doses (0 [placebo], 45, 90, and 180 microL) of metered nasal-sprayed testosterone daily for 16 weeks.[9] Interestingly, the middle dose of 90 microL was associated with more sexually satisfying events compared to all other doses and placebo. Unfortunately, a pregnancy was diagnosed at 20 weeks gestation in a single participant in one of the testosterone groups — a sober realization that testosterone use in a fertile population has potential risks for what may be considered a modest benefit.

So how should we view testosterone's role in female sexuality? Although modest improvements in some sexual outcomes are seen in PMP women, long-term benefit and safety has not been proven. Additionally, each of the trials was relatively short when you consider that sexuality is experienced over a lifetime. Finally, is one extra SSE over a 4-week period meaningful for most couples? It is naïve to think that a patch or spray will be a simple answer to all female sexual issues, particularly the ubiquitous problem of HSDD. The best approach is to sit down and talk to your patient about her concerns. Through discussion, you'll help her identify what she really wants out of her sexual relationship — not only for herself but also for her partner relationship.

Since the role of hormones and female sexual function is complicated, it's not surprising that testosterone levels and sexual outcomes are not correlated. Testosterone supplementation is not the easy answer to the epidemic of disappointment women feel about their sexual relationships. It's understandable that women and clinicians look for a magic bullet as the mass media distorts women's sexuality into something perverse, intangible, and marketable. It's not surprising that women feel confused and dissatisfied since there is very little healthy exposure to mature, monogamous love. Emerging data on the complexity of female sexuality emphasizes a multidimensional model that includes biologic, psychologic, sociocultural, and interpersonal dynamics to replace the antiquated Master's & Johnson's linear sexual response model (spontaneous desire leads to arousal that then allows orgasm followed by resolution). Basson's updated model of the female sexual response cycle stresses the role of emotional intimacy in a "sexually receptive" woman.[12] Openness to sexual cues in a thoughtful, safe environment governs a woman's arousability. Desire and arousal are often interchangeable and "lust" is usually not the force that motivates women to participate in a sexual exchange. In fact, 42% of women in the SWAN study reported never or rarely "sensing" desire but were "moderately or extremely satisfied with their sexual relationship."[13] As we learn more about female sexuality, we have come to understand that women are indeed different than men. So while we continue to try to focus on identifying the magic bullet of desire for women, we're missing the opportunity to encourage our patients to find ways to enhance intimacy. Positive sexual experiences and feelings for her partner are strongly correlated with sexual satisfaction and likely protect against dysfunction. It is through a fulfilling sexual encounter that a meaningful love relationship is sustained for both him and her. ■

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

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
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- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

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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. In the study by Nault et al, the positive predictive value of perceived weight gain with contraception was:
a. about 25%.
b. about 50%.
c. about 75%.
d. 99%.

2. What was the reason for the nested case-control study on statin use and cancer-related mortality?
a. To evaluate other agents that could affect cancer outcome
b. To control for tobacco use
c. To increase the sample size
d. To account for changes in treatment practices
e. To look at different endpoints that may be more relevant to prescriptive practices

3. Which of the following does not fit the data from the study by Gyamfi-Bannerman et al?
a. The low transverse cesarean section (LTCS) group had the highest rate of vaginal deliveries.
b. More of the prior myomectomy (PMM) group had vaginal deliveries then the prior classical cesarean (PC) group.
c. Twenty percent of the PC group had vaginal deliveries.
d. The LTCS group had the highest average gestational age at delivery.

4. Which of the following is correct?
a. The rate of rupture was highest in the LTCS group.
b. The chance of placenta accreta was not affected by the presence of placenta previa.
c. The PMM group had a 0% rate of uterine rupture.
d. The rate of accreta was higher in the LTCS group compared with the PC group.

In Future Issues: **LNG IUS vs Medical Therapy for Heavy Menstrual Bleeding**

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.*

Aspirin Use and Age-Related Macular Degeneration

In this issue: Aspirin use and AMD risk; using NSAIDs and antihypertensive agents; and FDA actions.

Does aspirin cause AMD?

Does regular aspirin use put patients at risk for age-related macular degeneration (AMD)? That is the finding in a highly publicized study from Australia published in *JAMA Internal Medicine* (formerly *Archives of Internal Medicine*). A prospective analysis was conducted from an Australian population-based cohort that included four examinations in 15 years as well as questionnaires regarding aspirin use. Of the 2389 participants with follow-up available, 257 (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular (wet) AMD. Regular aspirin users were more likely to develop neovascular AMD: The 15-year cumulative incidence was 9.3% in aspirin users and 3.7% in non-users. After adjustment for age and multiple cardiovascular risk factors, regular users of aspirin had an odds ratio of neovascular AMD of 2.46 (95% confidence interval [CI], 1.25-4.83). The association showed a dose response effect, with daily users at higher risk. Aspirin was not associated with geographic atrophy (dry AMD). The authors conclude that "regular aspirin use is associated with increased risk of incident neovascular AMD independent of a history of cardiovascular disease and smoking." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.1583). A related editorial points out that age-related AMD is the leading cause of blindness in Western countries, and this study suggests that regular aspirin is associated with an approximate 2.5-fold greater risk in incident AMD. The study is not a randomized trial, and although there is some biological plausibility in the association between aspirin use and development of AMD, this study is "not sufficiently robust to be clinically directive." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.2530.) The take-home message for now is that for patients who are likely to benefit from aspirin (secondary prevention of cardiovascular disease), practice should not change. However, for those patients who take aspirin for indications that are less compelling, we may want to rethink the recommendation until good trials on the relationship between aspirin use and AMD can be assessed. ■

NSAIDs and antihypertensive agents

Mixing certain antihypertensive agents with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal failure, according to a new study. In a retrospective cohort study of nearly 500,000 users of antihypertensive drugs in the United Kingdom, rate ratios of acute kidney injury associated with current use of certain antihypertensive agents with NSAIDs were assessed. After a mean follow-up of 5.9 years, 2215 cases of acute kidney injury were identified. Overall, current use of a single antihypertensive (either diuretics, angiotensin-converting enzyme inhibi-

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tors [ACEIs], or angiotensin receptor blockers [ARBs]), along with an NSAID was not associated with increased rate of acute injury. However, combining a diuretic with either an ACEI or ARB along with an NSAID increased the rate of acute kidney injury significantly (rate ratio 1.31, 95% CI, 1.12-1.53). This 31% increased risk of acute kidney injury was driven by a nearly two-fold increased risk in the first 30 days of use. The authors conclude that triple therapy consisting of diuretics with an ACEI or ARB along with an NSAID was associated with an increased risk of acute kidney injury, especially at the start of treatment (*BMJ* published online January 8, 2013. doi.org/10.1136/bmj.e8713). ■

FDA actions

An advisory committee to the FDA has recommended moving hydrocodone/acetaminophen (Vicodin, Norco) from schedule III to schedule II later this year. The move would put the drug in the same category as morphine and oxycontin, and would require a handwritten, tamper-proof prescription for every prescription and refill. Vicodin — the most widely prescribed drug in this country — is at the center of the controversy regarding prescription drug abuse, which has become "epidemic" in this country, according to the CDC. The United States consumes 99% of all the hydrocodone produced worldwide, and deaths attributable to prescription opioid abuse skyrocketed in the last 2 years, outpacing deaths from illegal opioid drugs, including heroin. The move is supported by some advocacy groups, including an endorsement by the American Academy of Pain Medicine, but not by others. Some physicians are concerned that the schedule change will be a major inconvenience for legitimate pain patients and their physicians, who will be required to write a tamper-proof prescription for each refill of the drug.

The FDA has approved an over-the-counter version of topical oxybutynin for the treatment of overactive bladder in women ages 18 and older. The approval is for women only, with oxybutynin available to men by prescription only. The anticholinergic drug has been used for years by prescription for this indication. In studies of more than 5000 subjects, it was determined that consumers can understand the labeling and "properly select whether the product is right for them." Merck will market the product as a patch that is replaced every 4 days under the trade name Oxytrol for Women.

The FDA has lowered the recommended doses for zolpidem (Ambien) for women. The agency based its recommendation on findings that the popular insomnia drug might impair alertness the next morning if taken at recommended doses. The recommendation is also based on findings that zolpidem stays in the body longer than previously thought, especially in women who process the drug somewhat slower. The new recommended maximal dose for women has been lowered from 10 mg to 5 mg for the immediate-release product, and from 12.5 mg to 6.25 mg for the extended-release (Ambien CR). The FDA further recommends that zolpidem and all insomnia drugs should be used at the lowest dose needed to treat symptoms in both men and woman.

The FDA has approved alogliptin for the treatment of type 2 diabetes. The drug is the fourth dipeptidyl peptidase-4 inhibitor after sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Takeda Pharmaceuticals has been seeking approval for more than 5 years, dealing with the FDA's tighter standards for new diabetes drugs. The approval was based on 14 trials involving about 8500 patients as well as five ongoing postmarketing trials. The agency also approved two additional combinations of alogliptin with metformin and pioglitazone. Alogliptin alone will be marketed as Nesina, alogliptin/metformin will be marketed as Kazano, and alogliptin/pioglitazone will be marketed as Oseni. Both combination products carry boxed warnings (for lactic acidosis associated with metformin and heart failure associated with pioglitazone). All three are distributed by Takeda Pharmaceuticals.

Johnson & Johnson is one step closer to approval of canagliflozin, the first of a new type of diabetes drug. The Endocrionologic and Metabolic Drugs Advisory Committee voted 10 to 5 in favor of approving the drug while still expressing some concern about the cardiovascular safety of the agent. Canagliflozin is an oral inhibitor of the sodium glucose cotransporter 2 (SGLT2) that reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion with a consequent lowering of plasma glucose levels as well as weight loss. If eventually approved by the FDA, it would be the first SGLT2 inhibitor on the U.S. market. The FDA denied a similar drug 1 year ago (dapagliflozin) because of increased risk of bladder and breast cancer. The favorable vote was based on clinical trials of more than 10,000 patients worldwide which showed that the drug improves blood sugar levels and led to modest weight loss as well as reduction in blood pressure. ■