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INSIDE

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VTE Prophylaxis in Gynecologic Surgery: Quo Vadis?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Venous thromboembolism (VTE) prophylaxis interventions in gynecologic surgery are meritorious, supported by Level 1 evidence and the subject of multiple guidelines, including those published by the American College of Obstetricians and Gynecologists. However, new evidence suggests nearly one-third of women undergoing hysterectomy in this country still receive no VTE prophylaxis, placing thousands of women at unnecessary risk for preventable morbidity.*

Source: Wright JD, et al. Quality of perioperative venous thromboembolism prophylaxis in gynecologic surgery. *Obstet Gynecol* 2011;118:978-986.

THE OBJECTIVE OF THIS STUDY WAS TO ESTIMATE THE USE OF VTE PROphylaxis in women undergoing major gynecologic surgery and to estimate the patient, physician, and hospital characteristics associated with their use. To examine these factors, a validated and regularly audited national commercial database (Perspective®) of inpatient hospital admissions was interrogated for VTE prophylaxis use over an 11-year period (2000 to 2010). VTE prophylaxis was classified as none, mechanical, pharmacologic, or a combination. A total of 738,150 women who underwent major gynecologic surgery were identified. In this study, only abdominal or vaginal hysterectomy with or without salpingo-oophorectomy for benign disease were included. In addition, laparoscopic/robotic procedures were excluded. No prophylaxis was given to 292,034 (40%) women, whereas 344,068 (47%) received mechanical prophylaxis, 40,268 (6%) pharmacologic prophylaxis, and 61,780 (8%) combination prophylaxis. VTE prophylaxis use increased from 54% to 68% over the observation period and was more com-

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monly used in older women, those with Medicare and more comorbidities, Caucasian women, patients treated at rural hospitals, patients treated at teaching facilities, and patients treated by high-volume surgeons and at high-volume centers. Factors associated with use of pharmacologic prophylaxis included advanced age, white race, noncommercial insurance, later year of diagnosis, greater comorbidity, treatment at large hospitals and urban facilities, and treatment by a high-volume surgeon. The survey data highlight that VTE prophylaxis use is substantially underutilized in women undergoing major gynecological surgery, despite clear recommendations from evidence-based guidelines. Hospital, physician, and patient factors influence use.

■ COMMENTARY

There are many things in surgery we can't control: age, preexisting anatomy, preexisting comorbidities, characteristics of disease, and patient compliance, just to name a few. However, there are those factors under our control that should be as automatic as getting informed consent. VTE prophylaxis is one of them! For more than 35 years, Level 1 evidence from randomized clinical trials has clearly demonstrated, in nearly every surgical discipline (including 15 randomized trials in gynecology/gynecologic oncology), that fatal VTE can be prevented by intervention.[1] Initially, unfractionated heparin given before and after surgery was advocated, but concerns for intraoperative and postoperative bleeding ushered in evaluation of alternative pharmacological agents and mechanical devices, such as graded compression stockings and intermittent pneumatic compression devices.[2,3] In addition, risk stratification of patients and procedures (types and lengths) where VTE prophylaxis might be optimized led to well-publicized guidelines in gynecologic surgery by American College of Obstetricians and Gynecologists and the American College of Chest Physicians.[4] With this proviso, it is hard to imagine that in 2010, nearly a third of patients undergoing major gynecologic surgery still were not given any form of VTE prophylaxis.

A second paper in this issue of *Obstetrics & Gynecology* suggests the quality of data among benign gynecology cohorts in their meta-analysis is not as strong as in others (e.g., oncology patients) and opines that the guidelines are viewed with tepid regard.[5] Nevertheless, it is estimated that VTE occurs in up to 3% of patients following benign gynecologic procedures, which translates into hundreds of preventable cases every year. In the current study, it was reassuring that the proportion has significantly increased in the last decade, and that it is practiced more often in urban training centers with high-volume surgeons and hospitals, as this holds promise that the practice will continue to increase as more residents and operating room staff trainees are exposed to Best Practices and Quality Improvement projects around this topic. Data like these are hard to come by, and as with any voluntary national registry, true compliance with guidelines (dose, duration, and timing of pharmacological prophylaxis and patient compliance with compression devices) is difficult to adjudicate. However, this should serve as a wake-up call to review the guidelines and our compliance in order to provide the best care to our patients. ■

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Oligohydramnios: A Reason to Deliver?

ABTRACT & 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 suggested that intervening in isolated oligohydramnios between 35 and 37 weeks is associated with higher rates of inductions, cesarean sections, and preterm birth as compared with expectant management.*

Source: Melamed N, et al. Perinatal outcome in pregnancies complicated by isolated oligohydramnios before 37 weeks. *Am J Obstet Gynecol* 2011;205:241.e1-241.e6.

In an otherwise normal preterm pregnancy, is oligohydramnios a reason to deliver? This question has popped up repeatedly, and an article in the September issue of the *American Journal of Obstetrics and Gynecology* addressed this conundrum.

In a retrospective study,[1] the authors reviewed data from 1996 through 2007 involving patients who had ultrasound evaluations prior to 36 weeks of gestation. Of the 21,718 patients reviewed, 980 (4.5%) were noted to have oligohydramnios (amniotic fluid index [AFI] < 5 cm). Of these, 108 (10.9%) were judged to be "isolated." Each of these patients was compared with three controls who had normal AFIs and were matched for gestational age. The isolated oligohydramnios group then was subdivided into those having intervention vs those having expectant management.

The average age at the time the oligohydramnios was found was 32 weeks in both oligohydramnios groups. In the intervention group, the average gestational age of delivery was 36 weeks vs 38.9 weeks in the expected management group. There were no differences between oligohydramnios and controls regarding the incidence of preeclampsia or intrauterine growth restriction (IUGR), and there were no cases of intrauterine demise in either group. In 10% of the oligohydramnios group, the AFI reverted to normal. In the oligohydramnios group, there was a significantly higher rate of preterm birth (26.9% vs 12.3%), induction of labor (50% vs 5.6%), induction failure (33% vs 6.4%), and cesarean birth (47.2% vs 16.9%). Not surprisingly, there was a higher rate of combined neonatal morbidity.

Interestingly, when comparing the intervention group to the expectant management group, the authors found that the intervention group (78) had higher rates of every morbid outcome (as listed above) compared to the expectant management group (30). Although there was a lower mean birth weight and a higher rate of meconium-stained amniotic fluid in the expectantly managed group, the overall rate of neonatal morbidity was the same as controls.

The authors concluded that "adverse pregnancy outcome in cases of isolated oligohydramnios diagnosed prior to 37 weeks appears to be related to a considerable degree of iatrogenic prematurity."

■ COMMENTARY

Oligohydramnios, in general, is definitely associated with adverse outcome, mostly because it is a byproduct of conditions which, of themselves, are responsible for the adverse fallout. In IUGR, oligohydramnios results mainly from the fetus sparing his/her brain at the expense of renal plasma flow. Fetal surveillance today is so much more sophisticated with regard to the fetal circulation that an indirect assessment of amniotic fluid volume has taken on much less importance as an indicator of when to deliver a given patient. In rupture of membranes, oligohydramnios is the rule, but we use other parameters to dictate when to intervene. In renal abnormalities, such as lower urinary tract obstruction, the presence of oligohydramnios only tells us that there is an impediment to urinary flow. Oligohydramnios is simply an accompaniment to a possible problem, but certainly is not the culprit itself. When it is isolated, it is not necessarily associated with anything adverse, and may even be only a fleeting finding (as it was in 10% in the above study). This is not surprising since amniotic fluid volume varies on a day-to-day basis.

A study by Zhang et al had similar results.[2] The authors focused on 113 women with isolated oligohydramnios, and found no difference in outcomes between these women and those with normal amniotic fluid volumes.

Also, oligohydramnios may be overdiagnosed depending on how it is defined. Magann et al found that in high-risk patients having biophysical profiles, the rate of oligohydramnios differed depending if AFI (38%) vs largest single vertical pocket (16%) was used.[3] This translated into a 30% vs 15% rate of induction, and a cesarean section rate of 13% vs 7%, respectively, with no difference in outcomes. Based on this information, many providers have abandoned the AFI in favor of the largest single vertical pocket method.

I chose this article to discuss because of a statement made in a Society for Maternal-Fetal Medicine mini-debate, published in the same issue of the *American Journal of Obstetrics and Gynecology*.[4] The debate focused on whether isolated oligohydramnios is reason alone to

deliver patients between 34 and 37 weeks. The author, who was assigned to take the proactive stance in isolated oligohydramnios, wrote that "*currently adverse outcome with expectant management is indefensible and a potential source of litigation*." This warning was issued in spite of the above article in the same journal and the author's acknowledgement that "**there are no current ACOG Practice Bulletins on this topic** or no RCTs."

I would argue that invoking the threat of a lawsuit is not enough to justify blanket intervention in patients with isolated oligohydramnios, especially given the recently well-publicized association between late preterm birth and increased rates of cesarean section and neonatal morbidity.[5] Today's nuanced forms of monitoring should allow us to identify those fetuses in this gestational age range that need to be delivered, and, just as importantly, which fetuses might benefit from being left alone. ■

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Which Is Better: Open, Laparoscopic, or Robotic? How Meaningful Is This Question?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

Synopsis: *This commentary challenges the urologic medical community to get past its "collective obsession with technology" and try to figure out why some surgeons have better outcomes, irrespective of the surgical approach taken.*

Source: Vickers AJ. Great meaningless questions in urology: Which is better, open, laparoscopic, or robotic radical prostatectomy? *Urology* 2011;77:1025-1026.

THE AUTHOR INFORMS US THAT THE WINNER OF THE 2010 Tour de France was Alberto Contador, riding a Specialized SL3 racing bike. The U.S. rider Chris Horner finished 12 minutes behind riding a Trek, Madone. The best rookie finisher, Daniel Loyd, rode a Cervelo S3, and finished more than 4 hours behind the leaders. The author opines that "no self-respecting urologist" would use this information to claim that the Trek is a faster bike than the Cervelo or that Loyd would have won the race had he ridden a Specialized.

The reader also is told that surgical complication rates among high-volume surgeons who perform radical prostatectomies range from < 5% to > 50%. He also cites in one study that functional outcomes differ by up to 40% with regard to erectile and urinary function. The author points out that the difference between surgeons and their performance dwarfs the inherent differences of the surgical approach. As in the Tour de France, where the focus should not be the bicycle, in urology, the focus should not be on the surgical approach when performing radical prostatectomies.

Comparative publications analyzing complications and success rates are unable to control for pathologists' skills, patient population characteristics, and/or definitions of "success" or "complication." He compares this to asking the three cyclists to go on a 100-mile ride, with the best bike being the one ridden by the first person to get to the finish line, irrespective of the route taken, weather, etc.

The analogy is carried further: The cycle judged to be the best cannot be the one that finishes first because of variables such as the experience of the rider. As with cycling, a skilled, experienced surgeon is different from a novice surgeon, and both are different from the "average" surgeon. In fact, the term "average" raises the statistical issue of results. Vickers points out that depending on how the results are collected and reported, surgical outcomes numerically may look similar, but, as far as patient outcome is concerned, may be very different.

The author concludes that Lance Armstrong said, "It's not about the bike." He asserts that some urologists seem to be saying, "No, but it is all about the robot." Studying how to get the best results should be the goal, but this will require "…far greater investment of time, resources, and scientific ingenuity than retrospective analyses of surgical databases."

■ **COMMENTARY**

Admittedly, you probably don't get this journal. Even if you did, you probably wouldn't think of this article (it's an opinion piece, not a research study) as something worth reading or reviewing since it's about radical prostatectomy. Forget the fact that none of us perform the procedure. When's the last time any of us even discussed the prostate with our patients? So why are you being asked to read about it? It's because if you squint your eyes a little, and allow the words to morph a bit, suddenly you're seeing someone discussing open, laparoscopic, or robotic hysterectomy, oophorectomy, lysis of adhesions, incontinence surgery, prolapse surgery, cancer surgery, etc. We're being challenged by the author, and he doesn't even know he's doing it! He suggests that urologists as a group get past its "obsession with technology" and try to identify factors that lead to some surgeons getting better results than others, irrespective of the surgical approach used.

Let's relate what the urologists are facing and compare the issues with our field.

First, I like that the author is a PhD in the Department of Epidemiology and Biostatistics at Memorial Sloan-Kettering Cancer Center. He isn't someone who does any of these procedures. In essence, there is less chance that he has a bias regarding one procedure or another. He also is unlikely to have a conflict of interest relating to an instrument company or another product being used during the surgery. We should be watchful for who is writing the articles that we read, particularly when it's involving surgical approaches and technique. Does someone have an axe to grind?

Second, I love the analogy. It makes sense and gives us a fresh perspective on how we look at surgical literature. Their issues of radical prostatectomy are similar to ours related to benign, malignant, and urogynecologic procedures. Unless you actually believe that one of the "cycles" is better than others, you can see how we, as gynecologic surgeons, need to focus on our patients and how to get them the best results.

Third, what defines "success?" In the case of radical prostatectomy, the urologists are trying to avoid recurrence and maintain intact sexual and urinary function. As our gynecologic oncologists look at endometrial and ovarian cancers, they similarly are looking at recurrence, but also at areas in which benign surgeons focus a lot of attention. When we perform benign surgery, is our goal a shortened convalescence? Shorter anesthesia time? Greater patient satisfaction? Improved cosmesis? Fewer complications? Greater physician satisfaction? Can our urogynecologists define success for sacral colpopexy as any case that doesn't require a laparotomy? What about a 5-year success rate? What would the world class cyclists define as "successful?"

Fourth, aren't there factors in the equation beyond just the surgeon's decision-making and skills? What about the patient who has done her "research" and knows the surgical approach that she feels is appropriate for her case? What about the role of the hospital and its administration who may be publicly extolling the virtues of a newly acquired (and very expensive) piece of equipment? How long a learning curve for new technology is acceptable? Is it the same for everyone? In order for a surgeon to gain needed experience, how long is it reasonable for patients who might not need the new technology to be treated with it?

Finally, you might notice that the cyclist wears a jersey boldly displaying the sponsor's name. I don't think any of us has seen any surgeons with similar commercialized garb entering the operating room (I know I haven't…have you?). Whether the influence of industry on us is subtle or overt, each of us is responsible for being as candid as possible with our patients regarding all surgical approach options … including no surgery at all. Informed consent requires that of us. We should expect that of ourselves. We should expect that of each other. Until definitive information is available (and, honestly, we may never get it), overzealous rushing to a new technology is probably no worse than an unswerving aversion to it.

I'm taking us far beyond our usual comfort zone by literally stealing the thrust of this thoughtful piece of writing in the urology literature and asking us as purveyors of women's health care to do the same: Let's get past our fascination with the latest technology and try to determine how to best serve our patients by getting the best outcomes. Sometimes newer is, indeed, better. Sometimes, it isn't. ■

Special Feature

Do We Have a Problem? Obesity and Contraception

By Alison Edelman MD, MPH

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Dr. Edelman reports that she is a subdermal implant trainer for Merck.

As U.S. waistlines continue to grow, so does the concern regarding obesity's effects on health and health care.[1-2] Our country is also battling epidemic levels of unplanned pregnancies — approximately 50% of all pregnancies.[3] If an interaction exists between the two, this could constitute a significant public health issue. Obesity is known to increase the morbidity and mortality of

pregnancy outcomes and maternal health,[4,5] but maternal obesity also has a long-term negative impact on the future health of any offspring — with higher rates of obesity, hypertension, and diabetes.[6-8] The ability to avoid, plan, or space pregnancies through the use of contraception is an important tool for women with chronic medical problems like obesity. However, what do we know about the effectiveness or safety of contraceptives in obese women?

Is Contraception Less Effective in Obese Women?

In 2001, a retrospective cohort study sounded the alarm that obesity might adversely affect contraceptive effectiveness, with obese users being at increased risk for failure.[9] A follow-up prospective cohort study from the same authors confirmed these findings.[10] However, cohort studies do not prove causality or mechanism of action. Is it plausible that contraception might not work as well in obese women? For a contraceptive method to be less effective, one or more components of the following equation needs to be impaired:

$$\frac{\text{Inherent drug efficacy} + \text{compliance} + \text{continuation}}{\text{Fecundity} + \text{coital frequency}} = \text{Effectiveness}$$

Although much speculation has been made regarding the possible socio-behavioral differences between women of obese and normal BMI,[11] to date no differences in drug compliance or continuation and/or coital frequency have been found. Granted all of these indices can be difficult to study and to track and may vary for different populations or age groups (i.e., teens).[12,13] Recently, a study suggested that obese women might be less compliant with birth control pills based on testing drug trough levels.[14] Obesity was strongly associated with a lower socioeconomic status, making it unclear which characteristic actually might impact compliance. Drug levels are known to be lower in obese women; perhaps the trough levels were too low to accurately detect.[15,16] The final piece of the equation before we move on to inherent drug efficacy is fecundity. Fecundity can be affected by extremes of weight but the majority of women, whether of obese or normal BMI, are able to get pregnant.[17]

The mechanism of action for contraceptive methods like sterilization, intrauterine devices (IUDs), and barrier methods is mostly mechanical or local in nature and thus should be unaffected by body weight.[18] The one caveat is that procedure-based contraceptive methods like sterilization and IUDs may be more difficult for the operator to complete or place.[18] As these two methods are highly effective, failure to complete a sterilization procedure or place an IUD would relegate a woman to a contraceptive method with known lower efficacy.

Hormonal contraceptive methods, on the other hand, all rely on the achievement of a certain threshold effect on the hypothalamic-pituitary-ovarian axis, endometrium, and cervix to provide contraception. Currently all of our hormonally based contraceptive agents are "one-size-fits-all."[17] The amount and level of suppression is based largely on the progestin component and is dose dependent. For example, lower dosed agents like the progestin-only pill cause endometrial thinning and thickening of the cervical mucus but not inhibition of ovulation, whereas a higher dose agent like the medroxyprogesterone acetate injection does all three. Can we expect the same for our obese patients? Unfortunately, hormonal contraception was never studied in women above 130% of ideal body weight,[18] which unfortunately is now 30-60% of our population, and the incidence of BMIs > 35 kg/m^2 appears to be growing.[1,2]

To determine if the efficacy of hormonal contraceptive methods are impaired in obese women, pregnancy would be the best outcome to examine. Although pregnancy is a discrete outcome on which to focus, it is hard to study because large numbers of women are needed. There are no published studies with significant numbers of obese women for hormonal contraceptive methods like pills/patch/ring, the medroxyprogesterone acetate injection, or the etonorgestrel subdermal implant.[19-28] The only FDA packaging that lists weight (90 kg or higher) as a potential factor for decreased efficacy is the contraceptive patch; however, the patch studies actually showed increasing pregnancies in women who weighed $\geq$ 74 kg.[20] These studies were not powered (i.e., sample size too small) to determine if the increased failure rate was true or just a random occurrence.

Secondary measures, such as drug levels or pharmacokinetics, do appear to be different in obese women as compared to women of normal BMI, but it is unknown if this correlates with increased contraceptive failure rates. The most concerning finding is that with a new start or following a traditional 7-day placebo week, it takes twice as long to reach a drug's steady state level in an obese woman (10 days) compared to a woman with a normal BMI (5 days).[15] A drug's steady state level typically is higher than the threshold level to obtain contraceptive effect, but that does not change the fact that it would take twice as long to get there. Even for normal BMI women, prolonging the placebo week appears to be the worst time to miss pills, placing a woman at greatest risk for contraceptive failure. A recent large postmarketing study based in Europe and the United States also demonstrates lower failure rates in pills with a shorter placebo week (3 days) vs the traditional 7 days.[29] One could easily make the leap that for any woman whether of obese or normal BMI that a shorter or no placebo week decreases contraceptive failures.

So where does this leave us? We may not have the exact answer to the question "does obesity influence contra-

ceptive effectiveness," but I argue that we can still counsel women no matter what their weight in the same way:

1. Offer the most effective options first — long-acting reversible methods or permanent contraception for those finished with childbearing.

2. Consider shortening the placebo week for the pill/patch/ring or even eliminating the placebo week in the pill/ring (most experts agree that they would not recommend eliminating the placebo week for the patch).

3. The use of contraception prevents more pregnancies than the use of no contraception.

Is Contraception Safe in Obese Women?

Perspective is always important when discussing risks. For contraceptive use, the "perspective" is pregnancy. The risks of pregnancy and the postpartum almost always trump the risk of contraceptive use in a woman with almost any chronic medical problem including obesity. This does not mean that contraceptive use is without risk, but the risk of contraceptive use is significantly lower compared to pregnancy and especially the postpartum state. Yet many clinicians have difficulty with this comparison since we play an active role when prescribing a contraceptive method, which places some of the "burden of risk" upon us (i.e., liability concerns); whereas pregnancy is a "natural" process where the "burden of risk" falls completely on the patient. This may be short-sighted, as a high-risk pregnancy places an even greater magnitude of risk upon us, the patient, her family, and the system.

Luckily, we now have evidence-based guidelines through the Centers for Disease Control (CDC). These guidelines will be regularly updated providing help in risk stratifying our patients with chronic illness like obesity.[30] The CDC guidelines categorize risk into four subgroups: category 1 (no restrictions for use), category 2 (advantages of use generally outweigh risk), category 3 (the risks usually outweigh the advantages), category 4 (unacceptable health risk). Since the obese are at increased risk of thromboembolic events at baseline, contraceptive use adds an additional risk that must be considered. For a healthy obese woman with no other cardiovascular risk factors, the CDC medical eligibility criteria for contraceptive use rates all methods of contraception a category 1 except for combined hormonal methods (pills/patch/ring), which get a category 2.[30] A large federally sponsored review of female sterilization procedures also found that there were slightly higher complication rates for obese women undergoing sterilization procedures as compared to a normal BMI woman — mostly wound infections.[31] This review only addressed sterilization procedures performed via an abdominal approach. It is unknown if complications are higher with transcervical sterilizations in an obese patient.[32]

And just to come full circle and get back to perspective, studies show that the risk of venous thromboembolism (VTE) in an obese woman on combined oral contraceptives appears similar to the risk of VTE in a pregnant woman of normal BMI.[18] Although your counseling of risk might change slightly with an obese vs a normal BMI patient who is otherwise healthy, your options of what to offer her for contraception should not. ■

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CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

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

CME Questions

1. Which of the following procedures were included in the DVT prophylaxis study by Wright et al?
   a. Ovarian cancer debulking with hysterectomy
   b. Laparoscopic assisted vaginal hysterectomy
   c. Vaginal hysterectomy with bilateral salpingo-oophorectomy
   d. Abdominal hysterectomy and lymphadenectomy for uterine cancer

2. Which of the following was *not* found to be more common in patients with oligohydramnios (vs controls)?
   a. Higher rate of inductions
   b. Higher rate of cesarean sections
   c. Higher rate of preterm birth
   d. A lower rate of neonatal morbidity

3. Which of the following is most appropriate regarding existing information on isolated oligohydramnios?
   a. Randomized controlled trials have had mixed results.
   b. ACOG has come out strongly for intervening.
   c. In about 10% of cases, oligohydramnios will give way to a normal amniotic fluid volume.
   d. AFIs under-call oligohydramnios, compared with single vertical pocket methods.

4. Combined oral contraceptives are contraindicated in an obese woman.
   a. True
   b. False

5. Shortening the placebo week appears to decrease the failure rate of combined oral contraceptives.
   a. True
   b. False

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.*

HPV Vaccine Now Recommended for Males

In this issue: New recommendations for HPV vaccine; guidelines for treatment of essential tremor; updates on smoking cessation drugs; and FDA actions.

HPV vaccine and anal cancer risk

The human papillomavirus (HPV) vaccine is routinely administered to adolescent girls; now the CDC's Advisory Committee on Immunization Practices is recommending the vaccine for 11- and 12-year-old boys as well. The vaccine has been approved for use in both adolescent girls and boys to protect them against HPV but has been somewhat underutilized in girls and rarely used in boys. HPV causes genital warts and cervical cancer in women and the vaccine effectively reduces the rate of both. The vaccine is generally recommended for 11 and 12 year olds when they get other routine vaccines, and before they become sexually active. Although the vaccine is approved for boys, the CDC had not made a recommendation on routine use until now. After evaluating data on efficacy in males, the committee felt that the vaccine could protect boys against genital warts, as well as throat and anal cancer caused by HPV, and could help prevent spread of the virus to girls.

In related news, a new study shows the HPV vaccine is effective in preventing anal intraepithelial neoplasia in men who have sex with men. In a double-blind study of 602 men (ages 16-26) who have sex with men, half were randomized to the quadravalent HPV vaccine and half to placebo. The vaccine reduced the risk of anal intraepithelial neoplasia caused by the four subgroups of HPV covered by the vaccine (HPV-6, 11, 16, and 18) by half in the intention-to-treat population and by 77% in the per-protocol population. Anal intraepithelial neoplasia caused by HPV of any type was reduced by 25.7% and 54.9%, respectively. Rates of anal intraepithelial neoplasia per 100 person years were 17.5 in the placebo group and 13 in the vaccine group in the intention-to-treat, and 8.9% placebo vs 4.0% vaccine in the per-protocol population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to HPV subtypes covered by the vaccine was reduced by 54.2% (intention-to-treat) and 74.9% (per-protocol). The vaccine was well tolerated. The authors conclude that the HPV vaccine reduced the rate of anal intraepithelial neoplasia in men who have sex with men and may help reduce the risk of anal cancer (*N Engl J Med* 2011;365:1576-1585). ■

Treatment of essential tremor

The American Academy of Neurology has published its updated guideline for the treatment of essential tremor. Propranolol and primidone remain first options with a Level A recommendation (established as effective). Alprazolam, atenolol, gabapentin as monotherapy, sotalol, and topiramate are graded as Level B (probably effective), while nadolol, nimodipine, clonazepam, botulinum toxin a, deep brain stimulation, and thalamotomy remain as level C (possibly effective). There is not enough evidence to make a recommendation for gamma knife therapy. The new guideline also states that there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozipine. Levetiracetam and 3,4 diaminopyridine are ineffective and flunari-

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zine is probably ineffective. The guideline was published online in *Neurology* October 19, 2011 (doi: 10.1212/WNL.0b013e318236f0fd). ■

Chantix and neuropsychiatric side effects

There is good news for the smoking cessation drug varenicline (Chantix). Following concern about neuropsychiatric side effects, the FDA sponsored two epidemiologic studies that evaluated the risk of neuropsychiatric hospitalizations associated with the drug. Neither study found a difference in risk of neuropsychiatric hospitalization between varenicline and nicotine replacement therapy, although hospitalization was the only endpoint evaluated and they did not rule out an increased risk of other neuropsychiatric events. While reassuring, the FDA is recommending that health care professionals and patients continue to follow the recommendations previously established and monitor for neuropsychiatric symptoms when prescribing or using varenicline. The manufacturer is conducting a large safety study of the drug to assess neuropsychiatric adverse effects but the results will not be available until 2017 (www.fda.gov/Drugs/DrugSafety/). In related news, the inexpensive partial nicotine agonist cytisine is an effective adjunct to smoking cessation, according to a new study in the *New England Journal of Medicine*. Cytisine is extracted from the seeds of *Cysisus laborinum L.* (Golden Rain acacia) and has been available worldwide for years, particularly in Eastern Europe, where it can be purchased for $6-$15 per course. Researchers randomized 740 smokers to cytisine or matching placebo for 25 days along with counseling. The rate of sustained 12 months abstinence was 8.4% in the cytisine group compared with 2.4% in the placebo group ($P = 0.01$). GI side effects were slightly more prevalent in the treatment group. The authors conclude that cytisine was more effective than placebo for smoking cessation and may be "an affordable treatment to advance smoking cessation globally" (*N Engl J Med* 2011;365:1193-1200). ■

FDA Actions

The FDA is continuing to review the association of oral contraceptives and thrombotic risk, particularly oral contraceptives containing drospirenone. On October 27, the FDA issued a preliminary Drug Safety Communication, with the full report due out in early December. Reviewing the records of Kaiser Permanente members in California and state Medicaid programs in Tennessee and Washington, which included 835,826 women receiving contraceptive prescriptions from 2001-2007, an increased risk of venous thromboembolism (VTE), deep venous thrombosis, and pulmonary embolism was noted with several contraceptives, with low estrogen hormonal contraceptives as a reference. Products containing drospirenone had relative risk of VTE of 1.74 (95% confidence interval [CI] 1.42-2.14). The norelgestromin/ethinyl estradiol transdermal patch was associated with relative risk of 1.55 (95% CI 1.17-2.07) and etonogestrel/estradiol vaginal ring was associated with a relative risk of 1.56 (95% CI 1.02-2.37). The risk was higher in younger users then older women (www.FDA.gov./DRUGS/DrugSafety/ucm277346.htm).

The FDA has approved the first generic olanzapine (Zyprexa) to treat schizophrenia and bipolar disorder. The generic carries the same warnings as the brand regarding increased risk of death in elderly people with psychosis or dementia. Generic olanzapine will be available from several manufacturers as tablets and orally disintegrating tabs.

The FDA has announced that drotrecogin alfa (Xigris) is being withdrawn from the market by Eli Lilly & Co. The withdrawal is based on the results of the recently completed PROWESS-SHOCK trial in which drotrecogin alfa failed to show a survival benefit in patients with severe sepsis and septic shock. The FDA is recommending that the drug should be stopped in any patients currently being treated and should not be initiated in new patients. All remaining product should be returned to the supplier.

The FDA has approved tadalafil (Cialis) for the treatment of benign prostatic hyperplasia (BPH) either alone or when it occurs along with erectile dysfunction (ED). The drug was approved in 2003 for treatment of ED. The approval was based on two trials in which men taking tadalafil 5 mg daily experienced significant improvements in BPH symptoms compared with those taking placebo. A third study in which men had both BPH and ED, tadalafil 5 mg daily improved both symptoms of BPH and ED compared to placebo. Tadalafil should not be used in patients taking nitrates or in combination with alpha blockers for the treatment of BPH.

The FDA has approved a combination of sitagliptin and simvastatin for the treatment of adults with type 2 diabetes and hypercholesterolemia. This represents the first combination drug for treating these two conditions. The fixed dose combination is available in three strengths: 100 mg sitagliptin/10 mg simvastatin, 100 mg/20 mg, and 100 mg/40 mg. The approval was based on "substantial experience with both sitagliptin and simvastatin" and is a "convenience combination," according to the FDA. Sitagliptin/simvastatin will be marketed as Juvisync by MSD International GmbH Clonmel in Tipperary, Ireland. ■