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INSIDE

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Is Prescribing Bed Rest Unethical?

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora

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

Synopsis: *A recent multicenter study has shown that restricted activity not only does not decrease the rate of preterm birth in nulliparous patients with cervical length < 3 cm, but it can actually double this risk.*

Source: Grobman WA, et al. Activity restriction among women with a short cervix. *Obstet Gynecol* 2013;121:1181-1186.

Bed rest is still frequently prescribed to prevent or treat various conditions in pregnancy. Yet, since it is intrusive and costly, the practice is periodically challenged. A recent paper provides some compelling data on the effect of "restricted activity" to prevent preterm birth in nulliparas with short cervices.[1]

Authors from the NICHD Maternal-Fetal Medicine Units Network recently published a study evaluating the efficacy of 17 alpha-OH progesterone caproate (17P) in preventing preterm birth in nulliparas with short cervices (< 3 cm) found with ultrasound in the second trimester.[2] In this study, data were available for secondary analysis on 646 of these patients regarding to what extent, if any, activity was restricted. These patients were classified according to whether they were put on "pelvic rest" (no intercourse) or work- or non-work-related restrictions. The decision to restrict activity was at the discretion of the managing providers. The primary outcomes analyzed were birth prior to 34 weeks and prior to 37 weeks.

Interestingly, 252 patients (39%) with short cervices had some form of restriction applied. These women were more apt to be older, to have private insurance, and to be non-white Hispanics. Also, there was a greater

tendency for these women to have shorter cervices and funneling. Before applying methods to account for the above confounding variables, the overall rate of preterm birth at < 37 weeks in "the resters" was 37% vs 17% and the "non-resters" (odds ratio [OR], 2.91; 95% confidence interval [CI]; 2.0-4.21). After controlling for age and confounding demographic, social, and cervical findings, there still was a significant difference between groups (OR, 2.37; 95% CI, 1.60-3.53). When using preterm birth < 34 weeks as a dependent variable, again, there were significant differences between the two groups (OR, 2.28; 95% CI, 1.36-3.80).

■ COMMENTARY

It is a rare clinician who has not recommended restricted activity for some obstetrical condition like preterm labor or hypertension. In some circumstances, it makes sense to simply "quiet things down." In fact, in a 1994 survey of obstetricians, 98% indicated they had recommended bed rest or decreased activity in some clinical situations,[3] and in a more recent survey, 71% of maternal-fetal medicine physicians said they recommended it after arrested preterm labor, despite most admitting that there was poor evidence to support this practice.[4]

An anticipated response might be "but it might help and it doesn't seem to hurt." Well, in fact, this may not be true. This study shows that it may actually hurt — at least if one were trying to prevent preterm birth. And there is ample evidence that bed rest predisposes patients to thromboembolism and bone demineralization, and it can also negatively affect psychological well being. Additionally, bed rest can significantly impact the financial state of the family. In 1994, Goldenberg et al calculated that the annual cost (to U.S. society) of prescribed antepartum bed rest was approximately $1 billion.[3] In 2013, the inflated cost would likely be more than double that figure.

In a companion article in the same issue of *Obstetrics &Gynecology*, McCall et al[5] reviewed pertinent Cochrane database studies that also showed no benefit from bed rest in the treatment of preterm birth,[6] hypertension,[7] pre-eclampsia,[8] threatened abortion,[9] or multiple gestation.[10] By applying the non-malfeasance vs beneficence (risk/benefit) analysis favored by bioethicists, the authors concluded that it was unethical to prescribe bed rest for the prevention or treatment of any of the above conditions. These authors even stated that "if bed rest is to be used, it should be only within a formal clinical trial."

That should get our attention! ■

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

Over-the-counter Access to Oral Contraceptives

ABSTRACT & COMMENTARY

By Rebecca H. Allen, MD, MPH

Assistant Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI

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

Synopsis: *In this global survey, investigators found that in nearly 70% of countries, oral contraceptives (OCs) are available without a prescription. The United States, Canada, Australia, and most of western Europe require prescriptions for OC use, while OCs are available over-the-counter informally in most of Central and South America and legally over-the-counter in Southern Asia.*

Source: Grindlay K, et al. Prescription requirements and over-the-counter access to oral contraceptives: A global review. *Contraception* 2013;88:91-96.

In this cross-sectional study from April 2011 to September 2012, the investigators collected data on prescription requirements and over-the-counter (OTC) availability of oral contraceptives (OCs) worldwide by distributing an online survey to ministries of health, pharmacy boards, family planning organizations, pharmaceutical companies, and other reproductive health specialists. The survey addressed countries' prescription requirements, health screening requirements for obtaining OCs without a prescription, and the informal commercial availability of OCs. Besides the survey, the authors searched country drug registries and other government websites for official documentation of OC prescription requirements. Countries were assigned to one of four groups: 1) OCs informally available without prescription, 2) OCs legally available without a prescription (no screening required), 3) OCs legally available without a prescription (screening required), and 4) OCs only available with a prescription. Countries were also classified as low to middle income, or high income as defined by the World Bank.

The authors obtained data from 147 countries. In 38% of countries, OCs were available informally without a prescription, and in 24% of countries, OCs were legally available without a prescription. OCs were legally available without a prescription but required health screening in 8% of countries and available only with a prescription in 31% of countries. Eighty-eight percent of the countries where OCs did not require a prescription were low and middle income. In sum, the United States, Canada, Australia, and most of western Europe require prescriptions for OC use, while OCs are available OTC informally in most of Central and South America and legally OTC in Southern Asia.

■ COMMENTARY

In the United States, approximately half of pregnancies are unintended, and 40% of these end in abortion.[1] One contributing factor to the unintended pregnancy rate is lack of access to contraception. Initiating OCs is associated with increased barriers in the United States because women must have access to a health care provider who can provide a prescription. Cost is an additional burden and women must either use existing (but often lacking) prescription insurance coverage or pay out-of-pocket for the prescription. In addition, continuing OCs can be a challenge for women, a factor that impacts the failure rates of oral contraception. Although OCs are highly effective if used perfectly, with failure rates of 0.3% in the first year, typical use is associated with a failure rate of 9%. Although missed pills often contribute to this higher failure rate,[2] another factor may be access to pill refills in order to start the next cycle on time. Studies have shown that running out of pill packs and needing a new prescription are reasons for missed pills.[3,4] Conversely, pill continuation rates are higher and unintended pregnancy rates are lower among women who have easier access to OCs, such as a 12-month prescription as opposed to a 3-month prescription.[5,6]

This survey shows that in the majority of the world, OCs are available without a prescription. Many reproductive health advocates are exploring the option of making oral contraception — either progestin-only or estrogen-progestin combination pills — OTC in the United States. In this way, women will be able to initiate and continue OCs by visiting their local pharmacy, rather than waiting for an appointment and prescription from their health care provider. A pilot project in Washington State using pharmacist provision of oral contraception was found to be feasible and acceptable to women.[7] The American College of Obstetrician Gynecologists recently released a committee opinion endorsing OTC status of OCs.[8] The only concern was the adverse effect that changing to OTC status might have on the cost of OCs for women both with and without insurance.

However, one criterion for OTC status of OCs is safety. The FDA would require that women are able to use the product safely without the supervision of a licensed health care provider. Therefore, women must be able to self-prescribe for appropriate use and self-diagnose for adverse effects and contraindications. While OCs are very safe, there are some contraindications to OC use. Nevertheless, there is good evidence that women can self-screen for

contraindications.[8] The most recent study evaluating this issue compared the proportion of contraindications among women obtaining prescription OCs from a provider and women who obtained OCs from pharmacies in Mexico.[9] The authors found that the proportion of any category 3 or 4 contraindication was 18%. More women in the OTC group had category 3 contraindications (13%) compared to women with prescriptions (9%). However, there was no difference in category 4 contraindications between the two groups (7% OTC vs 5% prescription). The authors concluded that with a self-screening tool and blood pressure measurement, OTC availability of OCs was feasible in the United States. However, they also stated that progestin-only pills, with inherently fewer contraindications, may be a better choice for the first contraceptive to switch to OTC status. In the meantime, it is important that we make OCs more available to women who are candidates for their use. For example, I try to give patients a 1-year prescription for OCs. In addition, when I am called to refill prescriptions for patients, I tend to allow refills, even if the patient has not been seen by our clinic for more than a year. Although we try to encourage women to present for annual gynecologic exams, we do not withhold pill refills if they are not able to present in a timely fashion. ■

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PAP 3.0 – The Next Generation

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *A new technique of evaluating liquid-based Pap smears has been developed to identify confirmed disease-specific mutations in patients with uterine and ovarian cancers. The new technique identified most uterine and some ovarian cancers and importantly, produced no false positive screens among normal, noncancer controls.*

Source: Kinde I, et al. Evaluation of DNA from the Papanicolaou test to detect ovarian and endometrial cancers. *Sci Transl Med* 2013;5:167ra4.

Since the introduction of the Papanicolaou (Pap) smear for cervix cancer screening, mortality rates from this disease have plummeted. Initial ascertainment of cells came from cervix lavage. This was quickly modified by direct sampling and remains a staple of use throughout the world. Advances in collection/preservation technology brought the opportunity to perform liquid-based collection, automation, and an iterative modification in diagnosis/triage with the performance of HPV testing. Since abnormal glandular cells from ovarian and uterine origin are occasionally found in cervical smears, the authors hypothesized that next-generation sequencing technology could provide the next transformative iteration of the Pap smear by identifying, with high confidence, mutational profiling in cancer present in the upper genital tract. To do this, they developed a panel of genes commonly mutated in endometrial and ovarian cancers by performing whole-exome sequencing on 22 endometrial cancers and interrogating known whole-exome sequencing datasets for other ovarian and endometrial cancers. They then used this panel (which included common abnormalities such as P53, PI3K pathway aberrations [PTEN, PIK3CA, Akt], MAPK pathway aberrations [BRAF, NRAS, KRAS], and CTNNB1) to search for mutations in 24 endometrial and 22 ovarian cancers. They identified at least one mutation in all 46 tumor samples. Then, from the corresponding liquid Pap smear specimens, they used a massively parallel sequencing method to look for the same mutations in cells and DNA in the fluid and cell pellet. Remarkably, they

identified 100% of the endometrial cancers and 41% of ovarian cancers. To confirm these observations, they developed a sequence-based method to look for mutations in 12 genes in a single-liquid Pap smear specimen without previous knowledge of the tumor's genotype. When applied to 14 positive cases, the expected tumor-specific mutations were identified. The test, called PapGene, also provided quantitative results for mutation frequencies and, importantly, was negative in all noncancer control patients. The authors concluded that mutational profiling can be accomplished via Pap testing and, although preliminary, could be used in early detection models and surveillance of disease.

■ COMMENTARY

The explosion of knowledge regarding cancer biology is largely based on understanding how genomic alterations drive disease. In these investigations, serial and cumulative gene expression and loss of expression have been identified and have provided unprecedented insight into the character of disease, particularly in diseases that share morphology but not natural history. Much of this progress is fueled by the global effort to sequence the human genome and individual tumors.[1,2] The current article incorporates the sophistication of next-generation sequencing with "leftover" DNA hidden in the specimen material from liquid-based Pap smears. The hypothesis is rational since, albeit with low specificity and sensitivity, abnormal glandular cells for extra-cervical origin have been found in routine Pap testing. The ability to identify DNA is already available for HPV, as well are multiplex systems to analyze in parallel multiple tissue samples for multiple genetic aberrations. PapGene combines these two advances and demonstrates, preliminarily, that genomic alterations and mutations that present within specific cancers can be identified in shed material resting in the endocervix, particularly for endometrial cancers.

As is well known, the success of any screening modality lies on its ease of administration on a large-scale audience, reproducibility between and within testing facilities, low cost, patient acceptability, high positive predictive value, and optimal sensitivity and specificity, so as to not harm patients without disease. Endometrial and ovarian cancer screening efforts are plagued by deficiencies in several of these tenets. The current test is a step in the right direction, provided it can be validated in the broader population. In addition, there are several other considerations that will need development, including increasing the detection rate among the ovarian cancer cases. The authors suggest that endometrial aspiration may be a way to collect more proximal tissue, but this has negative implications on patient acceptance and cost. The genomic portfolio could be greatly expanded, particularly as the body of knowledge grows, but this is challenged by cost and external validity. Finally, gene events occur in a continuum of the cancer process; for a diagnostic such as this to work, we would be most interested in early events where early-stage or preinvasive disease can be identified and acted upon to change the natural history. While these challenges await further exploration, the novel technology is an important contribution to the growing portfolio of non-invasive, next-generation screening efforts (such as circulating cell-free DNA)[3] combining our best understanding of the genome and how to best leverage its measurable elements.[4] ■

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Special Feature

Another Pill Scare: What Should Be Our Response?

By Jeffrey T. Jensen, MD, MPH

Synopsis: *The drospirenone venous thrombosis controversy remains a topic of interest in Europe and is influencing prescribing practices. Many clinicians and professional groups are recommending the use of levonorgestrel pills as first-line products, and some products have been removed from the market. In the United States, the issue has received less attention from clinicians, but is a hot topic for trial lawyers. This special feature will review the current information on pill safety with an emphasis on practice in the United States.*

I RECENTLY SPENT SEVERAL DAYS AT THE FIRST GLOBAL CONference on Contraception, Reproductive and Sexual Health in Copenhagen. During the 3-day meeting, the topic of venous thrombosis (VTE) and hormonal contraception received plenty of attention, with presentations during a special symposium, a plenary session panel discussion, a plenary session debate, and in four other free communication and congress forums. I had the opportu-

nity to participate in several of these sessions, and attend the others. I particularly enjoyed meeting and hearing first-hand descriptions of results from the Danish database studies presented by Professor Ojvind Lidegaard. Since I have presented my perspective on these studies in several *OB/GYN Clinical Alert* commentaries, I thought I should review the arguments shaping practice decisions in some European nations.

I admire Lidegaard for his determination and scientific diligence. He is an imposing figure and a relentless advocate. As a practicing clinician, he understands the problems we face each day in patient care, and he has deep concern for the welfare of women. His position is straightforward; the overwhelming majority of studies support a doubling of risk of VTE with drospirenone, third-generation, and cyproterone acetate combined hormonal methods when compared to levonorgestrel (LNG) pills. Since the only studies that do not support the increase in risk are post-marketing studies funded by the pharmaceutical companies, he argues that these findings are unreliable, even though many experts believe the opposite.[1,2] Although the increase in the attributable risk of VTE with use of the newer progestogens is low (about 2-3 cases per 10,000 women years of exposure), Lidegaard reminded conference attendees that real women are affected and some will die or suffer permanent disability. Since safer alternatives (e.g., LNG pills) are available, he maintains that women need to be counseled about this increase in risk with newer products, and that practice guidelines and government reimbursement policies should take these recommendations into account. Lidegaard believes that we have sufficient evidence to end the debate about whether these products increase risk, and that we should move directly toward implementation of policy. A "pill scare" can be avoided, he believes, by quietly implementing these policies without alarming the public or undermining confidence in hormonal methods. He claims that this approach has become policy in Denmark, and the shift in prescription habits toward safer pills is having a measurable impact on the population-based incidence of VTE risk (unpublished data presented at the meeting).

Let's evaluate these claims and determine if a course of action in our own clinical contraception practice is necessary. First, emotion runs high, and the science is often trumped by highly publicized media reports of unfortunate but rare serious adverse events in young women using combined hormonal contraceptives. A policy labeling some pills as safe and others as high-risk is not likely to be successful, as the public concludes that all pills and hormones in general are unsafe.

This is exactly what has occurred in France in response to reports of stroke and death in users of the 35 mcg EE cyproterone acetate (CPA) pill (Diane®). It is important to understand that Diane® received marketing approval in France in 1987, not as an oral contraceptive, but as a treatment for acne. Four deaths have been associated with thrombosis events in Diane® users over the almost 30 years of approved use. Ironically, since Diane® did not carry a labeling indication as a contraceptive, some providers would prescribe concurrent use of another oral contraceptive along with Diane® (in most of the other 135 countries where Diane® — or Dianette®, same pill, different name — was marketed, it had a duel indication for contraception). Also, since acne is associated with polycystic ovary syndrome and obesity, and obesity is an independent risk factor for VTE, Diane® users may have been at a higher baseline risk of VTE. Unfortunately bad press trumps good science, and the French regulatory authorities hastily called together expert groups. Diane® was pulled from the market, and the safety of other combined hormonal contraceptives questioned. In fact, an official statement from prominent French reproductive endocrinologists called for limitations on the prescription of other progestogens, and even suggested that prescription of combined pills should be restricted to gynecologists!

Since Diane® was never approved in the United States, this story has not received much media attention here. However, since the data linking CPA to an increase in VTE risk comes from many of the same database and case-control studies that support an increased risk with third-generation and drospirenone pills, you can bet that U.S. trial attorneys have been following this closely.

Although in Europe each nation independently controls and approves the sale of drugs within its borders, the European Medicines Agency (EMA, a central regulatory agency similar to our FDA) also exists. French regulatory authorities requested that the EMA review Diane® approval. On May 17, 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) released a supported continued approval for CPA/EE pills stating that the benefits outweigh its risks in certain patients, as long as measures are taken to minimize the risk of thromboembolism. The recommendations (adopted with a 31:1 majority) state that Diane® and its generics can be used in the treatment of moderate-to-severe acne related to androgen sensitivity or hirsutism in women of reproductive age when alternative treatments, such as topical therapy and oral antibiotic treatment, have failed. Despite the near unanimous recommendation of the PRAC, the French National Agency for the Safety of Medicine and Health Products suspended the marketing authorizations for CPA in France. The result of all of this publicity has been a decrease in oral contraceptive use; many abortion providers at the Copenhagen meeting presented anecdotal evidence that abortion rates are rising.

With this action, a new European war has erupted. On one side, the group led by Lidegaard believes that the consistency of the scientific studies have settled the debate on

safety, and that professional and regulatory groups should restrict or withdraw the use of certain products in favor of second-generation pills.[3-5] The other position, championed by Samuel Shapiro and other experts, suggests that the evidence of an increase in risk is not only insufficient but flawed, and that no practice changes are warranted.[6] Both sides claim to have the interest of women as their primary motivation, and accuse the other side of manipulating or ignoring data in a way that compromises the health of our patients. The net result of this disagreement has been a continuing decline in the public confidence regarding the safety of all combined methods.

In response to this new pill crisis, Johannes Bitzer in his role as President of the European Society of Contraception and Reproductive Health published a consensus paper signed by prominent gynecologists from several EU countries and the United States.[7] The statement (key points below) urges calm and a return to our shared objective of improving women's health by focusing on a clinical risk/benefit discussion that should serve as a basis for the prescription of various combined hormonal contraceptives:

1. It can be taken for granted that all parties involved in this "confrontation" share the same objective, namely to achieve the best for women's health and to put at their disposal effective and well-tolerated contraceptives.

2. Everybody concurs that contraceptive methods are needed that possess the greatest possible efficacy, safety and tolerability, and, if possible, additional health benefits. All these elements should be integrated in the individual risk/benefit evaluation.

3. Everyone is probably in agreement that no method currently available or likely to be developed at a later date will be 100% effective, risk-free, well tolerated by all users, and associated with non-contraceptive benefits justifying and facilitating its long-term use.

4. In view of this fact, everyone is likely to acknowledge that a large spectrum of methods should be available to tailor contraceptive choice to individual women's needs.

5. Everyone concerned undoubtedly also concedes that each contraceptive decision must be properly balanced and based on the best evidence on record about risks and benefits. This information should be delivered in a way that helps women understand the scientific evidence and takes into account women's needs and values so that, after having been fully informed, they are able to individually weigh up the relative importance of this evidence. By educating and counseling women in this way, they will be appropriately informed in respect of the decision-making process.

So how should we change practice in the United States? Although we don't have a crisis with CPA pills, we still need to counsel our patients effectively. About 18% of reproductive age women use combined hormonal products, and many do so to achieve important noncontraceptive benefits. We know that discontinuation and incorrect use of combined oral contraceptives often result in unintended pregnancy, a condition with a substantially higher absolute risk of VTE. We also know that tolerability increases compliance and continuation with use. Although we don't have Diane® in the United States, we do have combined pills with regulatory approval for the treatment of acne, premenstrual dysphoric disorder, and heavy menstrual bleeding. Although additional well-designed randomized comparator studies are needed to determine if these indications are unique, most clinicians recognize that tolerability of products is highly individual and that a range of different formulations provides the best option in female health care.

At the same time, the least expensive pills on the market are generic LNG, norethindrone, and norgestimate pills. These are widely available at discount pharmacies for $10 or less per cycle. Most women will tolerate these pills well. From a cost standpoint, it makes sense to recommend generic second-generation pills for all new starts unless other clinical considerations exist. One drawback to the generic pills is convincing data that suggest 24/4 dosing regimens are associated with a lower failure than 21/7 products.[8] In the United States, the only approved 24/4 regimens are an expensive, brand-name norethindrone product, and one branded and one slightly less expensive drospirenone pill. Although any pill can be adapted to 24/4 or continuous dosing, the instructions require more time and counseling. Many other women have specific indications to consider use of low-androgen pills as a first-line therapy. Be cautious when prescribing any oral contraceptive to obese women, as they are at increased baseline risk for VTE. For cost, low-androgenicity, and effectiveness, I recommend the 24/4 drospirenone pills to many new starts.

The recent surge in the use of long-acting reversible contraceptive methods has led to a decrease in the prescription of pills by many Ob/Gyn residents. The general safety of combined oral contraceptives has also led to a lack of vigilance by some providers when assessing a woman for suitability for a pill (patch or ring) prescription. Excellent guidance is available through both the World Health Organization and Centers for Disease Control and Prevention medical eligibility criteria (MEC) for contraception. Notably, neither group calls special attention to progestogen type in practice recommendation. Although the MEC provides guidance for a number of medical comorbidities, it is important not to forget the basics when prescribing a combined method. The most commonly overlooked condition is a personal or family history of VTE. Asking about this in a variety of ways (e.g., "have you or anyone in the family ever had a blood clot?" "did your mother or sisters have any complications in their pregnancies?" etc.) should be routine prior to pill prescription, particularly for new

starts. Obtaining a blood pressure is also mandatory. Both must be documented.

Moving back to the consensus statement, I think it is important to describe the current situation in plain terms to our patients. I generally approach the topic of pill prescription in terms of efficacy and safety. The pill is about 99% effective when used perfectly, but the real-world effectiveness is only 90% due to the difficulty in taking a pill each day. For this reason, taking the pill in a 24/4 or continuous regimen may make sense. Other factors that can influence success with taking the pill include cost and side effects. Most women will do very well on low-cost generic pills, and these generally should be recommended first. Some women may have baseline concerns about androgen-related side effects such as acne, and this should be taken into account during counseling. Although there are insufficient data to compare various preparations head-to-head, low androgen pills may be preferable under these circumstances. Other medical problems (cyclic mood disorders, heavy bleeding) also should be considered. All combined products carry an increase in risk of VTE that is 2-3 times higher than baseline, but about half as high as the risk seen in pregnancy. However, the absolute baseline risk of a clot in women with no personal or family history is low, so the additional risk due to pill use is only about 2-3 additional cases per 10,000 women. The risk of permanent injury due to a VTE puts the absolute number of affected individuals in the 2-3 per 100,000 to 1 million range, similar in magnitude to the impact of buying a second or third ticket on the chance of winning a lottery. There are some scientific data that suggest the risk of VTE may be slightly higher (1-2 additional nonfatal cases per 10,000 women) in pills containing drospirenone and desogestrel compared to pills containing LNG and norgestimate. The FDA has provided some of this information in the package inserts of drospirenone pills. During the clinical encounter, you and your patient need to decide on her priorities and goals for prescription of a combined hormonal method, and you should carefully document both the pertinent positive and negative findings on your history and exam, and the clinical decision-making used to choose a product. I believe this practice provides protection to you and choice to your patient. ■

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CME Questions

1. **In the featured study by the NICHD network, which of the following is correct regarding "reduced activity"?**
   a. It was associated with a more than doubling of the risk of preterm birth < 37 weeks.
   b. There was no significant difference in preterm birth < 34 weeks.
   c. There was no difference in outcome in patients who have very short cervices.
   d. There was no difference if there was funneling of the cervix.

2. **Which country is most likely to have oral contraceptives available without a prescription?**
   a. France
   b. Canada
   c. Peru
   d. Norway

3. **Which was *not* an observation in the current investigation of Pap tests to detect ovarian and endometrial cancers?**
   a. Somatic, but not germline mutations, were found in normal, noncancer controls.
   b. Uterine cancer mutations were found in 100% of corresponding Pap smears.
   c. PI3K pathway elements were among the panel of mutations tested.
   d. Ovarian cancer specific mutations were found in less than half of the matched Pap smears.

4. **Which of the following statements is true when counseling women on use of a combined hormonal contraceptive?**
   a. Women with a personal or family history of venous thromboembolism are at a substantially elevated risk of blood clot.
   b. All women of northern European background should have a screening test for the Factor V Leiden mutation.
   c. Obese women should always use a 30 µg pill to improve efficacy.
   d. The vaginal ring contraceptive has improved safety over oral contraceptives.

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

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Continuing Warfarin for Pacemaker/ICD Implantation is Safer Than Bridging

Source: Birnie DH, et al. *N Engl J Med* 2013;368:2084-2093.

The decision process to determine the optimal scheduling of antithrombotic therapy in the perioperative period is complex. The most recent AT9 CHEST guidelines suggest discontinuation of warfarin 5 days prior to pacemaker/implantable cardioverter-defibrillator (PCM-ICD) implantation, complemented with heparin bridging. This method is somewhat unwieldy, expensive, and has not been confirmed by a large, randomized trial as optimizing risk reduction. During transition from warfarin to heparin, an interval of increased risk for thromboembolism occurs in some, and the use of heparin has also been shown to frequently be associated with device-pocket hematoma.

In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial, 681 PCM-ICD patients were randomized to continued warfarin or heparin bridging. Patient selection criteria also included high baseline annual thromboembolism risk (≥ 5%). The primary outcome of the trial was incidence of significant device-pocket hematoma (DPH), which can result in prolongation of hospitalization, need to stop anticoagulation, or additional surgery.

There was a dramatic difference in risk for the DPH primary endpoint between subjects continued on warfarin uninterrupted (3.5%) and subjects randomized to heparin bridging (16%). Risk reduction through continuation of warfarin was not associated with any increased incidence of major surgical adversities compared with bridging. Continuation of warfarin, uninterrupted, was associated with more than 80% reduction in risk of DPH compared to bridging, while not compromising other measures of safety. ■

Bariatric Surgery Impact on Cholesterol Metabolism

Source: Benetti A, et al. *Diabetes Care* 2013;36:1443-1447.

Bariatric surgery techniques are often described as restrictive (e.g., gastric banding) or diversionary (e.g., biliointestinal bypass). While diversionary surgery (DIV) is associated with greater weight loss and more rapid metabolic changes than restrictive surgery (RES), the greater simplicity and reversibility of the latter are pertinent in selecting which intervention is preferred.

Although the impact of bariatric surgery on diabetes has been much publicized, the impact of bariatric surgery on cholesterol is less well recognized. To date, most of the favorable impact on cholesterol has been attributed to weight loss. Over the long term, DIV is associated with greater weight loss than RES. However, since DIV and RES are associated with similar overall weight loss during the first postoperative 6 months, one could compare cholesterol metabolism of the two types of surgery independent of weight loss.

Benetti et al compared cholesterol metabolism in DIV with RES (n = 20). They found that with DIV, reduced cholesterol absorption produced a decrease in LDL and non-HDL, associated with enhanced catabolic LDL receptor activity in the liver.

Because metabolic changes in both groups in reference to glucose, insulin, insulin resistance, and weight loss were similar, the authors suggest that these favorable cholesterol metabolic changes are induced specifically with DIV, and because weight loss over the specified interval was essentially equivalent, the changes in lipids are not fully explained by weight loss. ■

The Do-it-Yourself Diabetes Diagnosis Kit

Source: Bethel MA, et al. *Diabetes Care* 2013;36:1483-1488.

In the last decade, the threshold for diagnosis of diabetes has expanded to lower levels of fasting glucose, inclusion of reference laboratory A1c, and refinement of the definitions of prediabetes. Use of the oral glucose tolerance test (OGTT) appears to be less and less necessary, considering the relative convenience of other diagnostic tests. Could a self-administered OGTT change the balance and be a positive addition to the diagnostic portfolio?

Bethel et al report on a self-administered OGTT home use kit (SmartGRA) used by 30 diabetic and non-diabetic subjects. The kit includes instructions to guide the user through the process of timed capillary glucose measurement as well as a wireless data recorder for glucose levels, the results of which are *not* visible to the user (glucose measurements are wirelessly transmitted to the clinic for evaluation).

Was self OGTT accurate? In a word,

yes. Comparison of OGTT reports generated by SmartGRA vs office-based testing found comparable reproducibility of results. Although the results of home OGTT tended to overestimate glucose levels compared to the reference laboratory, this emerged as a problem with device calibration, which should be able to be remediated. Overall, subjects found the device easy to use.

As a proof-of-concept trial, these results lend credence to the idea that OGTT — generally conceded to be sufficiently unwieldy so that other diagnostic tests are preferred — might merit reconsideration if a well-calibrated, similarly patient-friendly device comes to market. ■

Low Creatinine Excretion Associated with Mortality in Type 2 Diabetes

Source: Sinkeler SJ, et al. *Diabetes Care* 2013;36:1489-1494.

Creatinine excretion (CER), as measured by the 24-hour urinary excretion of creatinine, has recently been noted to be associated with increased mortality, both in persons with underlying renal disease and the general population. CER reflects overall lean muscle mass, so that declines in CER may simply reflect deconditioning, loss of muscle mass, cachexia, malnutrition, etc., each of which may have a negative impact on mortality.

Sinkeler et al report on data accrued from two previously completed trials of angiotensin receptor blockers in diabetic nephropathy: Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy trial. Twenty-four hour urinary CER was measured at baseline for the majority (n = 2360) of participants. Since mortality data from both trials are available, the relationship between CER and mortality can be evaluated.

Across the population studied, each halving decrement of CER was associated with a doubling of mortality risk. Since the primary association of CER is with muscle mass, the authors pose the interesting question of whether efforts expended to improve muscle mass, such as enhanced exercise and nutrition, might favorably effect mortality in this population. ■

Diabetes and Cognitive Function

Source: Spauwen PJJ, et al. *Diabetes Care* 2013;36:1554-1561.

The relationship between vascular disease and type 2 diabetes is consistent: Risk for microvascular events (retinopathy, neuropathy, and nephropathy) and macrovascular events (stroke and MI) is increased compared to non-diabetics. Additionally, when diabetics suffer macrovascular events, the consequences are typically more severe than similar events in non-diabetics.

The etiology of cognitive impairment is often multifactorial, including vascular insufficiency. Diabetics have a higher prevalence of cognitive impairment than non-diabetics, but the rate of cognitive decline in diabetics has not been studied.

The Maastricht Aging Study is comprised of 10,396 adults residing in the province of Limburg, the Netherlands. A sample from this population (n = 1290) underwent extensive neuropsychological testing at baseline, 6 years, and 12 years. At baseline, approximately 5% of the population had type 2 diabetes, with an incidence of an additional 5% over subsequent 6-year intervals.

When compared with controls, diabetics had a significant rate of cognitive decline over 6 and 12 years. Even when adjusted for variables that are more commonly comorbid in diabetics (hypertension, dyslipidemia, obesity), the acceleration in cognitive decline was greater in diabetics. As might be intuitive, diabetics with baseline cognitive impairment progressed at a more rapid rate than those without. Whether any specific intervention among diabetics (e.g., better control of glucose, lipids, blood pressure) might ameliorate the exaggerated rate of cognitive decline remains to be determined. ■

Benefits of Screening for Lung Cancer with Low-Dose CT

Source: The National Lung Screening Trial Research Team. *N Engl J Med* 2013;368:1980-1991.

Lung cancer (LCA) is responsible for more deaths than any other cancer worldwide. The burgeoning growth of smoking in developing countries suggests that this dismaying fact is unlikely to diminish in the foreseeable future. Clinical trials of screening for LCA through chest x-ray (CXR) did not show improved outcomes, likely because of its relatively poor discriminative ability in early disease.

The National Lung Screening Trial enrolled smokers and ex-smokers with at least a 30 pack-year history. Participants were randomized to an annual low-dose CT × 3 (n = 26,714) or standard chest x-ray (n = 26,035).

A positive radiographic finding on at least screening was seen in three times as many CT screenees as chest x-ray (27.3% vs 9.2%). LCA was diagnosed in 1.1% of the CT group vs 0.7% in the CXR group.

Screening for LCA was found to reduce LCA-related mortality by 20% and all-cause mortality by 7%.

Most of the abnormalities detected by low-dose CT screening were benign, so that the positive-predictive value for a positive CT was only 3.8% (i.e., about 4% of study subjects with any positive suspicious finding on CT turned out to have LCA). Reassuringly, repeatedly negative low-dose CT had a negative predictive value of 99.9% (i.e., essentially no one who had negative sequential CT screening was diagnosed with LCA during the screening and follow-up period). ■

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Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
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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.*

Prostate Medications and Cancer Risks — New Evidence

In this issue: Risk of high-grade prostate cancers; clopidogrel and stroke risk; antibiotics and statins; and FDA actions.

Prostate cancer risk and 5-ARIs

The 5-alpha reductase inhibitors (5-ARI) finasteride (Proscar) and dutasteride (Avodart) are used to treat lower urinary tract symptoms in men. They are known to reduce prostate-specific antigen (PSA) levels and there was hope that they may also reduce the incidence of prostate cancer. But in two large trials, PCPT (finasteride) and REDUCE (dustasteride), despite a nearly 25% reduction in the overall rate of prostate cancer, the risk for high-grade prostate cancers was increased (Gleason score 8-10). Debate has raged for the last several years about the significance of these findings and whether the increase was real or spurious due to detection bias. A new study from Sweden attempts to clarify this issue. Using the National Prostate Cancer Register along with prescription data, nearly 27,000 cases of prostate cancer were identified along with some 134,000 matched controls. More than 7800 men were exposed to a 5-ARI, including 1500 with prostate cancer and 6300 controls. As noted in previous studies, the risk of prostate cancer decreased with increasing duration of use of a 5-ARI. With 3 years of treatment, the risk of prostate cancer was 28% lower in the treatment group (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.59-0.89; $P < 0.001$ for trend). The reduction was seen primarily for Gleason score 2-6 and score 7 tumors ($P < 0.001$ for trend for both). However, as opposed to previous studies, the risk for higher grade tumors was not significantly increased, although the risk was not decreased either. By 3 years, the OR was 1.23 (95% CI, 0.90-1.68; $P = 0.46$ for trend), but did not reach statistical significance. The ORs for shorter exposures were 0.96 for 0-1 year exposure, 1.07 for 1-2 years, and 0.96 for 2-3 years. The authors conclude that men treated with a 5-ARI for lower urinary tract symptoms had a lower risk of prostate cancer with Gleason scores 2-7 and no evidence of increased risk of Gleason score 8-10 of cancers up to 4 years of treatment (*BMJ* 2013;346:f3406). The FDA issued a safety warning in 2011 regarding finasteride and dutasteride and the risk of high-grade prostate cancers and it is unlikely that this study alone will reverse that, but it is reassuring for the millions of men who take these drugs for lower urinary tract symptoms. ■

Clopidogrel could reduce stroke risk

Adding clopidogrel to aspirin in patients with minor stroke or a transient ischemic attack (TIA) may help reduce the risk of stroke within the next 90 days, according to a new study from China. In a randomized, double-blind, placebo-controlled trial, nearly 5200 patients were seen within 24 hours after onset of minor ischemic stroke or high-risk TIA and randomized to a combination of clopidogrel with aspirin or aspirin alone. The combination group was given clopidogrel at an initial dose of 300 mg followed by 75 mg per day for 90 days along with aspirin 75 mg per day for the first 21 days, while the aspirin alone group got placebo plus aspirin 75 mg for 90 days. The primary outcome was stroke (isch-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

emic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Stroke occurred in 8.2% of the clopidogrel-aspirin group as compared to 11.7% in the aspirin alone group (hazard ratio 0.68; 95% CI, 0.57-0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients in the clopidogrel-aspirin group and eight in the aspirin alone group. The rate of hemorrhagic stroke was the same (0.3%) in both groups. The authors conclude that among patients with TIA or minor stroke who are seen within the first 24 hours of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the next 90 days. The combination does not increase the risk of hemorrhagic stroke or hemorrhage (*N Engl J Med* published online June 26, 2013). An accompanying editorial states that this trial "proves the concept that dual platelet therapy can be more effective than single platelet therapy in preventing early recurrent stroke in patients with acute symptomatic atherothrombosis...," and also shows that dual platelet therapy can be given without excess harm in patients with acute focal brain ischemia. There is slight concern that the results may not apply to non-Chinese patients with different forms of underlying arterial disease (*N Engl J Med* published online June 26, 2013). ■

Antibiotic coprescription and statins

Use caution if you prescribe clarithromycin or erythromycin to patients on statins. Both drugs (but not azithromycin) inhibit cytochrome P450 isoenzyme 3A4, which can increase blood concentrations of statins, especially atorvastatin, simvastatin, and lovastatin. Researchers from Canada looked at the records of continuous statin users who were prescribed clarithromycin (n = 72,591) or erythromycin (n = 3267) with azithromycin use as a comparator (n = 68,478). The risk of hospitalization for rhabdomyolysis within 30 days was the main outcome. Although the absolute risk was low, concomitant use of clarithromycin/erythromycin with atorvastatin, simvastatin, or lovastatin was associated with a higher rate of hospitalization with rhabdomyolysis, especially in those with acute kidney injury. There was also an increase in all-cause mortality when the drugs were combined (absolute risk for rhabdomyolysis 0.02%, with acute kidney disease 1.26%, all-cause mortality 0.25%, relative risks 2.17, 1.78, and 1.56, respectively). These data suggest that coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 (atorvastatin, simvastatin, and lovastatin) increases the risk of statin toxicity (*Ann Intern Med* 2013;158:869-876). ■

FDA actions

The FDA has approved paroxetine for the treatment of hot flashes (vasomotor symptoms) associated with menopause. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and has the same active ingredient in the antidepressant Paxil. It is the first non-hormone based drug approved for this indication. The safety and efficacy of the drug was established in two randomized, double-blind, placebo-controlled trials of 1175 postmenopausal women with moderate-to-severe hot flashes that showed paroxetine was more effective in relieving symptoms than placebo. This new form of paroxetine contains 7.5 mg of the drug and is dosed once daily at bedtime. Paroxetine for depression and other psychiatric indications is dosed at 10-40 mg. All forms of paroxetine carry a boxed warning about increased risk of suicide. There is also concern about reduced effectiveness of tamoxifen if both medications are taken together. Paroxetine 7.5 mg for hot flashes is marketed by Noven Therapeutics as Brisdelle.

The FDA has approved a new formulation of selegiline — a once-daily, orally dissolving tablet — for the treatment of Parkinson's disease (PD) in patients who are losing responsiveness to levodopa/carbidopa. Most PD patients start treatment with levodopa/carbidopa, but for many, the effectiveness wanes with increasing "off" periods during which time symptoms worsen. In clinical trials, the new combination of selegiline reduced "off" periods by an average of 2.2 hours per day compared to 0.6 hours for placebo. The dissolvable tablet uses a new system that delivers more drug at a lower dose. The drug company claims this results in fewer side effects. Selegiline, a monoamine oxidase (MAO) inhibitor, has been available as a generic and also as the branded drugs Eldepryl and Zelapar. Like other MAO inhibitors, it can cause severe, even fatal, reactions if given in combination with certain other drugs including meperidine, tramadol, SSRIs, TCA antidepressants, and the over-the-counter medication dextromethorphan. The new orally dissolving selegiline is marketed by Valeant Pharmaceuticals as Zelapar.

The FDA has approved the TNF blocker golimumab for the treatment of ulcerative colitis. The drug was previously approved to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The approval for ulcerative colitis was based on two studies of more than 800 patients, one group had failed other treatments and the other group were responders who were evaluated for maintenance. In both groups, golimumab was superior to placebo. Golimumab is marketed by Janssen Biotech as Simponi. ■