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INSIDE

Preventing unintended pregnancy **page 74**

Is intrauterine anesthesia beneficial for gynecologic procedures? **page 76**

Microarray for prenatal diagnosis **page 77**

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Repurposing an Old Drug for Cancer Control: What Does Metformin Bring to the Plate?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Metformin use was associated with better disease-specific survival in women who developed ovarian cancer. The data support (preclinical observations of) the anticancer activity of metformin in several solid tumors and provide rationale for planned and ongoing clinical trials.*

Source: Kumar S, et al. Metformin intake is associated with better survival in ovarian cancer: A case-control study. *Cancer* 2012; doi: 10.1002/cncr.27706. [Epub ahead of print].

In limited clinical trials, metformin has been shown to have anticancer activity. The objective of this study was to investigate whether patients taking metformin had better disease-specific survival compared to non-consumers. Since metformin use is generally reserved for control of diabetes, two control groups were used in the matched analysis: diabetic controls (those with ovarian cancer taking agents other than metformin for diabetic control) and non-diabetic controls (those patients with ovarian cancer that were not diabetic and did not receive metformin). Two cohorts of ovarian cancer patients were studied: those with ovarian cancer irrespective of histology (matched 1:2, case:control) and those with epithelial ovarian cancer (matched 1:3). Matching was based on age, stage, and residual disease.

In the *all* ovarian cancer analysis (72 cases and 143 controls), metformin cases had significantly better 5-year survival (73% vs 44%; $P = 0.0002$). In the *epithelial* ovarian cancer cohort (61 cases and 178 controls), metformin cases had significantly better 5-year survival (67%

vs 47%; $P = 0.007$). On multivariate analysis, metformin remained independently associated with better survival (hazard ratio, 2.2; 95% confidence interval, 1.2-3.8; $P = 0.007$) after controlling for disease stage, grade, histology, chemotherapy, body mass index, and surgical cytoreduction. The authors conclude that metformin use was associated with improved disease-specific survival in patients with ovarian cancer and is worthy of further clinical testing in prospective clinical trials.

■ COMMENTARY

As our knowledge expands into the molecular underpinnings of disease initiation, invasion, metastasis, progression, and emergence of drug resistance, we are increasingly "rediscovering" the utility of existing drugs developed under other indications. There are many examples, but one of the most striking is the history of the development, retraction, and redevelopment of thalidomide, a drug initially developed in the 1950s as an antiemetic and a sedative.[1] It was found to be particularly effective for hyperemesis gravidarum; as is well known, the agent was withdrawn after being found to be a teratogen. However, by serendipity, it was found to be active in relieving the symptoms of leprosy and gained approval in 1998 for this indication. It also was found to be a potent inhibitor of tumor necrosis factor alpha and angiogenesis.[2] Under these actions, it found a home in the treatment of multiple myeloma, where it was granted accelerated approval by the FDA in 2006.[3]

Metformin's effects on cancer biology are only beginning to be understood; there is clearly activation of an important mediator of PI3K pathway signaling, AMPK.[4] This enzyme regulates the activity of the tuberous sclerosis proteins (TSC1/TSC2), which blocks the downstream targets of Akt, an important mediator of growth factor signaling, including VEGF, IGF1, and EGF. We have found in our own studies that metformin may add to the efficacy of other agents targeting this pathway, providing another therapeutic angle (Coleman R, unpublished). The association drawn from this paper must be interpreted with caution, however. As with all retrospective studies, the conclusions are hypothesis-generating and need to be formally tested in prospective clinical trials. Since the duration and time of administration of metformin was unknown, the impact of diabetes itself on the natural history of disease is unknown. Additionally, there are a number of confounders including the influence of insulin use on metformin users (and vice versa), the impact of undocumented prediagnosis use of metformin, and the limited ability to control for important therapeutic effects of medicines (IP chemotherapy, dose-dense chemotherapy, targeted agents in recurrence, etc). Therefore, causation cannot be assessed properly. However, the therapeutic window for this agent, its availability, and its cost should favorably usher a robust repurposing program. ■

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Preventing Unintended Pregnancy

ABSTRACT & COMMENTARY

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

Synopsis: *In this large prospective cohort study, women who received free contraception had lower rates of abortion, repeat abortion, and teenage births compared to their regional and national peers.*

Source: Peipert JF, et al. Preventing unintended pregnancies by providing no-cost contraception. *Obstet Gynecol* 2012;120:1291-1297.

THE AUTHORS PERFORMED A PROSPECTIVE COHORT STUDY, the Contraceptive CHOICE Project, in which women at risk of unintended pregnancy in the St. Louis, Missouri, region received a reversible contraceptive method of their choice for up to 3 years at no cost. The purpose of the study was to promote the use of long-acting reversible contraception (LARC), and the participants were read a standardized counseling script which stated that intrauterine devices (IUDs) and the subdermal implant were the most effective methods of contraception. The women then chose their desired method and were followed prospectively. The authors compared repeat abortions in the St. Louis region with those in Kansas City, Missouri, and nonmetropolitan Missouri. In addition, abortion rates among participants aged 15-44 years and births among participants aged 15-19 years were compared with regional and national rates after standardization for age and race.

The CHOICE Project enrolled 9256 women between August 2007 and September 2011, of whom 46% chose the levonorgestrel IUD, 12% chose the copper IUD, 17% chose the subdermal implant, 9% chose oral contraceptive pills (OCPs), 7% chose the contraceptive vaginal ring, 7% chose the depot medroxyprogesterone acetate (DMPA) injection, and 2% chose the contraceptive patch. The teenage birth rate among participants was 6.3 per 1000 compared to a national rate of 34.3 per 1000. For CHOICE participants, the abortion rates from 2008-2010 ranged from 4.4-7.5 per 1000 after adjusting for age and race. These rates were lower than other women in St. Louis city and county as well as the national rate of 19.6 per 1000. The authors estimated that one abortion could be prevented for every 79-137 women who were given no-cost contraception per the study protocol. The proportion of abortions that were repeat abortions overall in St. Louis city and county decreased significantly compared to Kansas City, Missouri.

■ COMMENTARY

The study investigators finally have proven what we all know intuitively to be true: If access to contraception is increased for women, abortion rates will decrease. This should be a public health intervention on which we can all agree. In the United States, the unintended pregnancy rate currently stands at 49% and is a major public health problem.[1] The most common reversible methods of contraception used in the United States are oral contraception and male condoms.[2] Condoms and oral contraceptives are dependent on user adherence and therefore have higher failure rates among typical users. In contrast, LARC, due to its high efficacy and continuation rates, is considered in the top tier of contraceptive efficacy. This study was successful in promoting the use of LARC among its participants and uptake was even higher than the study investigators anticipated. The Contraceptive CHOICE Project investigators have previously reported continuation rates at 12 months of 88% for the levonorgestrel IUD, 84% for the copper IUD, and 83% for the subdermal implant.[3] Similar rates were found among teenagers and young women in the study compared to older women.[4] Satisfaction rates were also higher for LARC methods in the study compared to other methods of contraception such as OCPs and DMPA. Furthermore, the investigators have shown that CHOICE participants using the pill, patch, or ring were 22 times more likely to experience a contraceptive failure than those using the IUD, subdermal implant, and DMPA injection.[5]

Unfortunately, in the United States, only 5.5% of women practicing contraception used IUDs as of 2008 and implant users were even fewer.[2] For many women, the high up-front cost of IUDs and the contraceptive implant is a barrier to accessing the most effective methods of contraception. For other women, lack of provider knowledge and training or pre-insertion testing requirements are preventing increased LARC use.[6] It is notable that in the same issue of *Obstetrics and Gynecology*, a study reported that the risk of pelvic inflammatory disease in women receiving IUDs was very low and testing on the same day of IUD insertion, if indicated, was acceptable practice.[7] The Institute of Medicine has recommended that contraception be covered without cost to patients under the Patient Protection and Affordable Care Act of 2010. The Contraceptive CHOICE Project has shown in St. Louis, Missouri, how this policy will likely ameliorate the high unintended pregnancy and abortion rates in the United States. Many women in the CHOICE Project obtained their method immediately after abortion, a population at high risk for repeat abortion. Previous studies have shown that provision of LARC at the time of abortion decreases the chance of repeat abortion.[8] Currently, many providers are offering women immediate IUD or implant insertion after abortion, but this practice needs to be expanded.[9] Billing and insurance coverage issues such as device reimbursement and insertion on the same day as another procedure hopefully will be resolved by the Affordable Care Act. ■

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Is Intrauterine Anesthesia Beneficial for Performing Gynecologic Procedures?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

Synopsis: *Instillation of local anesthesia into the uterine cavity can reduce pain for endometrial biopsy, curettage, hysteroscopy, and possibly other procedures.*

Source: Mercier RJ, Zerden ML. Intrauterine anesthesia for gynecologic procedures: A systematic review. *Obstet Gynecol* 2012;120:669-677.

The authors performed a search of online databases as well as reference lists from published reviews that evaluated methods of pain control in gynecologic procedures using intrauterine instillations. Ultimately, 23 randomized, controlled trials (RCT) were deemed appropriate for inclusion in this systematic review. The two authors independently evaluated the quality of each article, using an independent reviewer if a disagreement occurred. A meta-analysis could not be performed due to the heterogeneity of the data in the studies. Conclusions could not be reached with regard to the efficacy of intrauterine anesthetic instillation in the case of induced abortion, intrauterine device insertion, tubal sterilization, and saline-infusion sonography. Moderate evidence provides support for its use in hysteroscopy. Although good evidence demonstrates that this technique is not useful in cases of hysterosalpingography, it is effective in reducing pain in endometrial biopsy and curettage.

■ COMMENTARY

This article is an excellent example of how peer-reviewed literature can answer a valuable clinical question. Mercier and Zerden conducted a methodologically sound review of 23 RCTs assessing the effectiveness of intrauterine instillation for outpatient endometrial procedures and summarized the findings in a logical and systematic fashion. This article is a real clinical gem since it serves as a "this-is-what-science-has-learned-about-this-subject-up-to-now" statement while presenting conclusions in a clinically accessible way. An added bonus of this article is the authors' review of the innervations of the uterine cavity (there are 2 plexus — the better known Frankenhauser plexus, which is targeted by the paracervical block, as well as other endometrial nerve plexus) and reminds us of appropriate dosing of common anesthetic medications (most of the studies used a maximum of 200 mg of xylocaine® [lidocaine] which is 20 mL of a 1% solution).

The authors also address why they believe this practice has *not* become more popular among practitioners. Possible explanations include lack of clinical effectiveness of intrauterine instillation, lack of awareness of research in this area, attitude that the procedure is not painful enough to warrant anesthesia, perceived risk of intrauterine infection, and perceived disruption to the usual workflow in the office. I would offer the possible addition of potential financial implications, because insurers may not universally pay for the equipment and supplies needed to provide intrauterine instillation, whereas a paracervical block has a recognized CPT code that is more likely reimbursable.

Another service of this article is that the authors point out that the quality of research in this area heretofore certainly leaves room for further investigation. Until data from larger RCTs are available, we might wish to put into practice the findings of the best current literature. This review provides good evidence that intrauterine instillation of a local anesthetic reduces pain in endometrial biopsy, endometrial curettage, and possibly hysteroscopy. Although the literature does not currently support its use

in other procedures, further research might change that landscape. Until then, our patients' comfort is worth our consideration. ■

Microarray for Prenatal Diagnosis

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *In diagnostic amniocentesis and chorionic villus sampling, microarray detects a wider breadth of clinically meaningful chromosomal abnormalities than standard karyotype.*

Source: Wapner RJ, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med* 2012; 367:2175-2184.

IT HAS ONLY BEEN A FEW MONTHS SINCE MATERNAL CELL FREE DNA (cfDNA) testing for trisomies 21, 18, and 13 burst onto the scene to shake up (in a good way) current prenatal testing protocols.[1] Now, in the December issue of the *New England Journal of Medicine*, a report has emerged that will further change the entire face of prenatal diagnosis.[2]

Microarray technology is based on the ability to detect small micro-deletions and duplications by pinpointing abnormal variations in the number of copies of particular DNA segments (copy number variants). Although microarrays have been used diagnostically in other clinical arenas such as stillbirth and pediatric neurological conditions (e.g., some forms of the autism spectrum), the study by Wapner et al is the first to apply this methodology to prenatal diagnosis.

The study enrolled 4406 women in 29 centers who had had an amniocentesis or chorionic villus sampling (CVS) for advanced maternal age (46.6%), abnormal aneuploidy screening (18.8%), or an abnormal ultrasound examination, suggesting the presence of a structural abnormality (25.2%). Invasive sampling was performed in the remaining 9.4% for various other reasons. The maternal blood was split into two parts. Half was subject to microarray and the other half was analyzed with standard karyotype.

In 98.8% (4340 patients), microarray was successfully completed. When a duplication or micro-deletion was found that had clinical significance (meaning it encompassed a region that previously had been associated with a documented phenotypic abnormality), this variation was deemed to be "pathological," and it was reported directly to the patient. If the copy number variant was not associated with a known abnormality, it was labeled as "benign." All others were individually reviewed by a committee of genetic experts who then separated each case out into a "likely benign" or "potentially significant" copy number variant.

All autosomal (7.4%) and sex chromosome (1.3%) aneuploidies detected by standard karyotype were also identified by microarray, including all unbalanced rearrangements. Importantly, in samples exhibiting normal karyotypes, the microarray picked up an additional 6% of clinically relevant deletions and duplications in fetuses with structural abnormalities and another 1.7% of rearrangements in fetuses whose mothers had invasive testing for advanced maternal age or non-reassuring screening. The microarray did not diagnose balanced translocations or any of the 13 cases of triploidy (three of whom had no abnormal ultrasound signs at the time of CVS). After expert review, these extra puzzling genetic variations (detected by micrioarry) were reduced to a mere 1.5% that remained "uncertain."

■ COMMENTARY

Microarray greatly increases the diagnostic spectrum of prenatal diagnosis. By including previously undetected copy number variants, clinically meaningful conditions, like autism-spectrum, can be identified. Since around 1% of U.S. children have been diagnosed with this condition, this study will likely get the attention of the public. Undoubtedly, this will result in a need for providers to increase the scope of their pre-test and post-test counseling. Not only will providers need to include a careful explanation of the risks and benefits of invasive testing but also the potential for expanded results beyond the classic aneuploidic conditions like trisomy 21 and Turner X0. Providers will now be expected to understand, counsel, and interpret results for an expanded number of conditions — some with "uncertain" clinical meaning and some "clinically benign" — that may provoke anxiety in expecting parents. It is quite clear that patients whose fetuses have structural abnormalities have a reason for microarray analysis, since approximately 6% of these fetuses, despite a normal standard karyotype, will have clinically significant micro-deletions or translocations.

However, a potential can of worms awaits the public. One limitation of microarray is that 1.7% of those having positive screening for Down syndrome or advanced maternal age "had clinically significant copy number variants." Some may interpret this to mean that, potentially, one in 60 patients in the overall population with structurally

normal fetuses may have a "positive" microarray result — raising alarm and concern in most patients. Since the American College of Obstetricians and Gynecologists has recommended that all patients, regardless of risk, should be offered the option of invasive sampling, this may result in a large increase in demand for amniocentesis and CVS before we are ready to use this new diagnostic tool.

Fortunately, this may be short-lived because progress is already being made into exploring the fetal genome through microarray in maternal blood.[3] ■

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Are Oral Contraceptives Risky or Protective in Women with Polycystic Ovary Syndrome?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *Women with polycystic ovary syndrome (PCOS) are more likely to experience a venous thrombosis (VTE) than women without PCOS. Although obesity increases the risk of VTE associated with oral contraceptive use, it is not proven that PCOS has an independent effect.*

Sources: Okoroh EM, et al. Is polycystic ovary syndrome another risk factor for venous thromboembolism? United States, 2003–2008. *Am J Obstet Gynecol* 2012;207:377.e1-8.

Bird ST, et al. Risk of venous thromboembolism in women with polycystic ovary syndrome: A population-based matched cohort analysis. *CMAJ* 2012 Dec. 3 [Epub ahead of print].

These two groups took slightly different approaches to assess the relationship between polycystic ovary syndrome (PCOS) and venous thromboembolism (VTE) using insurance claims databases. Okoroh and coauthors performed a cross-sectional analysis using the Thomson Reuters MarketScan Commercial databases for the years 2003 through 2008. For the study, the analysis was restricted to women between 18-45 years of age. The authors used International Classification of Diseases, Ninth Revision, (ICD-9) codes associated with each insured individual to classify women into four mutually exclusive PCOS phenotypes based on the three available criterion recommendations (National Institutes of Health, Rotterdam, and Androgen Society). Women were considered to have PCOS if their unique insurance identification numbers were linked with a diagnosis of hyperandrogenism, ovulatory dysfunction, and/or polycystic ovaries in the database. The authors also assessed the prevalence of potential confounders such as obesity, metabolic syndrome, and diabetes using applicable diagnosis codes. VTE was assessed using appropriate inpatient and outpatient codes for deep vein thrombosis (DVT) and pulmonary embolism. Information on demographic characteristics, medications (like oral contraceptives), and clinical comorbid conditions also was captured from the claims database. The authors calculated crude prevalence estimates of VTE for women with and without PCOS, and used multivariate logistic regression to adjust these estimates for age, pregnancy during study period, oral contraceptive use, region, obesity, and diabetes. A total of 23,941 VTE events were recorded among 12,171,830 women in the study group (overall 196 cases per 100,000 women). Compared with all women without PCOS (194 per 100,000), those with PCOS (374 per 100,000) were more likely to have VTE (adjusted odds ratio [95% confidence interval] 18-24 years, 3.26 [2.61-4.08]; 25-34 years, 2.39 [2.12-2.70]; 35-45 years, 2.05 [1.84-2.38]). Surprisingly, a reduction in DVT risk was found in PCOS women using oral contraceptives (adjusted odds ratio, 0.8 [0.73– 0.98]).

The paper by Bird et al also used a population-based cohort from another U.S. insurance database (IMS LifeLink Health Plan Claims Database). This database contains paid claims data from more than 102 managed care plans, and covered a longer time period (2001- 2009). However, in contrast to the Okoroh's study, these authors constructed cohorts (to calculate incidence data) based on exposure to an oral contraceptive and required a 1-year period of baseline enrollment in a plan to assess potential confounders (women with a history of cancer, cerebrovascular disease, cardiovascular disease, venous thromboembolism or prior anticoagulation [warfarin and heparin] were excluded). PCOS also was more narrowly defined by a single ICD-9 code (PCOS, 256.4). Women aged 18-46 years taking combined oral contraceptives and who had a claim for PCOS (n = 43,506) were matched to control women (n = 43,506) also taking oral contraceptives. To obtain a comparison to women with PCOS not using combined oral contraceptives, a random sample of 2 million women was used to create PCOS and non-PCOS cohorts of nonusers for the secondary analysis. Results from this study demonstrated that the incidence of VTE

among women with PCOS using oral contraceptives (237 per 100,000 person-years) was more than two-fold higher than that of matched controls using oral contraceptives (109 per 10 000 person-years) (HR 2.14 [1.41-3.24]). Among non-users of oral contraceptives, the incidence of VTE was 63 per 100,000 person-years among women with PCOS and 41 per 100,000 in matched controls without PCOS (RR 1.55 [1.10-2.19]). To summarize, PCOS is an independent risk factor for VTE (1.5-fold increase in risk), and a diagnosis of PCOS doubles the risk of VTE associated with oral contraceptive use.

■ COMMENTARY

A tale of two papers with similar design coming to entirely different conclusions about the risk of thrombosis with oral contraceptives; but is this a surprise? The literature surrounding VTE risk is as clear as mud. The muddy water flows directly from inherent weaknesses in study design and needs to be carefully navigated. Since DVT is a rare event in otherwise healthy young women, large numbers of individuals must be studied to obtain statistically valid comparisons. Since most epidemiologists don't have the funding to enroll subjects in large prospective studies (or the patience to wait for these results), shortcuts are used to obtain answers at a reasonable cost and in a manageable time period.

National and insurance claims databases seem like the perfect solution to the study of rare events like DVT, particularly when these databases link inpatient and outpatient diagnostic codes to prescriptions. Unfortunately, database studies are not truly prospective in nature, and cannot control for important baseline confounders such as obesity and preferential prescribing.[1] The papers highlighted in this review illustrate some of these difficulties. The manuscript by Okoroh et al published in the *American Journal of Obstetrics and Gynecology* made a classic error by failing to control for the interaction between oral contraceptive use and PCOS. If the decision to treat or not to treat PCOS with combined oral contraceptives is an indication of disease severity, then any analysis of health effects due to oral contraceptive treatment would be subject to confounding by indication. The surprising conclusion from this paper that oral contraceptive use reduced the risk of VTE in PCOS women is certainly explained by this confounder (e.g., healthier PCOS patients are prescribed oral contraceptives). The authors attempt to explain this by postulating that the effect was due to the suppression of ovarian androgens; this might fool a few epidemiologists, but it should not fool any student of endocrinology.

The paper by Bird's group tried to control for this bias by selecting a cohort of non-oral contraceptive users with the same characteristics of the oral contraceptive group, including PCOS. They also used a "prospective" approach to analysis — to calculate incident and not prevalent cases of VTE. Although this study is published in the more obscure *Canadian Medical Association Journal*, the findings are more plausible, robust, and consistent with known biologic mechanisms. The discussion is also much more relevant than the paper in the Gray Journal. The data demonstrate that PCOS is associated with an increased risk of DVT, and the use of oral contraceptives in PCOS patients increases the risk further. Keep in mind though that some of this interaction is due to obesity, and other factors such as abnormal lipids and insulin resistance certainly have an impact. So this study, while better, is also limited by the lack of baseline information on these important confounders.

The clinically important point from all of this is that the principle risk of combined hormonal contraception is thrombosis. The good news is that venous and arterial thromboses are rare events in otherwise healthy reproductive age women. Combined hormonal contraceptive methods are appropriate for most women, and the risk of VTE with pregnancy exceeds that of oral contraceptive use even in high-risk women.[2] The bad news is that not

all of our patients are healthy. Consider family history of thrombosis, metabolic syndrome, obesity, and lifestyle as important factors to discuss with your patients. Multiple risk factors are important to consider. Some PCOS women are relatively healthy, while others are not. Sometimes we have to balance potential benefits (reduction in androgens, menstrual regularity) with risks (increased VTE risk) in complicated conditions like PCOS. So look more carefully at your next patient with PCOS and use her overall health status to decide whether she is a good candidate for a combined hormonal method. ■

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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:

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
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CME Questions

1. **Which of the important prognostic factors were controlled for in the multivariate analysis of metformin's effect on overall survival?**
   a. Dose-dense chemotherapy use
   b. Neoadjuvant chemotherapy administration
   c. Diabetes mellitus
   d. Body mass index
   e. Secondary surgical debulking

2. **Repeat abortion rates decreased in the St. Louis, Missouri, area during the period of the Contraceptive CHOICE Project intervention.**
   a. True
   b. False

3. **Which of the following does not fit data in the microarray study by Wapner et al?**
   a. Microarray did not pick up unbalanced translocations.
   b. Microarray results were "uncertain" in only 10% of samples.
   c. Most of the samples tested came from patients who were of advanced maternal age.
   d. A committee of experts reviewed the "uncertain" results to further classify them into "likely benign" or "potentially significant."

4. **The Wapner et al study only dealt with samples obtained by either chorionic villus sampling or amniocentesis, and were not correlated with cfDNA results.**
   a. True
   b. False

5. **Compared with standard karyotype, microarray:**
   a. identified 1.5% more clinically significant rearrangements in those of advanced maternal age or those with abnormal aneuploidy screening.
   b. identified fewer unbalanced translocations or deletions.
   c. identified 3% more rearrangements in fetuses with structural abnormalities.
   d. was no better in identifying sex chromosome abnormalities.

6. **Women with polycystic ovarian syndrome have an increased risk of:**
   a. venous thrombosis with oral contraceptive use.
   b. hemorrhagic stroke with use of the etonogestrel implants.
   c. candida infections with use of the vaginal ring contraception.
   d. vitamin D deficiency with use of the copper IUD.

In Future Issues: **Testosterone in Women**

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.*

FDA Approves Apixaban for Patients with Nonvalvular AF

In this issue: Apixaban approval; new dental clinical practice guideline; apixaban for VTE; aspirin resistance; tamoxifen treatment; and FDA actions.

Apixaban superior to warfarin in trial

The FDA has approved apixaban — the long-awaited third novel oral anticoagulant (NOAC) — for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The drug follows dabigatran (Pradaxa) and rivaroxaban (Xarelto) for this indication, which has been traditionally treated with warfarin. The safety and efficacy of apixaban was demonstrated in the 18,000 patient ARISTOTLE trial, which showed that in patients with nonvalvular AF, apixaban was superior to warfarin in preventing stroke and systemic embolism, caused less bleeding, and resulted in lower mortality than warfarin. The FDA will likely allow the manufacturers of apixaban to market the drug as "superior to warfarin." Apixaban is dosed twice a day, similar to dabigatran; rivaroxaban is dosed once a day. Apixaban and rivaroxaban are factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. No head-to-head studies have been done among the three NOACs, which are expected to compete aggressively for this lucrative market that is worth billions of dollars in sales. All three lack a reversal agent, which could potentially increase the risk of serious bleeding. Apixaban is marketed as Eliquis by Bristol-Myers Squibb and Pfizer. ■

New dental prophylaxis guideline

The American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association (ADA) have jointly published a clinical practice guideline regarding dental prophylaxis in patients with orthopedic implants. The recommendations, which are based on very limited evidence, state that, "the practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures." The guideline further states that they are unable to recommend for or against topical oral antibiotics in patients with implants, but they do recommend that patients with joint implants should "maintain appropriate oral hygiene," even though there is no evidence regarding this recommendation. This guideline does little to settle the debate between orthopedic surgeons, who often recommend lifetime dental prophylaxis, and infectious disease specialists who generally recommend against dental prophylaxis after 1 year. This rather weakly worded guideline is probably not the guidance most primary care physicians were hoping for, since they are generally responsible for prescribing prophylactic antibiotics and are responsible for possible adverse effects. The full guideline is available at www.aaos.org/research/guidelines/PUDP/dental_guideline.asp. ■

Length of treatment for VTE

How long should we treat patients with venous thromboembolism (VTE)? VTE includes deep-vein thrombosis and pulmonary embolism. Current

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guidelines recommend 3-6 months of anticoagulation for unprovoked VTE — usually low-molecular weight heparin followed by warfarin. A new study suggests that an additional year of the factor Xa inhibitor apixaban (recently approved for stroke prevention in nonvalvular atrial fibrillation, see page 1) may be beneficial for these patients. In an industry-sponsored study, patients with VTE who had completed 6-12 months of anticoagulation therapy were randomized to an additional 12 months of apixaban (2.5 or 5 mg twice a day) or placebo. Nearly 2500 patients were included in the intention-to-treat analysis. Recurrent VTE or death from VTE occurred in 73 of 829 patients randomized to placebo (8.8%) compared to 14 of 840 patients on 2.5 mg of apixaban (1.7%) and 14 of 813 patients on 5 mg of apixaban (1.7%; $P < 0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group and 0.2% and 0.1% in the apixaban 2.5 mg and 5 mg groups, respectively. The rate of death from any cause was 1.7% in the placebo group and 0.8% and 0.5% in the apixaban 2.5 mg and 5 mg groups, respectively. The authors conclude that extended anticoagulation with apixaban at either a treatment dose (5 mg bid) or thromboprophylactic doses (2.5 mg bid) reduced the risk of recurrent VTE without increasing the rate of major bleeding (*N Engl J Med* published online Dec. 8, 2012. doi: 10.1056/NEJMoa1207541). In this study, the majority of patients were younger than age 75 without other comorbities such as low body weight or renal impairment. It is also unknown if the results of this study are applicable to other approved anticoagulants such as rivaroxaban. ■

Aspirin resistance and enteric coating

Could "aspirin resistance" be due to enteric coating? The concept of aspirin resistance is very controversial with some experts suggesting that it does not exist. A new study suggests that enteric coating of aspirin may be partially responsible for "pseudoresistance." Researchers recruited 400 healthy volunteers who were then screened for their response to a single, oral dose of 325 mg immediate-release or enteric-coated aspirin. Variable absorption caused nearly half of those taking enteric-coated aspirin to have apparent resistance (49%), while this was not seen in any of the subjects taking immediate-release aspirin. On re-exposure, all of those with variable absorption responded to aspirin. The authors conclude that the study failed to identify a single case of true aspirin resistance, but pseudoresistance, reflecting delayed and reduced drug absorption, complicates enteric-coated but not immediate-release aspirin (*Circulation* published online Dec. 4, 2012. doi: 10.1161/CIRCULATIONAHA.112.117283). This study seems to contradict the concept that up to 40% of the population is "aspirin resistant." There is a suggestion that the concept of aspirin resistance has been touted by the manufacturers of expensive brand-name aspirin substitutes. This study may question the wisdom of the routine use of enteric-coated aspirin, especially given that enteric coating has very little benefit with regard to gastrointestinal protection. ■

Is 10 years of tamoxifen better?

Ten years of tamoxifen may be better than the standard 5 years for women with estrogen receptor (ER)-positive breast cancer, according to a new study from the United Kingdom. Researchers randomized about 6800 ER-positive women with early breast cancer who had completed 5 years of adjuvant tamoxifen to another 5 years of treatment or stopping therapy. There were 617 recurrences in the 3428 women who took tamoxifen for 10 years vs 711 in 3418 women who stopped at 5 years ($P = 0.002$). There was also a lower death rate (331 vs 397, $P = 0.01$) and reduced overall mortality (639 vs 722, $P = 0.01$) in the 10-year group. There were higher rates of endometrial cancer (relative risk [RR] 1.74, 95% confidence interval [CI], 1.30-2.34) and pulmonary embolism (RR 1.87; CI, 1.13-3.07) in the 10-year group, but no higher rate of stroke and a lower risk of ischemic heart disease (RR 0.76; CI, 0.60-0.95). The authors suggest that 10 years of tamoxifen in ER-positive patients can approximately halve breast cancer mortality during the second decade after diagnosis (*Lancet* published online Dec. 5, 2012. doi.org/10.1016S0140-6736(12) 61963-1). ■

FDA actions

The FDA has approved pasireotide diaspartate injection for the treatment of Cushing's disease in patients who are not candidates for surgery or for whom surgery has not worked. The drug is considered an orphan drug. The safety and efficacy were evaluated in a trial of 162 patients with Cushing's disease who were randomized to one of two doses of the drug. About 20% of participants had normal urine cortisol levels within 6 months. Side effects included increased blood sugar levels and liver injury. The drug is administered subcutaneously twice a day. It is marketed by Novartis as Signifor. In February 2012, the FDA approved mifepristone (Korlym) for the treatment of Cushing's syndrome. ■