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INSIDE

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Do Combined Oral Contraceptives Worsen Breastfeeding Outcomes?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Use of combined oral contraceptives instead of progestin-only pills does not worsen breastfeeding outcomes.*

Source: Espey E, et al. Effect of progestin compared with combined oral contraceptive pills on lactation: A randomized controlled trial. *Obstet Gynecol* 2012;119:5-13.

THE AUTHORS PERFORMED A RANDOMIZED, DOUBLE-BLIND STUDY TO COMpare the effects of progestin-only and combined hormonal contraceptive pills on rates of breastfeeding continuation in postpartum women. Important secondary outcomes included infant growth parameters, satisfaction with breastfeeding, and contraceptive method continuation and satisfaction.

Research nurses approached postpartum women aged 15-45 years who intended to breastfeed and who planned to use oral contraceptives (OC) as their family planning method prior to their hospital discharge. Those who were willing to be randomized to either a progestin-only pill or a combined pill were enrolled if there were no maternal contraindications to combined pills or neonatal concerns that might pose concerns for feeding. Consenting subjects were randomly assigned to receive either a progestin-only (0.35 mg of norethindrone) or combined (1 mg norethindrone/35 mcg ethinyl estradiol; 21 active pills, seven placebo pills) OC starting 2 weeks after delivery. Assignment was concealed by the research pharmacist who removed pills from their approved blister packs and then repackaged them in identical red plastic capsules placing them in identical monthly pill dispensers to disguise their appearance and to maintain the correct order of pill administration (for the standard 21/7 combined pill regimen). Prior to initiation of the pill at 2 weeks postpartum, participants completed in-person questionnaires that assessed breastfeeding continuation and contraceptive use. These were repeated at 8 weeks postpartum along with assessment of infant growth parameters including weight, length, and head circumfer-

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ence. Telephone questionnaires assessing breastfeeding, contraceptive continuation, and satisfaction were completed weekly between these visits, and at 4 and 6 months. Breastfeeding continuation at 8 weeks (compared between groups using Cox proportional hazards regression) did not differ between pill groups (progestin-only 63.5%; combined hormonal 64.1%), and there was no difference in contraceptive continuation or infant growth parameters. Factors associated with decreased rates of breastfeeding in both groups were infant formula supplementation and maternal perception of inadequate milk supply.

■ COMMENTARY

This well-designed clinical trial addresses the two most common discharge dilemmas on the postpartum unit for healthy mothers. How do we increase rates of breastfeeding and how do we improve contraceptive compliance to reduce the risk of unintended pregnancy? According to the most recent results of the National Survey of Family Growth, about 20% of women will want to use the pill.[1] In many institutions, including my own, the postpartum discharge contraception discussion is relegated to interns, and we commonly recommend that women discontinue combined pills that they might be familiar with and like in favor of a progestin-only pill. Although we hope that this conversation is informed by upper-level residents and attending physicians practicing evidence-based medicine, frequently the routine nature of postpartum rounds to health care providers and the multiple distractions of new parents affect the quality of the interaction. The Espey study is notable as it attacks a well-established dogma with Level I evidence. The standard teaching is that estrogen adversely affects breast milk production. There is limited support for this hypothesis in the literature. An open-label, multicenter, World Health Organization (WHO) cohort study found that combined OCs caused a significant decrease in milk output and total energy content, as well as widespread changes in milk constituents, while none of these changes were observed in users of the progestin-only pill and depot medroxyprogesterone acetate. However, as the authors of the current study note in their discussion, the changes observed in the combined OC group were not associated with significant differences in infant weight or fat-fold, or in the rate of contraceptive discontinuation for failure to gain weight.[2] A 2003 Cochrane review by Truitt concluded "evidence from randomized controlled trials on the effect of hormonal contraceptives during lactation is limited and of poor quality; results should be interpreted with caution. The existing randomized controlled trials are insufficient to establish an effect of hormonal contraception, if any, on milk quality and quantity. Evidence is inadequate to make recommendations regarding hormonal contraceptive use for lactating women. At least one properly conducted randomized controlled trial of adequate size is urgently needed to address this question."[3]

Although the Espey study provides this much-needed evidence to alleviate the concern that breastfeeding success is reduced by the early initiation of a combined pill, a couple of other findings are worth noting before we lecture the interns on tomorrow's rounds. First, the most important factors associated with breastfeeding discontinuation in the study were self-identified concerns about the adequacy of milk supply and the use of any supplemental feeding. These were not affected by the contraceptive pill used. My pet peeve on morning rounds is the absence of a response from the medical team when a new mother announces that she plans to use "bottle and breast." The presence of formula in the patient's room is a sure sign that lactation will end early, and this is an important counseling point if we want to increase nursing success. The authors mention that breastfeeding characteristics in the study population were similar to other women in New Mexico, where 84% initiate breastfeeding but only 60% continue to breastfeed through 8 weeks. In the study cohort, 64% of randomized study participants were breastfeeding at 8 weeks, but only 28% were exclusively breastfeeding. While this small number of exclusively breastfeeding moms potentially dilutes the overall impact of estrogen use on breastfeeding continuation, there did not appear to be any difference in continuation based on the pill used, regardless of whether there were concerns about milk supply or the use of supplements. Infant growth parameters did not differ between groups over 8 weeks.

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Another important issue to consider is contraceptive efficacy. Women who exclusively breastfeed are at low risk for pregnancy during the first 4-6 months postpartum, while ovulation can occur as early as 3 weeks postpartum in non-breastfeeding women or as early as 6 weeks in women who are breastfeeding with supplementation.[4] In patient populations where the expectation for breastfeeding is low, it makes sense to initiate contraception early, with the most effective and reliable method possible. For many women, that may be a combination OC, particularly if they have had good success with the method in the past. The typical failure with progestin-only pills is about the same as combination pills,[5] so we should not hesitate to recommend these. However, the most important feature of success is correct and consistent use. The study was too small to consider pregnancy rates, but there was no difference in satisfaction or discontinuation of the contraceptive method. Unfortunately, the authors did not present any data beyond 8 weeks, where bleeding patterns become unsatisfactory for many women on the progestin-only pill.

My final point reflects the constant call of the physician to balance potential harm with potential good. Although the use of combined OCs may not affect success with breastfeeding or infant growth, is it safe for mothers? The WHO, Centers for Disease Control (CDC), and American Congress of Obstetricians and Gynecologists say no. The recently published CDC medical eligibility criteria (MEC) for contraceptive use assigns initiation of combined pills before 21 days postpartum as category 4 (unacceptable health risks) for thromboembolism, and initiation at 21-29 days for women at low risk (e.g., no other risk factors except recent delivery) for thromboembolism as category 3 (theoretical or proven risks generally outweigh advantages).[6] The WHO MEC[7] are even more conservative with a category 4 (unacceptable health risk) for initiation of combined pills within 6 weeks of delivery and a category 3 (theoretical or proven risks usually outweigh the advantages) for initiation of combined pills from 6 weeks to 6 months in primarily breastfeeding women. However, it is fair to point out that both of these recommendations are based on consensus opinion, as there is no direct evidence examining the risk for venous thromboembolism among postpartum women using combined pills. ■

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Is There an Increased Risk of HIV Transmission with Use of Hormonal Contraception?

ABSTRACT & COMMENTARY

By Maureen Baldwin, MD, MPH, and Alison Edelman, MD, MPH

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Dr. Baldwin reports no financial relationships relevant to this field of study. Dr. Edelman reports that she is a subdermal implant trainer for Merck.

Synopsis: *There may be an increased risk of HIV transmission among sero-discordant couples when the woman is using hormonal contraception, but this does not currently change the recommendations for contraceptive use in this population.*

Source: Heffron R, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: A prospective cohort study. *Lancet Infect Dis* 2012;12:19-26.

Heffron et al conducted a secondary analysis of two longitudinal studies (2004-2010) performed in Africa.[1] The original purpose of these studies was to

evaluate HIV-1 transmission in discordant couples when the HIV-positive (HIV+) partner was also infected with herpes simplex virus (HSV type 2) but taking acyclovir.[2] Initial HIV status was documented and couples were followed for an average of 18 months. A total of 3790 couples were studied; at the start of the trial, the male partner was HIV+/HSV+ in 1314 couples and the female partner was HIV+/HSV+ in the remaining 2476 couples. The uninfected partner was tested every 3 months for HIV status.

The main objective of this secondary analysis was to evaluate if hormonal contraception affected HIV acquisition in the uninfected partner. Contraceptive status was self-reported every 3 months. The proportion of women using hormonal contraception was low: 15% of uninfected women and 17% of infected women. Overall, new HIV infections doubled among couples where the female partner was using hormonal contraception (risk to men: 19/727 vs 40/2647 sero-conversions per person-years, adjusted hazard ratio [HR] 1.97; 95% confidence interval [CI], 1.12-3.45; $P = 0.02$; risk to women: 13/197 vs 60/1586, adjusted HR 1.98; 95% CI, 1.06-3.68; $P = 0.03$). In HIV- women using hormonal contraception, 13 women sero-converted (injectables = 10, oral contraceptives = 3). In HIV- male partners of HIV+ women using hormonal contraception, 19 men became infected with the same genetically linked HIV-1 strain as their partner (15 = injectables, 4 = oral contraceptives). Less condom use was reported in couples where the woman was HIV+ and using hormonal contraception.

■ COMMENTARY

Once again, contraception was the focus of negative media attention, with headlines around the world reporting that hormonal contraception causes HIV. Here are several important points to understand about this study:

1. Heffron's study did not find that hormonal birth control causes HIV; only HIV causes HIV. Birth control, with the exception of condoms, has never been touted as a way to prevent HIV.
2. This study originally was designed to determine if HSV increases the risk of HIV transmission.
3. Rates of hormonal contraceptive use was very low and self-reported, but not objectively confirmed.
4. Condoms were encouraged in all couples, but those using hormonal contraception reported less use.
5. Although this study found a potential two-fold increased relative risk of HIV sero-conversion in discordant couples when the woman was using hormonal contraception, the overall actual risk of transmission was low. (Remember, relative risk is only about the association between two things and does not provide any information regarding how many actual people this might affect.) In other words: if it's a rare risk, it will still be rare even if the risk is double.

The concern regarding HIV and hormonal contraception is not new; more than 40 studies have previously examined this relationship.[3-7] Unfortunately many of these studies suffered from significant flaws similar to this most recent study including:

1. Small sample size: Although the total population of couples tracked in this study was large, the actual number of couples utilizing hormonal contraception who experienced sero-conversion was very small — a total of 19 men and 13 women.
2. Self-report of crucial variables (as stated earlier): subjects self-reported their contraceptive use and sexual habits. These habits were not objectively confirmed.
3. High-risk behaviors in the groups observed for sero-conversion:
   a. Many of the cases of sero-conversion appear to be due to sexual exposures taking place outside the primary relationship. You might imagine that in a study of HIV transmission it matters whether couples are having sex with only each other and if condoms are regularly used. Couples in this study reported an average of 3-4 episodes of sex per month with each other. However, there were a significant number of sexual encounters outside the primary relationship — around 1% in women and 8-9% in men. Of the total number of participants that sero-converted, only 85% of women infected had their HIV linked to their primary male partner, whereas only 63% of men infected had their HIV linked to their primary female partner. This suggests that participants were underreporting sex outside the primary partnership, or that they were contracting HIV by some other means.
   b. Couples using hormonal contraception were less likely to use condoms.[8] HIV+/HSV+ women using hormonal contraception were more likely than those not using hormonal contraception to report sex without a condom (13% vs 10%, $P = 0.009$).
   c. At least one-quarter of the women in the study population were pregnant at some point during the 18 months. This proportion alone suggests that far more sex without condoms was occurring than reported, especially in the population not using hormonal contraception. Pregnancy is an independent risk factor for increasing the risk of HIV transmission from women to men. In fact, in this same study population, men

were more than two times as likely to get HIV when their partner was pregnant.[9]

Although researchers adjusted for the biggest confounders — unprotected sex, sexual frequency with HIV exposure, and pregnancy — these factors varied between the groups. With extremely small numbers of participants using hormonal contraception, adjusting for confounders is fraught with errors and can give the illusion of an effect when one does not exist. In other words, the HIV infections easily could have occurred from one of these other risk factors rather than due to the hormonal contraception.

Is there any biologic plausibility to the hypothesis that hormonal contraception increases the risk of HIV transmission? The thought is that perhaps there is increased viral shedding in HIV-infected women using hormonal contraception, thereby increasing the risk of HIV transmission to their male partners. Several studies have looked at the presence of HIV-1 RNA in cervicovaginal secretions of women, including Heffron's study.[10,11] HIV-1 RNA was found to be higher in women using hormonal contraception, particularly injectable methods. Interestingly, the amount of RNA in the cervicovaginal secretions was not associated with plasma HIV-1 concentrations. However, no analysis was performed to correlate if high levels of viral shedding were related to actual HIV acquisition. The story of male to female transmission is much less clear. There is no known association of higher levels of HIV-1 RNA in semen or penile secretions of infected men with uninfected female partners using hormonal contraception.

At the end of the day, can we condense this information into a clinically relevant recommendation? Although there are limitations to these data, we do not want to ignore something as significant and life-altering as becoming infected with HIV. Summarizing the findings in a different way might help. If we take the study at face value, then being in a high-risk relationship confers a 2% risk of HIV infection over 18 months and the use of hormonal contraception may increase this risk to 4%. However, the risks of not using contraception include pregnancy. The chance of pregnancy in such a population is about 5% while using hormonal contraception and about 15% without using hormonal contraception. HIV transmission in pregnancy also is doubled. Maternal mortality rates vary depending on location, but specific to Sub-Saharan Africa, it is extremely high and even higher for an HIV+ woman. Plus there is the risk of transmission to the unborn child. Clearly, systemwide recommendations need to take into account the significant benefits of contraceptive methods.

Current guidelines are based on composite data and recommend the use of effective contraceptive methods, including hormonal contraception and barrier protection in women with HIV and who are exposed to HIV. Based on these most recent data, the World Health Organization will convene in February 2012 to discuss further recommendations and will issue a position statement at that time. ■

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Hyperemesis Gravidarum and Adverse Perinatal Outcomes

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *A recent meta-analysis has suggested that there is a modestly increased risk for preterm birth, SGA, and low birth weight in patients suffering from hyperemesis gravidarum.*

Source: Veenendaal MV, et al. Consequences of hyperemesis gravidarum for offspring: A systematic review and meta-analysis. *BJOG* 2011;118:1302-1313.

How often are we asked whether a patient who has had severe nausea and vomiting in early pregnancy has a greater chance of adverse outcome in her pregnancy? Intuitively, one would think that there might be some effect on the fetus and/or placenta, but since there have been few red flags in the literature to the contrary, I have been inclined to be (and I guess I will continue to be) reassuring.

A meta-analysis recently published in the *British Journal of Obstetrics and Gynaecology* does show some elevation of risk in the 0.3-2% of patients with the most severe form of the spectrum, hyperemeis gravidarum (HG).[1] The authors reviewed 205 studies. After applying rigorous exclusionary criteria, 24 papers remained that dealt with the short- and long-term effects of HG. These studies were either cohort (n = 10), case-control (n = 13), or cross-sectional (n = 1) in design. Four studies were prospective.

Those who were admitted with, or simply diagnosed to have, HG had an increased chance of having a female infant (odds ratio [OR] = 1.27; 95% confidence interval [CI], 1.21-1.34). Low birth weight occurred in 6.4% in infants with HG vs 5% in controls (OR = 1.42; 95% CI, 1.27-1.58), and small-for-gestational age (SGA) occurred in 17.9% of those with HG, compared with 12.7% in controls (OR = 1.28; 95% CI, 1.02-1.68). There also was a significant increase in preterm delivery (OR = 1.32; 95% CI, 1.04-1.68).

The categories in which HG had no significant impact were in perinatal deaths, Apgar scores, and congenital anomalies. Only one long-term study was conducted involving HG and showed no differences in neurological outcomes at 1 year of age between groups. Interestingly, one study did show an increase in testicular cancer in men younger than 40 years of age whose mothers had HG.

■ COMMENTARY

I have been waffling when asked questions by pregnant patients about the possible ill effects of persistent nausea and vomiting because single reports in the literature have had conflicting results. Actually, I am surprised that a meta-analysis has not been put together before now. Now, we can say that there may be only a modest increase in low birth weight, SGA, and preterm birth, but not in perinatal death, anomalies, or long-term neurological outcomes. Nevertheless, it should be cautioned that these outcome data only apply to the most severe forms of nausea and vomiting in pregnancy, and, in fact, may not be due to the nausea and vomiting, per se, but rather to a separate predisposition for the outcomes in patients who are prone to this condition. This could not be addressed in the meta-analysis.

Since even less is known on how to best treat patients with HG, given the paucity of trials using various methods, one simply relies on anecdotal experience. First-line management should be trying to maintain adequate fluid and electrolyte balance, as well as avoiding vitamin deficiencies (especially thiamin). Some medications can help, most of which have not been studied adequately. These include various antihistamines and antiemetics. We definitely have had good success with the serotonin antagonist, ondansetron (Zofran), in many patients with intractable nausea and vomiting. Even some over-the-counter medications, such as Unisom (a nighttime medication), can work in milder forms of nausea. Acupuncture has been reported to be successful in some individuals.

Treating the fallout of HG is very important. If oral fluid replacement and small feedings do not work, home-based parenteral alimentation of IV fluid replacement is effective in keeping patients from needing repeated hospitalizations. Fortunately, the huge majority of miserable patients can count on their discomfort being short-lived. And yes, those grandmothers asserting that this first trimester nausea and vomiting means that their granddaughters' fetuses are girls are right more often than wrong. ■

Reference

1. Veenendaal MV, et al. Consequences of hyperemesis gravidarum for offspring: Asystematic review and meta-analysis. *BJOG* 2011;118:1302-1313.

Do We Have a New Standard of Care for Advanced Ovarian Cancer?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Dr. Coleman serves as an uncompensated scientific advisor for and has received research funding from Genentech/Roche.

Synopsis: *Bevacizumab, when added to standard chemotherapy and continued as maintenance therapy for women with advanced stage ovarian cancer, signifi-*

cantly improved progression-free survival, but at the expense of increased toxicity. Overall survival data are immature but unlikely to demonstrate a benefit.

Source: Burger RA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365:2473-2483.

Vascular endothelial growth factor (VEGF) is a key factor in the normal and tumor microenvironment regulating angiogenesis. VEGF expression in tumor has been linked prognostically with poor survival characteristics in epithelial ovarian cancer, and targeting it, via several pharmaceutical strategies, has suggested clinical efficacy in this disease. Bevacizumab, a humanized monoclonal antibody-targeting VEGF ligand, has shown single-agent and combinatorial activity in women with recurrent tumors. The current trial, GOG-218, was a double-blind, placebo-controlled, Phase 3 study randomly assigning women with newly diagnosed stage III/IV epithelial ovarian cancer to receive one of three treatments after primary debulking surgery. All three arms included paclitaxel and carboplatin IV at standard doses for six every-3-week infusions. Arm I used a placebo during chemotherapy (starting on cycle 2) continuing throughout the intended maintenance period (to cycle 22). Arm II used bevacizumab (15 mg/kg) every 3 weeks with chemotherapy, but continued with placebo during maintenance to cycle 22. Arm III used bevacizumab (same dose) during chemotherapy and maintenance. The initial primary endpoint was overall survival (OS), but was changed to progression-free survival (PFS) during the trial due to concerns of investigators and patients regarding post-progression blinding. Overall, 1873 women were enrolled. The median PFS for the three arms were: 10.3 months (control group [Arm I]), 11.2 months (Arm II), and 14.1 months (Arm III). Relative to Arm I, the hazard ratio for progression or death in Arm II was 0.908 (95% confidence interval [CI], 0.795-1.040; $P = 0.16$), and 0.717 (95% CI, 0.625-0.824; $P < 0.001$) in Arm III. At the time of analysis, 76.3% of patients were alive, with no significant differences in OS among the three groups. Some toxicities, particularly those associated with bevacizumab, were higher in the arms receiving the agent such as: hypertension requiring medical therapy (Arm II: 16.5%, Arm III: 22.9%, vs Arm I: 7.2%, $P < 0.05$), and gastrointestinal-wall disruption requiring medical intervention (Arm II: 2.8%, Arm III: 2.6%, vs Arm I: 1.2%, P = NS). However, others, such as gastrointestinal perforation, thromboembolic disease, proteinuria, and wound disruption, were no different between the arms. The use of bevacizumab during and up to 10 months after carboplatin and paclitaxel chemotherapy prolongs the median PFS by about 4 months in patients with advanced epithelial ovarian cancer.

■ COMMENTARY

The importance of VEGF in ovarian cancer has been known for more than 2 decades and antedated the first indication of bevacizumab in cancer therapy. Elegantly described was its role in ascites formation, tumor edema and perfusion, tumor growth and proliferation, metastases, and progression.[1] Since that time, and with the availability of multiple agents and strategies for targeting the VEGF:VEGFR axis and its downstream events, exploration in the clinic has been aggressively pursued.[2] Early enthusiasm driving the conduct of several small prospective Phase 2 trials predominately in patients with recurrent disease produced remarkable clinical activity, particularly for bevacizumab. These provided the necessary backdrop for funding the large Phase 3 studies conducted now in both frontline (GOG-218 and ICON7) and in the recurrent setting (OCEANS, GOG-213, and AURELIA). In this issue of the *New England Journal of Medicine*, the two frontline trials were reported.[3] The punch line from these two is similar and well known following their initial presentation at national and international meetings in 2010, both with updates in 2011. However, the results are thought-provoking, especially in light of the unprecedented and widely publicized FDA vs Genentech/Roche showdown last summer (with a final decision in late 2011) over the retraction of the FDA label of bevacizumab in metastatic breast cancer. At the core of that debate was modest gains for an intermediary endpoint, PFS, in the absence of gains in OS, and with an unfavorable toxicity profile.

The situation is remarkably similar to the data from the two newly published frontline ovarian trials. I've chosen to profile GOG-218 because this trial was conducted with regulatory intent and included several key controls and assessments lacking in ICON7. However, both trials raise a number of concerns about whether we can adapt these data for standard clinical care. The first is in the types of patients in whom the drug should be given. Ideally, a biomarker (blood, imaging, tumor) would help make that selection; however, it would appear that patients with the bulkiest disease might benefit the most. This may be because that cohort of patients is, in general, receiving bevacizumab until progression. The act of stopping bevacizumab at an arbitrary point before progression, as well as post progression bevacizumab use, probably explains the "catch-up" effect, which nullified the OS endpoint. The other issue, not addressed by either study, is whether administering bevacizumab only in the maintenance setting (and not with chemotherapy) could have delivered the same effect. The major issue for each of these trials relative to clinical care is how to balance interim gains, intended therapy, toxicity, and cost. The quality of life (QoL) survey performed in GOG-218 demonstrated no perceptible diminution despite the additional toxicity.

However, it has been estimated that given these results, to be cost-effective, the magnitude of benefit for the bevacizumab arm (Arm III) would have to be three times greater than control (around 31 months) or be one-fourth the cost.[4] And, if our strategy to maximize clinical efficacy is to administer bevacizumab, not for 22 cycles, but until progression, the cost would be even greater. One has to recall that about one-third of patients are cured with chemotherapy alone; in the absence of knowing who these individuals are, we are obligating them to a lifetime of therapy they never needed.

And so I raise the question, which titles this review, "Do we have a new standard of care?" The answer is not easy, but would be hard-pressed to support fully without FDA approval. It is reasonable, however, to consider it a standard in women with the most advanced disease (suboptimally debulked), but questions remain as to dose and duration, and when to administer the agent. Fortunately, two studies (one fully enrolled and one nearly fully enrolled) are poised to address some of these issues in the near future. Until then, there is opportunity to search for reliable biomarkers, other classes of agents to be looked at in combination with standard chemotherapy in this setting, and new strategies to use this clearly active and important biological therapeutic for our patients with ovarian cancer. ■

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CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

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

CME Questions

1. **Randomized trials comparing the use of a progestin-only pill and combined oral contraceptives prior to 6 weeks have demonstrated that:**
   a. combined pills increase the risk of venous thrombosis.
   b. progestin-only pills are more effective.
   c. combined pills are more effective.
   d. breastfeeding continuation at 8 weeks is not affected by type of pill.

2. **Confounders to the relationship between hormonal contraception use and HIV transmission include:**
   a. condom use.
   b. pregnancy.
   c. sexual frequency.
   d. All of the above

3. **Acupuncture can help some patients to relieve nausea and vomiting.**
   a. True
   b. False

4. **Hyperemesis gravidarum affects one in 15 pregnancies.**
   a. True
   b. False

5. **Which of the following bevacizumab-attributed toxicities was significantly higher in the arms of this trial containing bevacizumab relative to control?**
   a. Febrile neutropenia
   b. Arterial thromboembolism
   c. Proteinuria
   d. Gastrointestinal events
   e. Hypertension

PHARMACOLOGY WATCH

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

New, Shorter Treatment Regimen for Tuberculosis

In this issue: New treatment for TB; safety of dabigatran; quality of antidepressants; systolic hypertension treatment; and FDA actions.

Short course treatment for latent TB

Three months of two drugs administered once weekly is as effective as 9 months of daily isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI), according to a new study. An international team of researchers randomized nearly 8000 patients with latent tuberculosis (TB) to 3 months of directly observed once-weekly therapy with rifapentine 900 mg plus INH 900 mg or 9 months of self-administered daily INH 300 mg. The primary endpoint was confirmed TB after 33 months of follow-up. In the modified intention-to-treat analysis, TB developed in 0.19% of the once-weekly combination group and in 0.43% of the INH only group. Rates of completion were much higher with the short course, once-weekly regimen (82.1% in the combination-therapy group and 69.0% in the INH only group, $P < 0.001$). Rates of hepatotoxicity were higher in the INH only group. The authors conclude that use of rifapentine plus INH given once a week for 3 months is as effective as 9 months of INH in preventing tuberculosis and has a higher treatment-completion rate (*N Engl J Med* 2011;365:2155-2166). Based on this study and others, the CDC has issued a new recommendation on the use of short-course combination therapy for latent TB infection. The recommendation states, "The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients ≥ 12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB)." It also recommends that the new regimen may be considered for other categories of patients when it offers advantages. Daily INH continues to be the preferred regimen for children between the ages of 2 and 11 (*MMWR Morb Mortal Wkly Rep* 2011;60:1650-1653). ■

Bleeding concerns with dabigatran

Dabigatran (Pradaxa), Boehringer Ingelheim's blockbuster anticoagulant, is the subject of a December 7, 2011, Drug Safety Communication by the FDA regarding serious bleeding events. The FDA is evaluating postmarketing reports of serious bleeding events that may lead to serious or even fatal outcomes. Experts are working to determine whether the reports of bleeding associated with the drug are occurring more commonly than would be expected based on observations from large clinical trials. The drug was approved in October 2010 to reduce the risk of stroke in patients with non-valvular atrial fibrillation. More than a million prescriptions have been filled by nearly 400,000 patients since approval. ■

All antidepressants are created equal

When it comes to choosing an antidepressant, all modern drugs are roughly equivalent, according to a new study in the *Annals of Internal Medicine*. Researchers performed a large meta-analysis of 234 studies that looked at the treatment of major depressive disorder (MDD) with second-generation anti-

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depressants. There were no differences among the drugs with regard to efficacy or effectiveness for the treatment of acute, continuation, and maintenance phases of MDD. There were also no significant differences when accompanying symptoms were taken into account or other factors such as age, sex, ethnicity, or comorbid conditions. There were differences among the drugs with regard to onset of action, adverse effects, and some quality-of-life issues. There was also a significant difference in cost and dosing convenience. Drugs considered in the study were bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine. The authors suggest that familiarity with the broad spectrum of antidepressants is prudent given the difficulty of predicting which medication will be effective and tolerated by any given patient (*Ann Intern Med* 2011;155:772-785). ■

Benefits of treating systolic hypertension

Older adults with isolated systolic hypertension gained about 5 months of life when treated with chlorthalidone-based stepped care 2 decades after completion of the Systolic Hypertension in the Elderly Program (SHEP) trial. SHEP, conducted between 1985 and 1990, was a clinical trial of patients aged 60 years or older (mean age 72) with isolated systolic hypertension who were randomized to chlorthalidone-based antihypertensive therapy or placebo. Over a mean follow-up of 4.5 years, chlorthalidone-based therapy resulted in prevention of approximately 1 of 2 admissions for heart failure, 1 out of 3 fatal or nonfatal strokes, and 1 of 4 coronary heart disease events, but there was no effect on all-cause mortality or cardiovascular death. At the end of the trial, all participants were advised to receive active therapy. The new study reviewed cardiovascular death and all-cause mortality in SHEP trial participants 22 years after the study ended. Life expectancy gain between the active treatment group and placebo group was 105 days (95% confidence interval [CI], -39 to 242; $P = 0.07$) for all-cause mortality and 158 days (95% CI, 36-287; $P = 0.009$) for cardiovascular death. Each month of active treatment was associated with approximately 1 day extension in life expectancy. The authors conclude that treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up (*JAMA* 2011;306:2588-2593). This study may help convince older patients with systolic hypertension that compliance with diuretic-based hypertensive therapy is worth the effort as it will prolong their lives. ■

Aliskiren and ACEIs/ARBs don't mix

Aliskiren (Tekturna), Novartis' direct renin inhibitor, should not be combined with an ACE inhibitor or angiotensin receptor blocker (ARB) to treat hypertension, according to the manufacturer. Novartis recently terminated the ALTITUDE trial when it was found that patients with type 2 diabetes or impaired renal function who were given the combination of aliskiren with an ACEI or ARB had a higher incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension. More information can be found at www.novartis.com/newsroom/media-releases/en/2011/1572562.shtml. ■

FDA actions

The FDA approved generic atorvastatin (Lipitor) on November 30, 2011. Ranbaxy Laboratories will make the first generic in 10, 20, 40, and 80 mg strengths. Atorvastatin as Lipitor was first marketed in 1997 and became the best-selling prescription medication in history with sales of more than $125 billion. It has dominated the statin market in recent years, representing nearly a quarter of Pfizer's annual revenue, and the giant pharmaceutical company aggressively defended their patent against multiple challenges. Ranbaxy has 180 days of exclusivity on generic atorvastatin after which time multiple manufacturers are expected to seek approval for their generic version of the drug.

The FDA has approved Prevnar 13 for adults age 50 and older to prevent pneumonia and invasive disease caused by *Streptococcus pneumoniae*. The vaccine was previously approved for children up to 5 years of age. The approval was based on head-to-head studies with Pneumovax 23 which is already approved for use in adults. According to the FDA, "for the 12 common serotypes, Prevnar 13-induced antibody levels were either comparable to or higher than the levels induced by Pneumovax 23." Prevnar 13 is manufactured by Wyeth Pharmaceuticals.

Dronedarone (Multaq) should not be prescribed to patients with permanent atrial fibrillation (AF), based on results from the PALLAS trial which showed that the drug doubles the risk for cardiovascular death, stroke, and heart failure in such patients. The FDA is requiring revised labeling for the antiarrhythmic drug and has issued a Drug Safety Communication after a safety review was completed. If dronedarone is to be prescribed, the FDA recommends ECGs every 3 months and immediately stopping the drug if the patient is found to be in AF. The drug is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF (paroxysmal or persistent AF). Dronedarone is manufactured by Sanofi-Aventis. ■