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INSIDE

Term pregnancy **page 28**

What to do about microscopic hematuria **page 29**

Is it time to change the standard of care for low-risk GTN? **page 30**

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Progestins and Risk of Venous Thromboembolism: What's the Deal with Drospirenone?

ABSTRACT & COMMENTARY

By Elizabeth Micks, MD, and Alison Edelman, MD, MPH

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Dr. Micks reports no financial relationship to this field of study. Dr. Edelman is an Implanon trainer for Merck.

Synopsis: *The risk of venous thromboembolism was significantly higher for users of combined oral contraceptives containing drospirenone compared to users of pills containing levonorgestrel.*

Sources: Parkin L, et al. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: Nested case-control study based on UK General Practice Research Database. *BMJ* 2011;342:d2139. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: Case-control study using United States claims data. *BMJ* 2011;342:d2151.

TWO INDEPENDENT CASE-CONTROL STUDIES INVESTIGATING THE RISK OF venous thromboembolism (VTE) in users of oral contraceptives (OC) containing 30 mcg of ethinyl estradiol and a progestin component of either drospirenone or levonorgestrel found that VTE risk was two to three times higher in those using a drospirenone pill.[1,2] Data were extracted from the UK General Practice Research Database (2002-2009)[1] and from the PharMetrics database of U.S. insurance claims (2002-2008).[2] A VTE case was included only if it was not associated with other risk factors like pregnancy, surgery, trauma, or immobilization. In the UK General Practice Research Database, 61 VTE cases and 215 matched controls were identified out of 318,825 women

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using an OC with a drospirenone or levonorgestrel progestin component. Unadjusted odds ratio (OR) for VTE among drospirenone users was 3.2 (95% confidence interval [CI] 1.5-7.0). Adjusting for risk factors such as body mass index, smoking, history of varicose veins, and antidepressant use did not significantly change the odds ratio (OR 3.1, 95% CI 1.3-7.5). As for the findings based on the insurance claims data, 186 VTE cases and 681 matched controls were identified out of 937,408 users of OCs containing drospirenone or levonorgestrel. Unadjusted OR for VTE in drospirenone users was 2.3 (95% CI 1.6-3.2). This association did not change significantly when adjusted for duration of exposure. The effect was larger for women younger than 30 years old, with an OR of 3.7 (95% CI 2.0-6.9).

■ COMMENTARY

The alarm has sounded once again that an increased risk of VTE may exist with the use of a certain newer progestin. Two independent case-control studies investigating the risk of VTE in users of OCs containing 30 mcg of ethinyl estradiol and a progestin component of either drospirenone or levonorgestrel found that the VTE risk was two to three times higher in those using a drospirenone-based pill.[1,2] The authors conclude that drospirenone-containing pills should not be first line for oral contraception.

Should we stop prescribing drospirenone based on these findings? What other literature exists to help direct clinical practice? Four previous studies have examined the association between drospirenone and VTE risk;[3-6] two demonstrate an increased risk and two do not. All of the studies have significant methodological flaws, as do the two articles highlighted in this editorial. The two supporting an increased risk were retrospective, which means they have many potential sources of bias, such as in the diagnosis or reporting of VTE. One found a small but significant increase in the risk of VTE with drospirenone use (rate ratio 1.64, 95% CI 1.27-2.10),[3] while the other found a non-statistically significant increase in risk (OR 1.7, 95% CI 0.7-3.9).[4]

Two large prospective studies performed for post-marketing surveillance purposes (phase IV studies) found no increased risk associated with drospirenone. The first study, performed in the United States, did not find a difference in VTE risk in users of a drospirenone-based OC vs other OCs (RR 0.9, 95% CI 0.5-1.6).[5] This study did not separate out levonorgestrel users specifically like Parkin et al[1] and Jick et al.[2] The second study followed 58,674 OC new starts at several centers in Europe.[6] VTE incidences were similar among users of all types of pills. The hazard ratio for VTE comparing users of pills containing drospirenone vs levonorgestrel was 1.0 (95% CI 0.6-1.8), in other words, no difference.

Although these two new studies addressed certain methodological concerns from the previous retrospective studies, they have their own problems. For instance, Jick et al[2] and Parkin et al[1] only included "idiopathic" cases of VTE by excluding pregnancy, cancer, recent trauma, or surgery. However, chart reviews were unable to be performed for each case, and the authors did not have access to information regarding other important risk factors such as family history of VTE or prothrombotic mutations such as Factor V Leiden. While Parkin et al[1] ended up excluding four of 31 VTE cases based on additional chart review, they included all of the remaining 34 cases for which they had no information beyond what was in the database.

Furthermore, since initial studies showing increased risk of VTE in drospirenone users led to considerable publicity, the current studies are subject to diagnostic bias. The study period for the UK study extended to September 2009, and for the PharMetrics study until December 2008. Given the television ads from drug companies and from attorneys seeking women who took drospirenone contraceptive pills and developed blood clots, undoubtedly patients were more likely to seek care for unusual symptoms and physicians were more suspicious of VTE when evaluating users of these pills. Due to the small numbers of cases in these studies, this could have significantly increased the observed effect size.

It also is plausible that in these retrospective studies, the cases and controls differed in ways besides the progestin component of their birth control pill. Confounding by indication may have occurred if clinicians were more

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

Clinical Tips

- Estrogen-containing contraceptives (combination oral contraceptive pills, patch, and ring) should be avoided in women with VTE risk, such as those with a history of blood clots or known thrombophilic conditions. For medically complicated patients who desire contraception, the CDC Medical Eligibility Criteria for Contraceptive Use is an invaluable tool (available at www.cdc.gov/mmwr/pdf/rr/rr59e0528.pdf).

- VTE risk must be discussed and documented with any woman starting an estrogen-containing contraceptive.
  - VTE risk is increased with the use of any estrogen-containing contraceptive, but the absolute risk is low, and significantly less than the risk of VTE in pregnancy.
  - The increase in VTE risk associated with OCs containing drospirenone may be higher than the VTE risk with pills containing levonorgestrel, but the risk is still rare.
    - VTE risk in non-users: 4-5 cases per 100,000 women per year
    - VTE risk in levonorgestrel pill users: 10-20 cases per 100,000 women per year
    - VTE risk in drospirenone pill users: maybe 20-30 cases per 100,000 women per year
    - VTE risk in pregnancy: 48-60 cases per 100,000 women per year

- If women like the pill they are on and want to continue with that pill, then they should stick with it, since stopping and restarting any new OC, regardless of the progestin component, increases the risk of VTE.

likely to prescribe drospirenone pills to women thought to have polycystic ovarian syndrome or other medical conditions that would cause them to have a significantly higher baseline risk of VTE. The PharMetrics study showed that drospirenone users were in fact more likely to have menstrual disorders, though controlling for this factor did not change the odds ratio for VTE. And what about obesity? In the UK study, controlling for BMI did not decrease the observed association. In the PharMetrics study, BMI data were not available so the authors relied on ICD codes for obesity. Only 13% of cases and 6% of controls were found to have this code, which indicates that data on obesity were likely missing for a significant number of patients.

VTE "scares" appear to occur with every new pill formulation or contraceptive system. Remember the pill scare of the mid-1990s or the more recent patch scare?[7] It is known that the highest risk of VTE occurs in the first few cycles of any hormonal contraceptive and decreases over time.[8,9] Stopping and restarting the pill or switching to a different pill increases VTE risk. Efforts were made to control for the early use effect in both studies; however it is not clear that this was accounted for fully.[10]

As for biologic plausibility, two small observational studies found increased prothrombotic changes associated with contraceptive pills containing drospirenone vs those with levonorgestrel.[11,12] Women taking drospirenone pills had significantly lower free protein S levels, but levels of total protein S and tissue factor pathway inhibitor were not statistically significantly different.[12] Thrombotic biomarkers for 14 individual women who switched from levonorgestrel to drospirenone pills became less favorable.[11] However, thrombotic biomarkers have not been associated with actual risk of VTE. Also, it is not clear why drospirenone would have a different effect on thrombotic biomarkers than other progestins.

Most importantly, this new information must be kept in perspective, as prior pill scares have been associated with women acutely stopping their birth control, placing them at even higher risk for VTE due to pregnancy. VTE risk in modern-day OC users (12-20 cases/100,000 women per year) is significantly lower than compared to pregnancy (48-60 cases per 100,000 women per year).[8] Even if drospirenone is confirmed to have a two-fold or three-fold higher risk of VTE over other progestins, the absolute risk of VTE is still rare. The safest contraceptive is the one that a woman takes consistently.

For our patients who are happy with drospirenone-containing pills, we would not recommend that they switch to a different pill, particularly since VTE risk is highest when first starting or switching to a new pill. For women choosing to initiate oral contraception, we must consider the individual patient and possible non-contraceptive benefits that will promote long-term and consistent use of the method. For many patients, drospirenone-containing contraceptive pills will continue to be a safe and effective option. ■

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Term Pregnancy

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Two recent studies have shown that despite a significant trend toward increased early-term delivery rates and early-term delivery inductions over the last two decades in the United States, there is a significantly higher infant mortality rate for these babies, compared with those delivered at full term.*

Sources: Reddy UM, et al. Term pregnancy. A period of heterogeneous risk for infant mortality. *Obstet Gynecol* 2011;117:1279-1287. Murthy K, et al. Trends in induction of labor at early-term gestation. *Am J Obstet Gynecol* 2011;204:435.e1-6.

THE CONCEPT THAT "TERM" PREGNANCY APPLIES TO ANY pregnancy extending past 36 completed weeks has been recently strongly challenged. In fact, in some hospitals, protocols have been drafted to discourage doing elective or repeat Cesarean sections prior to 39 weeks, instead of a previously accepted threshold of 38 to 38½ weeks. Two recently published articles[1,2] have emerged that shed an interesting light on the timing of term deliveries — one involving perinatal death and the other focusing on trends in induction of labor at term. Although both articles deal with ethnic differences, the overall trends are enough to get our attention.

Reddy et al reviewed data from the National Center for Health Statistics from 1995 to 2006 and subdivided term pregnancy data into "early-term" (37/0 – 38/6 weeks) and "full-term" (39/0 – 41/6 weeks) categories.[1] The authors analyzed complete data sets on 46,329,018 singleton pregnancies where gestational ages were available — 25.3% were early term and 54.2% were full term. They found a steady rise in early-term deliveries from 21.8% in 1991 to 28.9% in 2006. Meanwhile, the rate of full-term deliveries decreased from 81.3% to 54.2%. The biggest increase in early-term deliveries occurred in non-Hispanic black mothers, rising from 31.4% to 38.3% during those years.

As suspected, early-term infants have higher mortality rates than full-term infants. For example, in 2006, the rate of early-term mortality was 3.9/1000 compared to 2.6/1000 for full-term deliveries. The good news is that during the study period there was an overall decline in infant mortality rates in both categories. Additionally, non-black Hispanics had a drop in early-term infant mortality by 34.4% and non-Hispanic whites by 22.4%. Unfortunately, the bad news is that during this time period the mortality rate for non-Hispanic blacks rose by 15.8%.

The authors concluded that there was an overall improvement during the span of 11 years in infant and neonatal mortality for early-term pregnancies. However, it was clear that those delivered < 39 weeks fared worse in all ethnic groups than full-term babies delivered at equal or greater than 39 weeks.

The second study reviewed the same data source from the National Center for Health Statistics from 1991 and 2006.[2] The authors were interested in trends in induction of labor for patients with early-term pregnancies, using the same definitions (37/0 – 38/7 weeks vs 39/0 – 41/6 weeks). They excluded patients with worsening intrapartum conditions such as premature rupture of the membranes or pregnancy-induced hypertension — in other words, those with seemingly valid reasons for induction. Patients with diabetes and chronic hypertension were included in the analysis, but broken out separately in the results.

The authors found that of 39,150,722 patients who were eligible, only 4.9% had early-term inductions (ETI). During the study period, the ETI rate rose from 2% in 1991 to 8% in 2006. Interestingly, those without chronic hypertension or diabetes had greater increases in induction rates (from 1.9% to 7.8%, representing a 317% increase) than those with diabetes (8% to 16.6% or a 108% rise) or chronic hypertension (13% to 27%, or a 103% rise). The largest increase in inductions across the board was in non-Hispanic white women.

■ COMMENTARY

The differences in mortality rates between early- and full-term deliveries may even be underestimated since the analysis included patients in the "full-term" category whose pregnancies had extended past 41 weeks. These patients may have an inherently higher perinatal mortality rate and could blunt the difference between groups.

With the exception of non-Hispanic black women, infant and neonatal mortality rates have improved since the early 1990s, which probably has to do with better neonatal care. However, mortality rates are significantly higher for those neonates delivered between 37 and 39 weeks than for those delivered later. Given the now documented increase in ETIs, especially in non-Hispanic white patients, it is hoped that this will not translate into a large increase in later neonatal/childhood morbidity. The messages from both studies are not new, but these two studies have huge numbers and the most concerning trend is the alarming increase in ETIs in the United States. One wonders how many of these were for questionable reasons, including patient or provider convenience. The above data certainly lend credence to a more conservative approach to the timing of delivery. ■

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2. Murthy K, et al. Trends in induction of labor at early-term gestation. *Am J Obstet Gynecol* 2011;204:435.e1-6.

What To Do About Microscopic Hematuria

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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Dr. Ling reports no financial relationship to this field of study.

Synopsis: *Three or more red cells per high power field in two of three clean-catch midstream urine specimens warrants consideration of further evaluation to include urine cytology, cystoscopy, and upper tract imaging.*

Source: Erekson EA, et al. Microscopic hematuria in women. *Obstet Gynecol* 2011;117:1429-1434.

This case-driven discussion of microscopic hematuria includes important guidelines, definitions, and reminders to aid the clinician in managing this common finding. The definition of 3 rbc/hpf on two of three clean-catch midstream samples comes from the American Urological Association and minimizes the unnecessary work-up of transient causes of microscopic hematuria including menstrual contamination, vigorous exercise, intercourse, or trauma. Urine dipsticks can show false-positive results because of hemoglobin, myoglobin, or povidone-iodine. True positives are classified into renal, extrarenal, urogenital, and other sources. The most common etiologies in women are cystitis and calculi. Although uncommon, bladder cancer, which has 1.4 new cases/100,000 annually, is a more common cause of death than cervical cancer. High-risk factors include age over 40, history of pelvic radiation, history of exposure to dyes and chemicals, smoking, analgesic abuse, and history of gross hematuria.

■ COMMENTARY

I bet you didn't know that bladder cancer is the cause of more deaths in women than cervical cancer. We face the issue of microscopic hematuria multiple times everyday, don't we? How many urine dipsticks have you reviewed in the last 48 hours? How often is there a trace of blood? What does it mean? When should we be concerned? This article is jam-packed with good information to help make decision-making easier, and, more importantly, evidence-based. I'm particularly sensitive to the topic because my 100-year-old mother is a bladder cancer survivor from many years ago.

The authors provide us with a very nice algorithm for

microscopic hematuria, factoring the appropriate collection (and recollection if necessary) to ensure that the finding is a real one and not a false positive. Assessment of the upper urinary tract can be done with retrograde pyelogram and fluoroscopy, IVP, or CT scan, each having some advantages over the others, but none proving superior. Upper tract ultrasound is not considered adequate to evaluate the urothelial tract for causes of hematuria, although it is useful to identify renal cysts and calculi.

If you've ever had any of the following questions, then this is the article for you:

* How common is microscopic hematuria and how is it defined?
* What is the prevalence of bladder cancer in women?
* What are bladder cancer risk factors?
* What is the appropriate evaluation in pregnant and nonpregnant women?
* Should there be routine screening for microscopic hematuria?
* When should the gynecologist refer the patient to a urologist?

This article is not only good reading for the gynecologist, but it is even very good reading for non-physician personnel in any office caring for women. The algorithm is simple to understand, the answers to the above questions are evidence-based, and the actions to be taken are clear. A copy of this article should probably be available at every desk in your respective offices for reference at any time. ■

Is it Time to Change the Standard of Care for Low-risk GTN?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Source: Osborne RJ, et al. Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: A gynecologic oncology group study. *J Clin Oncol* 2011;29:825-831.

Synopsis: *Biweekly dactinomycin produced a higher complete response rate, required half the number of treatment cycles, and was associated with earlier recognition of treatment failure relative to weekly methotrexate in women with low-risk gestational torphoblastic neoplasia.*

THERE ARE AT LEAST SIX DIFFERENT COMMONLY USED CHEMOtherapeutic regimens in practice to treat patients with low-risk gestational trophoblastic neoplasia (GTN) with no consensus or previous formal evaluation as to which may be best. The Gynecologic Oncology Group (GOG) sought to examine two commonly used regimens: methotrexate (30 mg/m^2 administered weekly, intramuscularly) or dactinomycin (1.25 mg/m^2 administered biweekly, intravenously) in women meeting "low-risk" criteria (*see Table*). The primary endpoint for this randomized Phase 3 study was complete response (CR), defined as resolution of quantitative □hCG to 0 mIU/mL (or equivalent institutional normal). Overall, 240 women were enrolled over 7.5 years; 216 were evaluable for the primary endpoint. The overall CR rate for women receiving dactinomycin was significantly higher than those receiving methotrexate (70% vs 53%, $P = 0.013$). Success with either treatment was reduced in women with higher World Health Organization (WHO) scores and those with choriocarcinoma, but still favored dactinomycin. The average number of cycles administered to women with a CR was 8 for methotrexate and 4 for dactinomycin (total treatment time was an average of 8 weeks). Patients who did not achieve CR were subsequently managed with alternative chemotherapy, surgery (hysterectomy), or both. Two patients (one in each arm) had a potential recurrence following CR. All patients for whom long-term follow-up was available were cured of their disease. No patients were removed from study treatment due to toxicity and, in general, both treatments were well tolerated. The authors conclude that dactinomycin is associated with a higher CR rate relative to methotrexate in low-risk GTN.

■ COMMENTARY

GTNs are rare malignant transformations of gestational trophoblastic tissues arising from the fetal chorion and most frequently are associated with an antecedent complete hydatidiform molar pregnancy.[1] They also may occur after a normal pregnancy or even more uncommonly following a partial hydatidiform molar pregnancy. They are part of the spectrum of gestational trophoblastic disease (GTD), which, in addition to molar pregnancy (complete and partial), also includes placental site trophoblastic tumor, epithelioid trophoblastic tumor, and choriocarcinoma. GTN is a disease in which a diagnostic biopsy is not required, and is predominately declared by

Table. Diagnostic Criteria for Gestational Trophoblastic Neoplasia (GTN)

Criteria	Pre-2002	Post-2002
Declining βhCG (amount - time)	< 10% over 3 weeks (4 values)	Same
Rising βhCG (amount - time)	> 20% over 2 weeks (3 values)	> 10% over 2 week (3 values)
Persistent βhCG (time)	> 4 months	> 6 months
Choriocarcioma	Yes	Same
Metastatic Choriocarcinoma	Vaginal	-
	Lung < 2cm (No computed tomography)	
	Parametria	

lack of biomarker (βhCG) resolution in surveillance. The criteria of what constitutes an aberration have changed some in the last decade (*see Table*); patients meeting the diagnosis are then "staged." The current GTN staging system combines FIGO anatomical staging with a composite score (Modified WHO Prognostic Scoring System) based on age; parameters of antecedent pregnancy event (type and duration to diagnosis); βhCG level; tumor location, size, and number; and previous treatment (if any).[2] Low-risk disease (WHO scores of 0-6) is highly curable with single-agent chemotherapy, several of which are touted. The current study was undertaken to assess two popular strategies: weekly IM methotrexate and biweekly IV dactinomycin. The primary endpoint was CR, which was demonstrated to be superior in the dactinomycin arm. It also was associated with fewer treatment cycles and superior activity among higher WHO scores and patients with choriocarcinoma. The trial spanned the 2002 amended WHO classification criteria, which designated patients with WHO scores of 5 or 6 as "low risk." In response, the trial was amended to include these patients (n = 17 or 8% of the treatment population) in the randomization. It is clear from this report that methotrexate 30 mg/m^2 IM is not acceptable therapy for these patients. However, tolerance and compliance were high with both strategies and all patients completing follow-up were cured, predominately by either switching over to the alternate arm, receiving multiagent chemotherapy, surgery, or some combination of these.

The question remains as to whether methotrexate (the treatment standard for "low-risk" GTN) should be replaced by the more active dactinomycin. Although on the surface the substitution would seem warranted, several factors should be considered. The first relates to the methotrexate dose and administration. The experience from several institutions, including trophoblastic centers, report much higher cure rates with this agent administered at higher doses and in different infusion schedules.[3] This has been a major criticism of the trial despite previous experience from the GOG demonstrating the absence of a dose-response in "low-risk" GTN. A second major concern is safety. Methotrexate has a large body of safety data upon which to draw questions about long-term effects on inducible (secondary) malignancy and fertility preservation.[4] At this point there is no comparative data set for patients treated with dactinomycin, which under common infusion schedules may be associated with myelosuppression, alopecia, and nausea. Further, although short-term adverse events were similar between the cohorts in this study, the margin of error for dactinomycin is narrower, as the agent is a strong vesicant and is most safely administered via central venous access. In general, our practice is to continue to treat patients with methotrexate either with daily treatment for five days or every other day with leucovorin rescue, and reserve dactinomycin for low-risk patients in whom this treatment has failed. Future randomized trials will investigate more contemporary methotrexate regimens, including better pretreatment imaging and more precise pretreatment stratification. ■

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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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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

15. Risk of VTE in users of oral contraceptives containing drospirenone is higher than the risk in pregnancy.
a. True
b. False

16. Oral contraceptive pills with levonorgestrel, but not those with drospirenone, are safe to use in women with other risk factors for blood clots.
a. True
b. False

17. The estimated VTE incidence for users of oral contraceptives containing drospirenone is_____.
a. 4-5 cases per 100,000 women per year.
b. 10-20 cases per 100,000 women per year.
c. 20-30 cases per 100,000 women per year.
d. 48-60 cases per 100,000 women per year.

18. Which of the following does *NOT* fit the data in the above studies?
a. Early-term delivery is associated with a higher rate of perinatal mortality than full-term pregnancy.
b. The early-term delivery mortality rate dropped between 1995 and 2006.
c. Non-Hispanic blacks had a decrease in infant mortality rates over the same time.
d. The full-term delivery infant mortality rate dropped during the study window.

19. The largest increase in early-term delivery between 1995 and 2006 occurred in non-Hispanic black patients.
a. True
b. False

20. Which of the following is the most appropriate interpretation of the data in the Murthy et al study?
a. Early-term inductions doubled between 1991 and 2006.
b. The greatest rise in early-term induction occurred in patients with diabetes.
c. The ethnic group with the greatest rise in early-term induction was non-Hispanic whites.
d. Those with chronic hypertension had the greatest rise in early-term induction.

21. Which of the following statements is *TRUE* about observations in the Osborne et al randomized clinical trial?
a. Weekly methotrexate was almost as effective as dactinomycin in patients with choriocarcinoma.
b. The time to complete remission was the same for both arms of the trial.
c. The number of cycles need to induce complete remission was the same in each arm of the trial.
d. The success for both arms was similar when comparing patients with WHO scores of 0-4 and WHO scores of 5-6.

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.*

FDA issues Multiple Drug Warnings

In this issue: FDA issues multiple drug safety alerts; ARBs and cancer risk; and FDA actions.

Avoid high-dose simvastatin

The FDA is advising physicians to avoid high-dose simvastatin (Zocor) because of the risk of myopathy and rhabdomyolysis. The agency is advising that patients should not be started on the 80 mg dose and patients who already are on 80 mg should be continued only if they have been on that dose for 1 year or longer. The recommendations are based on results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocystine (SEARCH) trial — a 7-year randomized, controlled trial comparing the efficacy and safety of simvastatin 80 mg vs simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction. There was no significant difference in the incidence of major vascular events between the two doses; however, 52 patients (0.9%) in the 80-mg group developed myopathy vs one patient (0.02%) in the 20-mg group. Of the high-dose group, 22 patients (0.4%) developed rhabdomyolysis vs no patients in the 20-mg group. The risk for myopathy and rhabdomyolysis with simvastatin 80 mg was highest in the first 12 months of treatment. Of concern, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, particularly diltiazem. The majority of patients who developed myopathy also had a genetic variant that affects coding of the transporter responsible for simvastatin uptake in the liver, resulting in higher serum simvastatin levels. The FDA not only recommends against using simvastatin 80 mg, but also suggests that the drug is contraindicated for use in patients taking itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. The maximum dose of simvastatin should be only 10 mg in patients taking amiodarone, verapamil, and diltiazem while the maximum dose is 20 mg in patients taking amlodipine and ranolazine. The new guidance recommends using a different statin if the patient's LDL targets aren't met with the 40-mg simvastatin dose. The loss of high-dose simvastatin comes as a blow to cost-concious consumers who now likely will be prescribed brand name atorvastatin (Lipitor) or rosuvastatin (Crestor). Generic atorvastatin is likely to be available in late 2011. ■

Increased risk of prostate cancer

The FDA has issued a somewhat controversial warning regarding an increased risk for high-grade prostate cancer associated with the 5-alfa reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn). Ironically, the new warning stems from studies designed to evaluate whether the drugs offer protection *against* prostate cancer. Both drugs are marketed to treat benign prostate hypertrophy and both are known to significantly decrease the prostate-specific antigen levels. In separate studies, both drugs were investigated to see if they reduce the incidence of prostate cancer. FDA experts reviewed the results of the Prostate Cancer Prevention Trial (PCPT), which evalu-

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ated finasteride vs placebo for 7 years, and the Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), which compared dutasteride to placebo for 4 years. Prostate cancers were significantly reduced in both trials; however, the reduction was limited to low-grade prostate cancers with a Gleason score of 6 or lower. The rate of cancers with a Gleason score of 8-10 was increased in both studies. Previous analyses of these data have suggested that finasteride did not increase the risk of high-grade prostate cancers, but rather made them easier to diagnose by decreasing the volume of the prostate (*Clin Cancer Res* 2009;15:4694-4699; *J Natl Cancer Inst* 2007;99:1366-1374). The FDA panel, however, disagrees and feels it prudent to add a warning to labeling of both medications regarding increased risk of high-grade prostate cancer associated with use of the drugs. The guidance further recommends that prior to initiating therapy patients should be evaluated to rule out other urologic conditions, including prostate cancer, that might mimic benign prostatic hypertrophy. ■

Actos and bladder cancer risk

The diabetes drug pioglitazone (Actos) is the subject of a new warning from the FDA regarding possible bladder cancer risk associated with use of the drug. The FDA ongoing safety review suggests that use of pioglitazone for more than 1 year may be associated with increased risk of bladder cancer based on review of a 5-year interim analysis of an ongoing 10-year epidemiologic study. Patients who had been on pioglitazone the longest and who had the highest cumulative dose of the drug had a slightly increased risk of bladder cancer. This warning falls on the heels of a French study that also showed increased risk of bladder cancer. Based on these findings, France's drug regulatory agency has suspended use of the drug. While the FDA is not recommending withdrawing the drug from the market, it does recommend avoiding pioglitazone in patients with active bladder cancer and using it with caution in patients with prior history of bladder cancer. Thiazolidinediones — including pioglitazone — have also come under scrutiny in recent years because of increased risk of congestive heart failure and bone fractures in females. ■

Chantix and cardiovascular events

The FDA has issued an alert regarding varenicline (Chantix) regarding a small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The warning regarding the smoking cessation drug was the result of review of a randomized, double-blind, placebo-controlled trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. The overall rate of adverse effects was low but cardiovascular events, including heart attack, were reported more frequently in the treatment group. The warning will result in a change in labeling for the drug and the FDA is also requiring Pfizer, the drug manufacturer, to conduct an analysis of other trials to further assess the risk. Varenicline already carries a box warning regarding neuropsychiatric symptoms including suicidality. ■

ARBs and cancer risk

Finally some good news from the FDA. After a 2010 meta-analysis showed a possible link between angiotensin receptor blockers (ARBs) and cancer, the agency has completed its own review and has found no evidence of increased risk of "cancer events" including new cancers, cancer-related deaths, breast cancer, lung cancer, or prostate cancer associated with the drugs. The agency conducted a much larger meta-analysis than the original study, including more than 150,000 patients in 31 long-term, randomized, controlled clinical trials. The rate of cancer events in the ARB group was 1.82 per 100 patient years while the rate in the non-ARB group was 1.84 per 100 patient years (relative risk of incident cancer in patients taking ARBs 0.99, 95% confidence interval, 0.92 to 1.06) There was no statistically significant difference in cancer death rates or incidence of individual cancer types. The agency continues to monitor this issue but currently states that the benefits of ARBs continue to outweigh the potential risks (summary available at FDA.gov/drugs/drugsafety/). ■

FDA actions

The FDA has approved the first generic version of levofloxacin (Levaquin). The popular fluoroquinolone is commonly used for treatment of respiratory infections, sinusitis, prostatitis, pyelonephritis and skin infections. Generic forms will include tablets, oral solutions, and injectable solutions.

The FDA has approved an abuse-resistant short-acting oxycodone tablet. Pfizer Pharmaceuticals has licensed the "AVERSION Technology" from Acura Pharmaceuticals. The technology prevents dissolving and injecting tablets by creating a gel when mixed with water or other solvents that prevents snorting crushed tablets by burning nasal passages, and also prevents intentional swallowing of excess quantities by adding niacin which causes intense flushing, itching, and sweating. Long-acting oxycodone (OxyContin) was similarly reformulated in 2010 to prevent misuse and abuse. ■