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INSIDE

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Thrombophilia and Pre-eclampsia

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Pre-eclampsia in pregnancy may be associated with thrombophilia.*

Source: Kahn SR, et al. Inherited thrombophilia and preeclampsia within a multicenter cohort: The Montreal Preeclampsia Study. *Am J Obstet Gynecol* 2009;200:151.e1-151.e9

ONE OF THE MOST CONFUSING AREAS IN MEDICINE, WHICH SPILLS over into obstetrics, is thrombophilia, and seemingly every year a new antibody affecting the clotting system emerges that causes worry. One of the worries involves a possible link with pre-eclampsia. This recent study from Montreal has addressed the possible relationship between three polymorphisms associated with thrombophilia (prothrombin gene mutation, Factor V Leiden, and methyltetrahydrofolate reductase [MTHFR] deficiency) and pre-eclampsia.

The authors studied 5162 women who were cared for in the McGill University and Montreal University hospital systems between 1993 and 2003. Each had a visit and blood drawn in the first trimester and an ultrasound examination at 16-18 weeks, along with regular clinic visits thereafter. The patients were interviewed during their pregnancies, and their records were reviewed after they delivered. One hundred thirteen (2.2%) developed pre-eclampsia, and 28% were judged to be severe. Four hundred and forty-three patients were chosen as controls.

Not surprisingly, women with pre-eclampsia had much higher rates of intrauterine growth restriction (IUGR), diabetes, preterm birth, and cesarean delivery. There was also a tendency for pre-eclamptics to have higher a body mass index (BMI; odds ratio [OR] = 4.7; 90% confidence interval [CI], 1.1-22.8) and to have higher

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rates of chronic hypertension (OR = 3.4; 90% CI, 1.3-9.1) and previous pre-eclamptic pregnancies (OR = 4.7; CI, 1.5-15.0). "Under-perfused" placentas were more commonly found in the pre-eclamptics. Interestingly, smoking seemed to have a protective effect — something noted by other investigators.

What did not correlate with pre-eclampsia were any of the above polymorphisms, even in combination. Homocysteine levels were not higher in pre-eclamptics, but folates were lower in those with under-perfused placentas.

■ COMMENTARY

Although the above three factors have been implicated in many pregnancy complications, this study shows that pre-eclampsia is not one of them. It should be pointed out that this case-control study does not address other problems, such as thrombotic events, but certainly this study's findings should negate the need for a full thrombophilia work-up in every patient developing pre-eclampsia.

Now, let's move on to another part of the thrombophilia spectrum — the antiphospholipid antibodies (APLs). These are directed against beta-2 glycoprotein-1, resulting in enhanced platelet activation. The three potential troublemakers are anticardiolipin antibodies, lupus anticoagulant, and beta-2 glycoprotein-1 antibodies. First, like the polymorphisms studied in the Montreal case-control study, these APLs are often found in women with normal pregnancies, and only when the latter two antibodies are found in moderate-to-high levels, should they get our attention. Also, they must be persistently present 12 weeks after they initially were found. Even then, for us to consider therapeutic action, the patient should have evidence of antiphospholipid antibody syndrome (APS). This would mean that any patient with these antibodies must have a history of one or more of the following: 1) an unexplained stillbirth after 10 weeks; 2) three consecutive spontaneous abortions prior to 10 weeks; 3) either venous or arterial thrombosis; and/or 4) IUGR. It is of note that studies have shown that pre-eclampsia is not increased in patients with APL alone.[1-4]

Earlier investigation has demonstrated the benefit of low-dose aspirin in preventing severe pre-eclampsia, in general, but no studies have shown a decrease in the incidence of pre-eclampsia with bigger guns, such as unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH).[5] The standard dose has been one baby aspirin (84 mg) daily, but there is a suggestion in the stroke literature that two pills per day may be better in discouraging micro-clotting. Large studies have shown no downside of low-dose aspirin in the second and third trimester, although in one study there was a suspicion of a slightly higher rate of gastroschisis with aspirin delivered in the first trimester.[6]

If patients have a past history of venous or arterial thrombosis alone, then they would benefit from prophylactic doses of UFH (5000 U q 12 hrs) or LMWH (Lovenox® 40 mg q 24 hrs). If the patient has documented APS, then an "intermediate" regimen of UFH (5000 U to anti-Xa of 0.1-0.3 U) or LMWH (Lovenox 40 mg q 12 hrs) could be used. This regimen can be used in conjunction with low-dose aspirin, and if thrombosis is a component of the history, prophylactic anticoagulation should be carried out postpartum. If the patient has only APL without APS, prophylaxis would not be necessary, although low-dose aspirin may well be useful if the patient has abnormal uterine artery waveforms.

Lastly, MTHFR has become a thorn in our side. In the Montreal study, 14% of their control population was homozygous for MTHFR. Others have shown that far more pregnant women are heterozygous for this factor. MTHFR affects the clotting process by elevating levels of homocysteine, which in turn is associated with decreased folate levels. It is very rare for a heterozygote (other than upping the dose of folic acid), and in the 14% who are homozygous, we would not treat them unless there was an additional clinical factor of concern. Therefore, our work-up for thrombophilia does not

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Questions & Comments
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include MTHFR, and has been coned down to the biggest troublemakers: 1) anticardiolipin antibody; 2) Factor V Leiden; 3) beta-2 glycoprotein-1; 4) prothrombin gene mutation; and 5) lupus anticoagulant. ■

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Fertility Following Oral Contraceptives

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr. Edelman has served on an advisory board and as an Implanon® trainer for Schering-Plough and receives grant/research support from the Society for Family Planning.

Synopsis: *Oral contraceptive use does not appear to adversely or beneficially affect fertility following discontinuation.*

Source: Barnhart KT, Schreiber CA. Return to fertility following discontinuation of oral contraceptives. *Fertil Steril* 2009;91:659-663.

A REVIEW OF ANY PUBLICATION FROM 1960 TO 2007 with the main outcome of time to fertility following oral contraceptive discontinuation was performed. Return to fertility within 12 months of oral contraceptive discontinuation was similar (72-94%) to fertility following discontinuation of intrauterine devices, progestin-only pills, condoms, and natural family planning. Additionally, fertility after prolonged use of cyclic oral contraception was not affected. Although the research is not extensive, continuous or extended dosing of oral contraceptives appears equivalent to cyclic dosing in regard to fertility return following discontinuation.

■ COMMENTARY

Fertility issues weigh heavily on the minds of most of our patients; whether they are trying to prevent it or pursue it. Women choosing reversible contraception want assurance that their fertility will be unaffected by their choice in contraceptive method — not an unreasonable expectation. Conflicting myths abound regarding fertility following the birth control pill, including that the pill causes infertility, improves fertility, a break from the pill is needed to retain fertility (only if you want to be pregnant NOW!), and even increases the likelihood of multiples. Most of the concern regarding pill-induced fertility impairment was generated from higher-dose pills and also from the use of pills in women with pre-existing menstrual dysfunction.[1] Barnhart and Schreiber present a comprehensive evaluation of the literature regarding fertility following discontinuation of the birth control pill. In addition, they also specifically look at fertility following chronic pill use (1 year) and continuous-dosing (longer than 28 days of active pills). As the most popular form of contraception in the United States,[2] it is important to reassure ourselves and our patients of the pill's reversibility and to dispel these myths.

This review reports the aggregate conception rates at 12 months following oral contraceptive (cyclic dosing) discontinuation as compared to discontinuation of other common contraceptive methods. Oral contraceptives were found to have very similar conception rates (72-94%) as compared to the levonorgestrel-releasing intrauterine device (75-79%), the copper intrauterine device (71-92%), and barrier methods (95%). In addition, the authors found several studies demonstrating no ill effects of chronic use of oral contraceptives on fertility. Although not statistically significant, one study even demonstrated increased fertility with 1-2 years of oral contraceptive use (97%) as compared to 6 months or less (84%).[2] Finally, continuous and/or extended dosing of oral contraceptives has not been found to impair fertility. Now this review mainly focused on fertility over a 12-

month period; however, they did mention that when looking at the first 3 months after oral contraceptive discontinuation there may be a slight delay in fertility.

We can continue to be reassured that oral contraceptives do not impair fertility even if used for an extended duration or if dosed continuously. "Taking a break" from oral contraceptives isn't a good plan unless a pregnancy is desired or a woman wants to/needs to switch birth control methods. That being said, oral contraceptives do not protect women from a major cause of infertility — chlamydia. Women and providers do not seem to be as concerned with one of the most common sexually transmitted diseases. An obscene number of opportunities are missed for testing (over 80%).[3] Use your patient's concern regarding fertility issues to reassure her regarding her birth control, but also as an opportunity to discuss how to prevent, diagnose, and treat an actual cause of infertility. ■

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Arzoxifene for Prevention of Osteoporosis

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Arzoxifene increases bone density in postmenopausal women.*

Source: Bolognese M, et al. Effects of arzoxifene on bone mineral density and endometrium in postmenopausal women with normal or low bone mass. *J Clin Endocrinol Metab* 2009 Apr 7; Epub ahead of print.

ARZOXIFENE IS BEING DEVELOPED BY ELI LILLY AND Co. to prevent bone loss and treat osteoporosis. A 2-year, randomized trial compared the bone density responses in 331 postmenopausal women treated with either arzoxifene (20 mg/day) or placebo. Bone density was slightly increased in the spine and the hip in the treated group compared with placebo. There was no evidence of endometrial stimulation in the treated group either on biopsied specimens or by measurement of endometrial thickness by transvaginal ultrasonography. Three patients in the placebo group and none in the treated group developed breast cancer. There were no cases of venous thrombosis, and hot flushing was equally prevalent in the two groups.

■ **COMMENTARY**

Arzoxifene is an estrogen agonist-antagonist similar to raloxifene, originally studied for the treatment of breast cancer. Preclinical studies indicated that arzoxifene is an estrogen agonist in bone and on lipids, but an estrogen antagonist in endometrial and breast tissue. Arzoxifene, therefore, had the potential to be as effective as tamoxifen but be free of the risk of endometrial stimulation, and perhaps, venous thrombosis.

A phase III clinical trial comparing arzoxifene and tamoxifen for the treatment of advanced local breast cancer or metastatic tumors was disappointing.[1] The trial was terminated when it became apparent that the results with arzoxifene were inferior to tamoxifen with regard to survival times and treatment failure times. Two other members of this drug family, droloxifene and idoxifene, have also failed to yield superior results to tamoxifen for the treatment of breast cancer. For this reason, attention was turned to another use for these agents. Clinical trials assessing the efficacy and safety of arzoxifene for prevention of fractures and breast cancer are now under way.

Various drug companies are pursuing members of this drug family, such as arzoxifene, lasofoxifene, and basedoxifene, hoping to develop a patent-protected drug that would compete with raloxifene. Keep two important points in mind as new data emerge in this slow and expensive process:

1. **Comparison phase III clinical trials are essential.** Preclinical studies indicate potential, but only head-to-head comparisons tell us if a new drug is any better than what we already have. The comparison of these agonist-antagonist drugs with tamoxifen is a good example. Hoped-for superiority of the new drugs failed to emerge. In addition, the new drugs will have to perform better than the aromatase inhibitors. Comparison data are also required to determine whether one of the new drugs is superior in avoiding hot flushing and venous thrombosis.
2. **Fracture data for both hip and spine are necessary.** These drugs differ in potency as measured by bone density and biochemical markers of bone metabolism. Preclinical studies suggested that arzoxifene was more

potent in regard to preventing bone loss compared with raloxifene, and the clinical trial data support this conclusion. Greater potency, therefore, of arzoxifene gives some hope that one of these new drugs will overcome the serious drawback of raloxifene treatment, a lack of effect in preventing hip fractures. Bazedoxifene has demonstrated about a 50% reduction in hip fractures in a phase III clinical trial.[2] ■

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Prognosis for Spontaneous Labor in Women with Uncomplicated Term Pregnancies

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Synopsis: *Maternal and fetal morbidity in low-risk patients entering the hospital in spontaneous labor at term is extremely low and this can be kept in mind when patients are considering planned cesarean section for non-medical reasons.*

During the last two months an unusual number of papers were published which, while not having earth-shaking scientific value, should have some clinical impact. Although the *OB/GYN Clinical Alert* format requires reviewing one article, I have decided this month (only) to attempt three "quick hits" so that more than one message can be conveyed.

Let's start with a no-brainer. In the April issue of *Obstetrics & Gynecology*, a group from Dallas studied 103,566 low-risk patients delivering between 1988 and 2006 who were at term (37-41 weeks) and who entered in spontaneous labor. Ninety-six percent had vaginal deliveries. Not surprisingly, nulliparas had higher rates of forceps deliveries (8% vs 1%), cesarean deliveries (8% vs 2%), and third- and fourth-degree lacerations (13% vs 2%), while multiparas had a higher rate of macrosomia (9% vs 4%).[1]

Most importantly, the overall perinatal mortality rate was only 0.3 rate per 1000 births in this group of low-risk patients. Low five-minute Apgar scores were very rare (1.5 per 1000), as were cord blood pH < 7.0 (3 per 1000) and admissions to the NICU (4 per 1000).

The authors pointed out that "virtually all of the above women" (representing about 4 out of 10 deliveries at Parkland Hospital) "can anticipate safe vaginal deliveries for themselves and their infants."

The second study, published in the April 2009 issue of the *American Journal of Obstetrics & Gynecology*, demonstrated the value of adding glucose to IV fluids during labor.[2] Since skeletal muscle works better when individuals undergoing prolonged exercise are adequately hydrated and loaded with carbohydrate, the authors postulated that the smooth muscle of the uterus would respond similarly during labor. The group randomized 300 women in labor with IV drips in place to one of three groups: normal saline (84), 5% dextrose/saline (D/S) (76), or 10% dextrose/saline (72).

The length of the second stage of labor almost doubled in those without the glucose (106 min vs 69 min with 5% D/W and 62 min with 10% D/S). Also, the incidence of prolonged labor (> 12 hrs) was much higher in the saline-only group (22% vs 9.3% and 6.8%, respectively).

Lastly, in other *OB/GYN Clinical Alerts*, the evils of smoking in pregnancy have been touched upon, as well as the benefits of quitting — even when using nicotine substitutes. In a recent issue of the *British Medical Journal*, a group from New Zealand and Australia published a collaborative study comparing outcomes in women who were nonsmokers (1992), stopped smoking before 15 weeks (261), and continued smoking (251).[3]

The results were dramatic. Those who stopped smoking before 15 weeks had no difference in rates of preterm birth and intrauterine growth restriction (IUGR), compared with nonsmokers (4% vs 4% and 10% vs 10%, respectively). However, there were statistically significant differences in these outcomes between those who quit smoking compared with those who did not. Smokers had rates of preterm birth of 10% (vs 4%) and IUGR of 17% (vs 10%).

■ COMMENTARY

The Dallas group acknowledged in their paper that their population has a lower percentage of "uncomplicated" pregnancies (37%) than the 50% incidence estimated by the CDC or from data from the state of Massachusetts between 1995 and 2005. The authors

point out that these women who do not have a compelling medical reason for having a cesarean section are the ones who might be considering a planned primary section, a practice that occurred in 20% of low-risk women in the United States in 2006.

At the recent meeting of the Society for Maternal-Fetal Medicine, Olson et al presented data from a California state database showing that those low-risk women who had planned cesarean sections had a 10- to 20-fold increase in cardiac complications, a 4- to 8-fold increase in major maternal infection, and a 3-times greater risk of anesthetic complications.[4] Also, there was a higher rate of combined neonatal morbidity, which included increased rates of RDS and transient tachypnea of the newborn (TTN). When one considers that there is a tendency now to plan elective deliveries earlier (37% of elective repeat cesarean sections in 2007 were carried out before 39 weeks[5]), then there is even greater potential for unnecessary maternal and neonatal morbidity. The Dallas data can serve as a guideline for patients to use for comparison when considering elective primary cesarean section.

Regarding the paper on intravenous dextrose in labor, I have no idea how many hospital use saline alone for maternal hydration, but this article strongly suggests that there is benefit of 5% D/S, but no real advantage to 10% D/S.

We have had many women who quit smoking after the first trimester, and yet, on ultrasound scans, their placentas in the second and third trimester often are heavily laced with calcium. It is heartening to know that, despite this observation, some neonatal outcomes are no worse than those seen in nonsmokers. ■

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Special Feature

Swing and Miss?!? Efforts in Front-line Ovarian Cancer Chemotherapy Development

By Robert L. Coleman, MD

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Dr. Coleman is a retained consultant for GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer; and serves on the speakers bureau for OrthoBiotech.

DATA FROM THE SURVEILLANCE EPIDEMIOLOGY AND End Results (SEER) registry have consistently demonstrated improved life expectancy for women with epithelial ovarian cancer every year since 1973.[1] The modest gains in this parameter can be attributed to several important programmatic developments, including establishment of a sub-specialty devoted to the science and treatment of women with gynecological malignancies (Society of Gynecologic Oncologists, SGO); the identification of efficacious chemotherapy, such as platinum and its analogues, as well the taxanes (e.g., paclitaxel); better pre-, intra- and post-operative care; higher rates of optimal surgery; specialized nursing and support services; development of supporting medications (e.g., 5-HT_3 antagonists) to enhance the therapeutic:toxicity ratio of the chemotherapy; development of new delivery methodologies of therapy (e.g., intraperitoneal chemotherapy); and continued novel agent discovery. A closer look at the components of these positively sloped survival curves demonstrates that most of the benefit afforded women is in life gained in the presence of disease, rather than cure. Indeed, the cure rates from ovarian cancer have remained relatively flat over these 3 decades, adding no more than approximately 2 weeks per year in the overall gain of life expectancy. This is clearly due to the unmovable percentage of advanced stage cases still indicative of the most common clinical presentation (stage III/IV), and underscores the

immense impact even a slight stage migration could have on the overall clinical performance of women with this disease.

However, until that strategy is elucidated, the burden is to rationally develop new agents in hopes that better primary and recurrent disease control will continue to extend the lives of these patients. There have been many important milestones in this effort. Gynecologic Oncology Group (GOG) protocol #111 established the current standard in this disease in 1996, when the combination of paclitaxel and cisplatin was found to be superior in nearly every parameter studied (e.g., complete response [CR] rate, negative second-look rate, progression-free survival [PFS], and overall survival [OS]).[2] While the regimen was quickly adopted to an outpatient regimen by shortening the infusion of paclitaxel and substituting cisplatin with carboplatin,[3] the regimen has essentially been unaltered over the last 13 years. Intraperitoneal chemotherapy (using these same agents) appears to offer somewhat of a greater benefit over IV in selected (optimally cytoreduced) patients.[4] Yet, definitive new agents in primary disease have been slow to come.

The genesis of most new therapeutics tested in the front-line setting come from promising clinical investigation in the recurrent setting. The benchmarks are not standardized, but "positive" clinical observations, combined with rational preclinical data and substantial financial support, can make a good case to compete with the current standard in an effort to move the survival "line in the sand." Recently, one such effort, meeting each of these criteria, was published.[5] The study (GOG 182) tested 4 experimental arms against paclitaxel and carboplatin. Each of the arms was based on provocative preclinical and clinical information that was felt to add substantively to the taxane and platinum backbone. Two of the arms addressed the hypothesis that a non-cross-resistant agent added to paclitaxel and carboplatin (as a triplet) would increase efficacy by attacking different growth mechanisms in the known heterogeneous tumor microenvironment of bulky ovarian cancers. Two other arms were constructed to capitalize on drug-drug synergy seen in preclinical models of the disease and delivered as sequential doublets.[6,7] To make the trial robust and relevant to a broad audience of ovarian cancer patients, eligibility included all women with stage III and IV disease. To sufficiently evaluate the treatment arms against paclitaxel and carboplatin, 4000 patients were required. This was approximately 3 times the size of any prior chemotherapeutic study conducted in the worldwide gynecologic oncology community. While a daunting effort, the GOG, in collaboration with the Gynecologic Cancer Intergroup (GCIG) recruited nearly 1200 patients per year, ultimately accruing 4312 patients to the study and providing an unprecedented look at the power of cooperative groups working collaboratively to address a singular hypothesis. Global randomization ensured the 860 or so patients per arm were well balanced in terms of age, percent stage III (vs IV), measurable (vs evaluable), and primary ovarian cancer (vs peritoneal). There was also balance in the stratification factors of those undergoing interval surgery and those left with tumor residuum following primary surgery.

Unfortunately, the immense success in accrual was not matched in the evaluation of its primary and secondary endpoints. Each experimental arm was individually compared to the control arm; in each case, no statistical difference was observed in either OS or PFS. Among strata and subgroups, no modification in this conclusion was reached. The arms had different toxicity profiles: The triplets were associated with more neurotoxicity, the gemcitabine arms with more thrombocytopenia, but equal numbers of patients completed intended therapy.

In all, while this important phase III clinical study missed its endpoints, it provided convincing evidence that novel hypotheses could be addressed with appropriate power in the global community. Given the rapidity of new agents being developed, particularly those addressing growth signaling, survival, and proliferation in the microenvironment, this coordinated effort of our

Table

Outcomes from phase II clinical studies of bevacizumab

	Cannistra et al[8] (n = 44)	Garcia et al[9] (n = 70)	Burger et al[10] (n = 62)
Previous regimens			
1		100%	34%
2	52%		66%
3	48%		
Response rate			
Complete response	0%	0%	3%
Partial response	16%	24%	18%
Gastrointestinal perforations	11%	6%	0%
Arterial thrombosis	7%	4%	0%
Bevacizumab-related deaths	7%	4%	0%

committed global investigators and patients will have the palpable opportunity to deftly respond with new trials incorporating innovative designs. Currently, 5 large phase III clinical studies are under way, 2 in front-line and 3 in recurrence, which are evaluating the impact anti-angiogenesis therapy (e.g., bevacizumab and cediranib) has on chemotherapy for women with ovarian cancer. This direction was again chosen based on promising preclinical and clinical data of the response of ovarian cancer models and patients to this modality of therapy. Indeed, the clinical activity of single-agent bevacizumab in ovarian cancer *(see Table, page 15)*, is nearly 2-3 times the rate observed in the disease where the agent is now FDA approved.[8-10] The apparent "addiction" of ovarian cancer cells to an angiogenic milieu has prompted many to have great optimism in this strategy.

It is once again hoped that these rationally constructed novel treatment arms will move the bar of expected outcome in this disease. Fortunately, the investigational infrastructure is in place and being exercised to enable an answerable hypothesis. ■

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CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

CME Questions

6. Which of the following is *not* associated with a higher rate of preeclampsia?
a. IUGR
b. Early delivery
c. Smoking
d. Increased rate of cesarean sections

7. Which of the following is *not* a criterion for APS?
a. Unexplained stillbirth after 10 weeks
b. Abnormal uterine artery waveforms
c. Three consecutive spontaneous abortions at < 10 weeks
d. A thrombotic event

8. Chronic use of oral contraceptives does impact fertility.
a. True
b. False

9. The following statements regarding estrogen agonists-antagonists are true *except*:
a. The new drugs in development are related to raloxifene.
b. All these drugs increase hot flushing.
c. An increase in the risk of venous thrombosis with the new drugs has not been apparent in studies to date.
d. This family of drugs appears universal in lack of impact on the endometrium.

Answers: 6. c, 7. b, 8. b, 9. b.

PHARMACOLOGY WATCH

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

Guidance on the Appropriate Use of NSAIDs

In this issue: NSAIDs in the elderly; managing GI and CVD risk with NSAIDs; low-dose naltrexone and fibromyalgia; treating glucocorticoid-induced bone loss; FDA Actions.

NSAIDs and dementia

Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the elderly may increase the risk of dementia and Alzheimer's disease according to a new study. This is in contrast to previous studies that suggested that NSAIDs may actually be neuroprotective. The current study from Seattle looked at members of Group Health who were age ≥ 65 years (median, 74.8 years) and free of dementia. Patients were followed for up to 12 years to identify dementia and Alzheimer's disease. Of the 2736 patients studied, 351 (12.8%) were heavy users of NSAIDs at enrollment and another 107 became heavy users during follow-up. Over the course of the study 476 individuals developed dementia including 356 who developed Alzheimer's disease. Those defined as heavy NSAID users showed an increased incidence of dementia (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.24-2.24) and Alzheimer's disease (HR, 1.57; 95% CI, 1.10-2.23). The authors suggest that this study looked at an older cohort than previous studies. Decreased rates of dementia seen in the previous studies may have reflected a delay in onset of dementia, which may explain the increased incidence seen in the older patients in this study (*Neurology* 2009 April 22; epub ahead of print). ■

GI and CVD risk with NSAIDs

In a related story, the Canadian Association of Gastroenterology Consensus Group has published guidelines on use of long-term NSAIDs in patients at risk for GI bleeding and cardiovascular disease. The guideline includes the recommendation that NSAIDs should always be used at the lowest effective dose for the shortest possible duration of treatment and that patients should be evaluated for the need for gastroprotective strategies and cardiovascular risk. For patients at low GI risk but high cardiovascular risk, the group recommends naproxen because of potentially lower cardiovascular risk than other NSAIDs or COX-2 inhibitors. For patients at high risk for GI side effects and low cardiovascular risk, a COX-2 inhibitor alone or traditional NSAIDs with a PPI offers similar protection. For patients at very high risk for GI bleeding, a COX-2 inhibitor plus a PPI is the safest option. In patients with both GI and cardiovascular risks, NSAIDs should be avoided if possible, but if anti-inflammatories are needed, and the patient is already on aspirin, the recommendations included naproxen plus a PPI if cardiovascular risk is the main concern or a COX-2 plus a PPI if GI side effects are the primary concern (*Aliment Pharmacol Ther* 2009;29:481-496). ■

Low-dose naltrexone and fibromyalgia

Perform a Google search of "low-dose naltrexone"

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and you will find a myriad of anecdotal testimonies to the benefits of the drug in a wide range of diseases including fibromyalgia. Now a small study suggests that naltrexone may be of some benefit in this difficult condition. Naltrexone (not to be confused with naloxone) is an opioid receptor antagonist used primarily for treatment of alcohol dependence and opioid dependence. Because of multiple internet reports of benefit in patients with fibromyalgia, researchers from Stanford performed a single-blind, placebo-controlled crossover study of 10 patients with moderately severe fibromyalgia who were not on opioids. The dose of naltrexone used was 4.5 mg per day, which is less than 10 times lower than the dose used for addiction (50 mg per day). Patients on active treatment reported a 32.5% reduction in fibromyalgia symptoms compared to baseline vs a 2.3% reduction for placebo (P = 0.003 vs placebo). Side effects, which included insomnia and vivid dreams, were rare. Interestingly, patients with higher sedimentation rates had the greatest reduction in symptoms and best response to low-dose naltrexone. The authors hypothesize that low-dose naltrexone may inhibit the activity of microglia and reverse central or peripheral inflammation, thus reducing symptoms of fibromyalgia, although more studies are needed. They also suggest that naltrexone can be used in addition to other medications commonly used for fibromyalgia (*Pain Med* 2009 April 22; epub ahead of print). ■

Treating glucocorticoid-induced osteoporosis

For patients with glucocorticoid-induced osteoporosis, a once-yearly infusion of zoledronic acid is as effective as daily risedronate for the prevention and treatment of bone loss according to a new study from *Lancet*. In a 1-year, international, randomized, double-blind, placebo-controlled, non-inferiority study, 833 patients with glucocorticoid-induced osteoporosis were randomized to receive zoledronic acid 5 mg as a 100 mL IV infusion over 15-20 minutes on day 1 plus oral placebo or 5 mg of risedronate daily and 100 mL IV placebo infusion on day 1. Patients were allocated to a prevention or treatment subgroup depending on the duration of glucocorticoid use preceding study. Zoledronic acid infusion was non-inferior and superior to risedronate for increase of lumbar spine bone mineral density in both the treatment (P = 0.001) and prevention groups (P < 0.0001), respectively. Adverse events were more frequent in patients given zoledronic acid primarily because of increased flu-like symptoms within the first 3 days after the infusion. The authors conclude that a single 5 mg intravenous infusion of zoledronic acid is non-inferior and possibly more effective and more acceptable to patients than 5 mg of oral risedronate daily for prevention and treatment of bone loss associated with glucocorticoid use (*Lancet* 2009;373:1253-1263). An accompanying editorial suggests that once-yearly zoledronic acid seems to have obvious advantages over an oral regimen but the long-term safety is still unknown and also raises the question of whether anabolic drugs, such as teriparatide, which stimulate bone formation by acting on osteoblasts and osteocytes, might eventually be a better option (*Lancet* 2009;373:1225-1226). ■

FDA Actions

Plan B, the so-called "morning after pill" will soon be available to women age 17 and older without a prescription. Previously the FDA and the Bush administration had limited the access of the drug to women 18 and older but a U.S. district judge ruled in March that the older age limit was "arbitrary and capricious." The judge also directed the agency to evaluate clinical data to determine whether there should be any age restrictions on use of the drug. The FDA has no plans to appeal the court's decision. Duramed Pharmaceuticals must file paper work with the FDA, a process that is expected to take 30 days. Plan B is levonorgestrel in a 2-pill pack, the first to be taken within 72 hours of unprotected intercourse and the second pill 12 hours later.

The FDA has approved a new TNF-alpha blocker monoclonal antibody for the treatment of rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis. Golimunab is given once a month as a subcutaneous injection in combination with methotrexate for rheumatoid arthritis. It may be used with or without methotrexate for psoriatic arthritis and as monotherapy for ankylosing spondylitis. As with all TNF-alpha blockers, the FDA is requiring a risk evaluation mitigation strategy (REMS), which includes a medication guide for patients and a communication plan for physicians regarding potential side effects. Also similar to other drugs in this class, golimumab will carry a boxed warning regarding the risk of tuberculosis and invasive fungal infections. Golimumab was developed by Centocor Ortho Biotech, a division of Johnson & Johnson. The drug will be marketed under the trade name Simponi™. ■