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INSIDE

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More Good News from the WHI

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Women age 50-59 treated with estrogen in the WHI had less atherosclerosis.*

Source: Manson JE, et al. Estrogen therapy and coronary-artery calcification. *New Engl J Med.* 2007;356:2591-2602.

The Women's Health Initiative (WHI) Coronary-Artery Calcium Study (WHI-CACS) was an ancillary study of estrogen-only participants in 28 of the 40 WHI centers.[1] A total of 1064 women out of the 1742 eligible participants underwent computed tomography (CT) examinations of the heart, on average 1.3 years after the conclusion of the trial, which occurred after a mean 7.4 years of treatment. Coronary-artery calcium scores were measured at a blinded, central reading center (Wake Forest University School of Medicine). Calcification in the coronary arteries is located in atheromas and is correlated with the degree of atherosclerosis. The treatment group (0.625 mg conjugated estrogens daily) and the placebo group did not differ in baseline characteristics, including cardiac risk and lifestyle factors. The average calcium score in the treated women was 83.1, compared with 123.1 in the placebo group. All analyses indicated significant differences, including adjustments for age, race, and ethnic group. The difference was greater in the women adherent to treatment for at least 5 years. The odds ratio for extensive coronary-artery calcification was 61% reduced in the adherent group. The authors concluded that women 50 to 59 years old receiving estrogen had a lower prevalence of subclinical coronary artery disease.

COMMENTARY

This report on coronary-artery calcium levels in the estrogen-only arm of the WHI confirms previous observational studies.[2, 3] The argument that hormone therapy benefits the heart in younger postmenopausal women is further strengthened, an argument that is consistently supported by more than 20 years of basic and animal research, plus many observational studies. It is increasingly clear that once the blood vessels are involved with atherosclerosis, the

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ability to respond favorably to estrogen is progressively lost, until a state is reached when exposure to estrogen is associated with thrombosis originating in unstable atheromatous plaques. Kudos to Tom Clarkson for leading the way in clarifying this bivalent response with his hormone trials in monkeys.[4]

This evidence is unequivocal and very robust. Now it is time to resurrect the contention that estrogen therapy can provide primary prevention of coronary heart disease, at least when administered to younger postmenopausal women. This possible benefit of estrogen was diminished with the popularity and promotion of statin treatment. However, estrogen may have a very important advantage over statins. Studies have failed to document a slowing of coronary artery calcium progression with statin treatment.[5, 6] This is a striking difference, although the statin studies were limited by a treatment duration of only one year. The possibility that estrogen has a greater impact on calcification in atheromas deserves further study; is it possible that estrogen therapy would be even more efficacious in preventing coronary disease?

For now, patients deserve to know that women under the age of 60 receiving estrogen therapy have less atherosclerosis, fewer cardiac events, a reduction in new diabetes, fewer fractures, and even fewer strokes.[7-9] The risk of venous thrombosis is lower and clinical events are rare in women under age 60.[10]

An important question remains: is there a meaningful clinical difference comparing estrogen-only therapy to treatment with estrogen-progestin combinations? I want to emphasize once again that it is not appropriate to compare the two cancelled arms of the WHI and make conclusions regarding the addition of progestin exposure. To do so requires that the participants in the two arms are identical, or near-identical, and they are not even close.[11] Some indication may arise in the on-going primary prevention trials using measurement of carotid intima media thickness as a marker. Keep in mind that in Clarkson's monkey model that thus far has yielded information that agrees with human data, the effects on atherosclerosis of estrogen alone and estrogen combined with progestin were similar.[12]

Finally, the story is becoming clear, and it is time to repair the damages done by the WHI. ■

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Reproductive and Sexual Function in Long-term Ovarian Cancer Survivors after Platinum-based Chemotherapy

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *Long-term results of reproductive and sexual function of ovarian germ cell tumor survivors after platinum-based chemotherapy.*

Source: Gershenson DM, et al. *J Clin Oncol.* 2007;19:2792-2797.

Reproductive and sexual functioning following treatment for malignant ovarian germ cell tumors (GCTs) has been sparsely studied since the introduction conservative surgery and chemotherapy. While successful pregnancy has been reported in small series, the impact on quality of life in these young survivors is largely unknown. The current cohort study of GCT cancer survivors and control unaffected women, evaluated fertility and quality of life (QoL) concepts of sexual functioning and social networks. Cases were identified by their participation in one of several Gynecologic Oncology Group or University of Texas, M. D. Anderson Cancer Center chemotherapy protocols. Both were extensively interviewed and case patients were to be disease-free a minimum of 2 years prior to participation. Each case was age, race and education-matched for analysis. Just over half of the case women underwent fertility sparing procedures. Of this group, over 85% reported return of normal menstrual functioning which was similar to the control cohort. Approximately one-third of the women, who were able to become pregnant, had done so and delivered 37 children after cancer treatment. There was no difference in medical problems or miscarriage between the groups. Relative to controls, GCT survivors reported significantly more concerns with reproductive functioning, less sexual pleasure and lower scores on the Sexual Activity Scale. However, they had better dyadic consensus, dyadic satisfaction and dyadic cohesion. The authors concluded that return of menstrual function and potential fertility was common following GCT cancer therapy. While survivors reported more reproductive concerns and lower sexual satisfaction they were more likely to have stronger and more positive relationships with their significant others.

COMMENTARY

Women diagnosed with malignant germ cell tumor are typically younger and have a better survivorship potential than their epithelial cell counterparts. This is in part due to the response to treatment of these tumors and the stage at which the diagnosis is made, which is typically limited. Nonetheless, years ago, these otherwise rapidly growing and lethal malignancies were addressed with radical surgery and radiation rendering the survivors infertile. Documentation of chemosensitivity has opened the opportunity for parturition through less radical (fertility-sparing) surgery and adjuvant treatment. Early evaluation of the safety of this option demonstrated that return of menstrual function and normal pregnancy outcome in those who desired fertility was feasible but little was known about their quality of life. The current report substantially extends our understanding through careful evaluation of a number of measures including reproductive outcomes, sexual functioning, and dyadic adjustments (relationships). Clearly demonstrated is the expected return to normal menstrual function in the majority of women treated with platinum-based chemotherapy and the ability to have normal pregnancy(ies), if desired. Relative to non-cancer controls these women also demonstrated better and stronger relationships with their significant others but, as expected, were more likely to have reproductive concerns and less sexual satisfaction. The information is vitally important to clinicians caring for these young women as the "cancer" diagnosis is usually associated with images of atten-

uated lifespan, infertility, castration, and premature menopause. While many of these concerns can be allayed, the latter in non-castrates is not well known and will require longer follow-up to evaluate fully. Equally important will be further insight into the full spectrum of physical and psychological health of these women. Nonetheless, despite the incomplete profile, a very positive message can be introduced to these survivors, hoping to regain pre-cancer functionality. ■

Is a Genetic Amniocentesis Indicated for Isolated Choroid Plexus Cyst or Echogenic Cardiac Focus?

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

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

Synopsis: *Genetic amniocentesis is not warranted when isolated choroid plexus cysts or echogenic cardiac foci are noted on prenatal ultrasound.*

Source: Ouzounian JG, et al. Isolated choroid plexus cyst or echogenic cardiac focus on prenatal ultrasound: is genetic amniocentesis indicated? *Am J Obstet Gynecol.* 2007;196 (6): 595.e1-595.e3

Aside from advanced maternal age, two of the most common reasons for referral for a genetic sonogram are fetal choroid plexus cysts (CPCs) and echogenic intracardiac foci (EIFs). Likelihood ratios for Down syndrome with EIF vary appreciably in the literature, as do likelihood ratios for trisomy 18 with CPCs. Since both findings are quite common, it has become extremely important to find data that will put these findings in proper perspective when they are "isolated," especially in patients at low risk for either trisomy 21 (T21) or trisomy 18 (T18).

In a recent report, data were culled from a California Kaiser Permanente database from 1998 to 2004. During this time, 515 patients were noted to have fetuses with isolated EIF (240 or 46.6%) and/or CPCs (275 or 53.4%). Those with risk factors (AMA, elevated risk for aneuploidy by second trimester biochemistry) were analyzed separately. Since Kaiser is a closed system, the authors were able to obtain amniocentesis and birth data on all patients getting care within the study period.

Of the 515 patients with EIF/CPC, 429 (83.3%) were isolated and in low-risk mothers. Eighty-six (16.7%) had risk factors and/or other ultrasound findings. Thirty-six percent of the former group and 43.3% in the latter group had amniocenteses. In those having amnios with risk factors, 2 had fetuses with T18. In the low-risk group, none of the amnio patients were positive for aneuploidy. Of the 20,122 live births recorded during the study period, there were 27 infants with aneuploidy, all of whom had T21. None of these had isolated CPCs or EIFs. Therefore, isolated CPC/EIF had a positive predictive value of 0% in a low-risk population. The authors concluded that their study had the statistical power to detect a difference in outcome when isolated EIF or CPCs were found and that "amniocentesis does not appear to be warranted in low-risk patients with isolated CPCs or EIFs."

■ COMMENTARY

It is clear that there is an association between EIF and T21, as well as between CPC and T18. However, Bromley and others have shown no association between CPCs and T21. Likelihood ratios have been derived for both EIF and CPCs based on the percentage of fetuses with aneuploidy that have had them and the prevalence of the findings in an accompanying normal population of fetuses. These positive likelihood ratios have varied from 1.5 up to 7. The problem is that even in studies where the findings were judged to be "isolated," (especially in the older studies) one wonders what isolated really meant. Were other markers for T21 and T18 really evaluated or did the search only involve major abnormalities? Also, in some cases, how diligent were the sonologists/sonographers in investigating other signs when the patients were about to have an amniocentesis?

An EIF represents an increase in density in the papillary muscles, generally, in the left ventricle, and the brightness can vary according to the patient's body habitus, the frequency of the transducer used, and the angle at which the heart is approached. At least one quarter of patients referred to us do not have an echogenic focus that is as bright as adjacent bone. Also, the prevalence of this finding depends upon the population studied. For example, one study shows up to 15% of Asian fetuses will have EIFs. CPCs vary in size between simply a mottled appearance of the plexus to some that measure over 5 mm, and often some disappear by the time they get to us. However,

CPCs have little meaning once other signs of T18 have been excluded, since it is extremely rare for a fetus with this condition to not have at least 2 and up to 8 abnormal findings. Also, the quad screen is an excellent exclude of T18 despite statements in the literature (and in some laboratory reports) that the sensitivity is only 60% for this condition. However, this is at a screen positive rate of 0.5%. If the bar is set at 5%, then over 90% of fetal T18 will be screened in.

So, the take home message is that if a CPC or EIF is found, a diligent attempt should be made to look for other markers for Down syndrome (with an EIF) or T18 (with CPC), and if none is found, and the patient is in a low-risk category, the likelihood is no greater than her pre-scan risk. Also, under these circumstances the risk for T18 is most likely less than the risk of amniocentesis (see Jan. '07 *OB/GYN Clinical Alert* on amniocentesis risk). ■

Effect of Trauma and Post-traumatic Stress Disorder on Chronic Pelvic Pain

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

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

Synopsis: *Close to half of all women referred to a pelvic pain clinic had a physical or sexual abuse history while over 30% had a positive screen for post-traumatic stress disorder.*

Source: Meltzer-Brody S, et al. Trauma and Posttraumatic Stress Disorder in Women with Chronic Pelvic Pain. *Obstet Gynecol.* 2007;109:902-908.

A questionnaire was administered to 713 consecutive patients referred to a pelvic pain clinic. In addition to the high frequency of a history of sexual and/or physical abuse, patients with a history of such trauma were found to have worse daily physical functioning due to poor health, more surgery, more time in bed, more medical symptoms, and more dysfunction due to pain. The importance of clinicians screening for trauma and post-traumatic stress disorder is reinforced by these findings.

■ COMMENTARY

This is another in a long series of useful publications from the group of researchers at the University of North Carolina. In this case, the most disquieting and uncomfortable of the etiologies of chronic pelvic pain in women is addressed. As surgeons, gynecologists (and I certainly include myself) must constantly be reminded that not every patient fits into the category of someone who can be helped with an operation. The old adage "Don't let the abdominal wall stand between you and the diagnosis" should certainly not be universally applied. When we're operating, we can be objective and technical. We don't have to be so "touchy/feely." I would suggest, however, that our colleagues here have reminded us once again, that there is potentially so much more to women with chronic pelvic pain than initially meets the eye.

So let's look at what may well be going on in our respective offices today. First, chronic pelvic pain has a prevalence of 15% among women of reproductive age. It accounts for 10% of gynecologic consultations. In my practice, also a referral center for pelvic pain, the percentage is much higher. The fact is, many clinicians find this condition difficult to deal with, so referral to someone like myself, who actually wants to see these patients, is an option that is welcomed. While seeing these patients, who inevitably end up in the gynecologist's office, it should be remembered that posttraumatic stress disorder (PTSD) is an anxiety disorder which is initiated by serious trauma in the individual's past. Women are twice as likely to develop PTSD when compared to their male counterparts. Overall, 25% of patients with a trauma history will develop this serious condition.

What pearls of wisdom should we be taking from this article into the examination and/or consultation room? First, don't hesitate to ask the question about sexual and/or physical abuse. You'd be surprised how often a patient wants to tell someone, but is never given the opportunity. A question as straightforward as "Have you ever been touched against your will, either as an adult or child?" is enough to open the door. The patient may not walk through that door today, but she may well do so on a future visit. Second, look for evidence of abuse now. Admittedly, PTSD would not show up as recent physical abuse, but bruises now might suggest a pattern of behavior. Don't hesitate to ask how various bruises on different parts of the body got there. Third, look for signs and symptoms of anxiety. We've all seen anxious patients, but we should not simply write it off as general anxiety disorder (GAD), but should, instead, consider a PTSD diagnosis. Fourth, you might wish to contact the local abuse shelters and/or the American College of Obstetricians and Gynecologists to obtain written mate-

rial that can be placed in the bathrooms in your office offering support and resources to patients who are victims of abuse. Placing the brochures or pamphlets in a private area will allow patients to pick them up without fear of being seen by others.

All of us need reminders like this article to remember that in this technology-driven profession, imaging tests and bloodwork don't necessarily always hold the answers to the tough questions. By no means am I suggesting that every patient with pelvic pain be put through an exhaustive psychiatric evaluation. That would also send the wrong message. What we can do, however, is maintain a vigilant watch for evidence that would link a patient's complex and often confusing clinical picture to their heretofore undiagnosed trauma history and/or PTSD. As the sergeant on the old television series *Hill Street Blues* used to tell the squad shortly before they were sent out to their daily duties, "Be careful out there." ■

Does Test Order Affect Sensitivity in Vulvodynia?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

Synopsis: *The order of testing for sensitivity in the vulva and thumb does not affect the results.*

Source: Reed BD, et al. Effect of Test Order on Sensitivity in Vulvodynia. *J Reprod Med.* 2007;52:199-206.

THIS RESEARCH TEAM LOOKED AT THE SENSITIVITY measurements to pressure at both the vulva and thumb as they randomly assigned the order of tests. This was repeated a week later on the contralateral side. Among 13 women with vulvodynia and 20 control patients, there was a strong correlation between the two visits, and there was no order effect noted.

COMMENTARY

Don't you just love articles like this one? It's like finding a nugget of gold when you weren't even looking for anything valuable. When I first read the title, I had no idea of where the authors would lead me, but I'm glad I stuck with it. It reinforces concepts that we all have learned, but sometimes forget in the midst of a busy practice.

The concept is straightforward enough. The authors wanted to know whether it made any difference in sensitivity if the vulva was tested first, or if a peripheral site (in this case the thumb) was touched first. Why would they even ask the question? I think we have all had the experience and possibly the suspicion that certain physical findings we discovered were due to a previous aspect of the examination. Essentially, the accuracy of our physical examination might be tainted by the order in which various maneuvers are done.

Here the authors chose an area far from the vulva. They also evaluated patients with a chronic condition that was unlikely to change week to week. By using standardized pressure (you'll have to read the article to see the ingenuous testing device), they looked at whether sensitivity testing of the vulva was affected if that area were evaluated before or after the thumb, an area unlikely to have cross-sensitization. Since the areas are so far apart, it shouldn't surprise us that there was no effect of the order of testing and that the sensitivity was stable over time, both in the patients with vulvodynia as well as the pain-free controls.

So now you're asking why I'm taking up your valuable time and wasting precious space in this issue to address what should be something that we could each have logically deduced on our own. It's because we run across this every day in our practices, but don't realize it and don't appreciate it. In fact, this may be something very new to some of the readership, so read on.

In the evaluation of the patient with pelvic pain, and especially the patient with dyspareunia, we sometimes forget that the order in which we do the examination might make a difference. More specifically, we sometimes forget that the introitus should be looked upon as a separate entity, an anatomic site from which specific pain symptoms might arise. Let's be more concrete to make a point: if a patient presents with dyspareunia, question to ask whether it's deep or entrance pain. Admittedly, sometimes the patients won't know specifically, but it helps to try to get that answered before the examination starts. Before a bimanual is performed, and even before a speculum is placed, the introitus and particularly the vestibule should be evaluated. The most effective technique to check for vulvar vestibulitis is to gently separate the labia and press the Skene's and Bartholin's gland duct openings with a moistened cotton tip swab.

The patient should be asked if that is their coital pain or not. If there is not tenderness, then the rest of the examination should proceed as usual; however, if there is tenderness, differentiating whether that is their pain or a different pain is a critical piece of the puzzle. If we forget to do this introital Q-tip test, we run the risk of looking right past the etiology of her

pain, doing a bimanual, and finding that she is tender throughout the pelvic area. In reality, the pain may well be coming from a sensitized and now very painful introitus that is being stretched by our vaginal fingers as part of the routine pelvic.

So that is the clinical take home lesson from what might otherwise be considered a not very useful research article. (And you thought that the Q-tip test was associated with checking for urethral support). Not so! I'll wager that the Q-tip test that you do in patients with entrance dyspareunia will be far more useful than in those patients with incontinence issues. ■

Making the Diagnosis of Adenomyosis

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

Synopsis: *Despite technology such as transvaginal sonography, magnetic resonance imaging, computed tomography, and even myometrial biopsy, the clinician's ability to make an accurate preoperative diagnosis of adenomyosis is still limited.*

Source: Levgur M. Diagnosis of Adenomyosis: A Review. *J Reprod Med.* 2007;52:177-193.

THE AUTHOR HAS SYSTEMATICALLY REVIEWED THE literature between 1949 and 2005, searching for research related to adenomyosis as well as the diagnosis thereof. Although superior to transabdominal sonography, the transvaginal route has a sensitivity of only 50-87%. MRI is comparable to ultrasound and is most effective for both focal and diffuse adenomyosis. CT is of limited value because normal myometrium and adenomyosis result in similar images. Myometrial biopsy is superior to ultrasound, but its routine use is brought into question.

COMMENTARY

Do you want my bottom line first? OK, here it is: in my opinion, there's really nothing new under the sun relating to adenomyosis. Now, in the words of Paul Harvey, if you want "the rest of the story," read on.

The author has systematically looked at the English literature over the past half-century to see what is helpful in diagnosing adenomyosis. The histologic criterion of endometrial glands and stroma existing 2.5 mm or half a lower-power field below the endomyometrial border is still useful. It is recognized that the posterior uterine wall is most affected, with the condition being either diffuse or focal. Except in rare circumstances, the uterus is rarely over 12 weeks in size. The classic description of patients presenting with pelvic pain, menorrhagia, and dysmenorrheal still works, as does the expected physical finding of a tender uterus. That's all the same as we could find if we looked at a gynecologic textbook of 25 years ago. (I know because I did look it up.)

The difference is that we now have alternative imaging and minimally invasive diagnostic modalities available to us. Whether any of them have true clinical relevance in the diagnosis of adenomyosis appears well-documented. The author reviews data that don't seem to lend credence to any of them being very useful. The interesting phenomenon, however, is that these tests are still being done. Why?

First, we must remember that not everyone who orders tests in women who ultimately have adenomyosis as a diagnosis is familiar with the gynecologic literature, or is even a gynecologist for that matter. Second, tests are often performed to rule out other conditions which are amenable to different types of treatment. For example, an endometrial polyp and/or small fibroids could certainly present like adenomyosis and would be more readily treated with surgery short of hysterectomy. The issue of treatment of adenomyosis was not addressed in the article, but suffice it to say that there isn't anything new in that regard either. Third, patients often drive what tests are ordered and clinicians must balance what they believe is helpful with what they feel is needed to treat the overall patient.

I highly recommend the article to anyone who sees patients with suspected adenomyosis, ie, I recommend the article to anyone who treats women with pain and menorrhagia. My guess is that includes anyone and everyone who reads this periodical. The condition is common and the management is not complicated. Sometimes we can be our worst enemy in making a diagnosis. Let's face it: common things occur commonly. Patients who present with signs and symptoms suggestive of adenomyosis may well have it. How you diagnose and treat it hopefully has not changed a lot over the years, because there isn't anything available that should have altered good medical decision-making. Doesn't that make you feel good? Sometimes the tried and true methods are still the best. ■

CME Questions

14. The following statements are true regarding the cardiovascular data in the WHI except:

a. An increased risk of coronary events was present only in the oldest women in the trial.
b. Estrogen therapy is associated with primary prevention of coronary events in the youngest women in the WHI trial.
c. Estrogen therapy is associated with a small increase in venous thrombosis.
d. Estrogen therapy is associated with an increase in strokes in the youngest women in the WHI trial.

15. Regarding sexual function, case patients were more likely to report lower scores on all the following EXCEPT:

a. sexual pleasure
b. total sexual activity
c. sexual self schema
d. reproductive concern

16. Which is not a feature of EIF?

a. it is dependent upon the frequency of the transducer
b. it is angle-dependent
c. its prevalence varies according to the population studies
d. it is most frequently seen in the right ventricle

Answers: 14 (d); 15 (c); 16 (d)

Correction: In last month's issue of *OB/GYN Clinical Alert*, questions number 11 and 14 were duplicated, so this month's questions will begin with number 14.

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.

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SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■