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Postmenopausal Hormone Therapy and Coronary Heart Disease

ABSTRACT & COMMENTARY

A secondary prevention trial did not detect any adverse or beneficial cardiovascular effects of postmenopausal hormone therapy in older women with existing heart disease. The Women's Health Initiative is revealing an increase in heart attacks in the first two years of hormone treatment, followed by a reduction.

Herrington and colleagues have reported the results of a multicenter trial examining the effect of postmenopausal hormone therapy on the progression of coronary atherosclerosis as assessed by angiography. The results of this study, entitled Estrogen Replacement and Atherosclerosis (ERA), were presented on March 13, 2000, at the 49th Annual Meeting of the American College of Cardiology. A total of 309 women were randomly assigned to receive either unopposed estrogen, 0.625 mg Premarin (Wyeth-Ayerst Laboratories) per day; a daily combination of estrogen and progestin, 0.625 mg Premarin and 2.5 mg medroxyprogesterone acetate (PremPro; Wyeth-Ayerst Laboratories); or placebo. More than 3.5 years of treatment angiography did not detect any differences in disease progression between any of the groups. The women in this study had documented heart disease on entry and were a relatively older group of women (mean age, 65.8 years). Half had had a previous myocardial infarction (MI). There were no reported increases in cardiac events in any of the three treatment groups.

The large American randomized clinical trial examining the effects of postmenopausal hormone therapy, the Women's Health Initiative (WHI), is informing the women in the study that a "small increase" in heart attacks, strokes, and venous thrombosis has been observed in the first two years of the study comparing hormone treatment with placebo. This increase is reported to be present in all treatment arms, including the group treated with estrogen alone. This information was made available by the Data and Safety Monitoring Board (DSMB); therefore, the actual data will probably not be revealed until the completion of the study. The DSMB has recommended that the study continue; it is scheduled for completion

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in 2005; another year should be required for data analysis.

COMMENT BY LEON SPEROFF, MD

It is unusual for us to review unpublished reports; however, I believe an acute response is important because of the anticipated reactions and widespread publicity. The ERA trial joins the HERS trial in demonstrating no secondary preventive effect of postmenopausal hormone therapy in older women with significant coronary heart disease. Comparing the two trials, however, there are several important observations.

Some have argued (most notably, Tom Clarkson and colleagues[1-3]) that the lack of a beneficial effect of estrogen in the HERS trial was because of the attenuating action that resulted from the daily presence of medroxyprogesterone acetate (PremPro). The ERA trial contained an estrogen-only arm, and the absence of a difference between the estrogen-only arm and the PremPro arm argues against a negative effect due to the daily administration of medroxyprogesterone acetate.

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The HERS trial was not a totally null result. In the first year of the trial, there was a 52% increase in clinical events in the women treated with PremPro, and in years three and four there was evidence of emerging protection against cardiac events in the treated group. Like the HERS trial, the WHI is reporting evidence of protection in the last months of the first two years of the study. Why were similar observations not present in the ERA trial? Most likely, the answer lies in the numbers of patients combined with duration of treatment, 2763 women studied four years or more in the HERS trial compared with 309 women studied for 3.5 years in the ERA trial (ultimately a relatively small number of women finished the study in each treatment arm). The ERA results are not sufficiently robust to eliminate the concern arising from the HERS trial that there exists a group of women with heart disease in whom exposure to hormone therapy increases the risk of adverse events in the first months of treatment.

Further analysis of the HERS data has indicated that the increase in adverse events in the first year occurred in the first eight months of treatment, most likely, in my view, due to a prothrombotic effect of oral estrogen. Are these events occurring in a susceptible, vulnerable group of women, perhaps sicker women with unstable atherosclerotic plaques? We will have to await the full publication of the ERA data to see if there is a time and age distribution of importance, but this is unlikely because of the relatively small numbers.

The report from the WHI also provides a strong argument that medroxyprogesterone acetate is not preventing beneficial estrogen actions on the cardiovascular system (because, like the HERS trial, the adverse effects were present in the estrogen-only arm as well as with estrogen-progestin treatment).

The actual number of events upon which the WHI report is based totals less than 1% of WHI women (less frequent than in the HERS trial, probably less than several hundred events, including all three diagnoses—heart attacks, strokes, and venous thrombosis). The absence of an increase in cardiac events in the ERA trial also indicates that the risk is not a large one. I can't help but believe that any increase must be small in terms of actual incidence, otherwise our clinical consciousness would have been imprinted with these experiences.

There are several important questions that hopefully can be answered by analysis of the WHI data:

- Is the increase in heart attacks confined to a susceptible group of women and, if so, what are their characteristics?
- What is the age distribution of the clinical events; are the heart attacks concentrated in older women? It is of

importance to be aware that many of the subjects in the WHI are relatively older women who began treatment years after menopause. Thus, some of the participants had evidence of preexisting cardiovascular disease (including heart attacks, bypass surgery, angina, and angiographic procedures). Is the increase in events concentrated in this segment?

- Will a beneficial effect become significant with longer duration of treatment (as suggested in the HERS trial)?

The secondary prevention trials have led to the recommendation that older women with significant coronary heart disease should avoid initiating postmenopausal hormone therapy. Until the report from the WHI, there was reason to believe that the results from the secondary prevention trials did not imply that primary prevention, hormone therapy administered to younger postmenopausal women without evidence of coronary heart disease, would not be effective, as predicted by the many case-control and cohort studies. Furthermore, these reports are contrary to a huge number of biological studies documenting favorable actions of estrogen on the cardiovascular system.

Other studies presented in 2000 at the American College of Cardiology were uniformly consistent with a beneficial effect of estrogen on the cardiovascular system, even in women with existing atherosclerotic disease. An Italian double-blinded study indicated that estrogen treatment improved brachial artery resistance and increased forearm blood flow in women with risk factors for coronary artery disease (CAD). A short-term (3 months) study at Mt. Sinai in New York revealed that estrogen reduced thrombus formation in elderly women with evidence of cardiovascular disease. A study on serum lipids concluded that combined estrogen-progestin therapy together with a statin produced a greater favorable response than either treatment alone. In both a post-mortem histopathological study and a CT scan study of coronary arteries, coronary artery calcium content and atherosclerotic plaque area were lower in hormone users compared with nonusers. Premenopausal women with CAD in the Women's Ischemia Syndrome Evaluation (WISE) study were reported to have lower estrogen levels compared with women without disease. These studies add to a large body of biological evidence that estrogen and estrogen combined with a progestin have effects that should provide protection against cardiovascular disease. Why such favorable effects were not apparent in the ERA trial remains a mystery. Is a three-year study too short to demonstrate beneficial effects on clinical events, especially with relatively small numbers? Is angiography as a method of assessment too limited, unable to detect important effects that are not expressed in anatomical changes? Will the WHI yield more favorable data as time passes?

Is it possible that the results of these trials are not real? There is one concern in my mind that makes this question reasonable. These studies cover a period when the efficacy of statins was established. The increasing use of statins, especially in older women who are not hormone users, makes it difficult to have a true placebo group in studies of coronary heart disease. We will need to carefully assess the degree and effect of statin use by the women in these trials. Specifically, is the early increase in events in the HERS and WHI trials due to a statin-induced decrease in events in the placebo groups?

I fully expect that these surprising results will reinforce those who have argued that the case-control and cohort studies of postmenopausal hormone therapy and coronary heart disease have been biased by the healthy user effect (hormone users are healthier than nonusers and therefore observational studies find less coronary heart disease in hormone users). But it seems to me that we should not discount the enormous literature that over and over documents favorable biological effects of estrogen on the cardiovascular system—effects that should produce protection against coronary heart disease. All the pieces are not fitting in this puzzle. It seems logical to me that the WHI results reflect a prothrombotic effect of estrogen in a susceptible group of women. With some urgency, we need to determine if such a group exists, and, if it does, what are the characteristics of these women?

Conclusions

1. These trial results are reasons to be conservative regarding hormone therapy for older women with evidence of coronary heart disease. Certainly we should not promote estrogen as a first-line drug to prevent further clinical events in women with CAD, especially in women who have had a recent MI. Multiple clinical trials have established that treatment with statins is effective in preventing clinical cardiac events.
2. The ERA and WHI results indicate that there is no need to avoid the use of medroxyprogesterone acetate.
3. The results of the WHI make an argument that the optimal approach to postmenopausal hormone therapy is to start treatment close to the menopause, avoiding a significant period of exposure to low estrogen levels prior to beginning therapy.
4. With evidence accumulating that a beneficial effect emerges with increasing duration of treatment, we need to intensify our efforts to improve and maintain compliance.
5. There continues to be good reason to believe that long-term therapy has preventive benefits.
6. These results indicate the need and importance of studying the question of whether older women should

be started at lower doses of estrogen. Doses may need to be titrated according to patient characteristics. Another question that emerges from these studies is whether women with coronary heart disease would benefit from hormone therapy if treatment were to begin after stabilization is achieved with a period of exposure to statins.

7. We should continue to advise current users of postmenopausal hormone therapy that it is unwise to discontinue treatment.
8. We need to determine whether the transdermal route of delivery yields different effects on the cardiovascular system.
9. Because the events in the WHI occurred early, followed by a reduction, clinicians should encourage participants in the study to remain enrolled, impressing upon them the importance of this large clinical trial. ❖

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Positive Margins After Conization and Risk of Persistent Lesion

ABSTRACT & COMMENTARY

Synopsis: *Cytology and colposcopy follow-up in cases of positive conization margins may help to establish justification for the choice of reoperation, thereby limiting morbidity following repeated surgery.*

Source: Narducci F, et al. *Gynecol Oncol* 2000;76: 311-314.

Narducci and associates investigated a method to reduce the frequency of uterine reoperation with no persistent lesion and to identify factors predictive of persistent or recurrent lesions. Of 505 conizations performed by the same surgeon, 71 had positive margins (average patient age = 35.7 ± 7.7 years). The patients underwent either immediate reoperation or monitoring with a Pap smear and colposcopy. Histologic assessment of the cervical cone after conization showed positive margins in 14.1% of cases (endocervical and exocervical margins affected in 50 of 505 [9.9%] and 21 of 505 [4.2%] cases, respectively). Of 59 of these patients (83.1%) who underwent follow-up monitoring over an average of 35.2 months, 12 patients (average age = 40.8 ± 6.4 years) underwent immediate hysterectomy and 47 (average age = 34.0 ± 7.4 years) benefited from monitoring first (secondary discovery of 19 persistent lesions within 6 months and 9 recurrences within 18 months on average [range, 8.8-48 months]). Of the nine patients with recurrent lesions, seven underwent reintervention and two monitoring. Of the 19 patients with persistent lesions, 18 underwent reintervention and one monitoring. Normal histology was observed in 29.4% of patients undergoing secondary reoperation for an abnormal smear compared with 66.7% of patients undergoing immediate reoperation (P = 0.04). Severity of lesion and age of patients could not be used to predict the incidence of a persistent or recurrent lesion. Seventy-nine percent of conizations had positive endocervical margins in patients with a recurrent or persistent lesion compared with 48% in patients with normal follow-up (P = 0.03). Narducci et al conclude that cytology and colposcopy follow-up in cases of positive conization margins may help to establish justification for the choice of reoperation, thereby limiting morbidity following repeated surgery.

COMMENT BY DAVID M. GERSHENSON, MD

What is the appropriate management for a patient with positive margins of a conization specimen? As highlighted in this article from France, there is no single management option. In general, options include either reoperation—repeat conization or, more often, hysterectomy—or close follow-up with Pap smears and colposcopy. There are no definite criteria for selecting one course over another. Factors that should be considered include the type of positive margin (cervical intraepithelial neoplasia [CIN] vs microinvasion), extensiveness of positive margin (focal vs multifocal or diffuse), patient age, patient reliability for follow-up, and the patient's desire for future fertility and attitude about reoperation vs. follow-up. In this article, 10 of the 12 patients who underwent immediate reoperation (an average of 2.8 months after the initial conization) had microinvasion on the initial conization specimen; most were older, and all underwent hysterectomy. Not unexpectedly, in 67% of the subsequent specimens,

there was no residual disease. For the patients who were followed after initial conization, Narducci et al found no difference between patients with normal follow-up and those who had a recurrent or persistent lesion with respect to age or severity of lesion. Other investigators have found age, lesion severity, and smoking to be predictors for recurrence. In conclusion, I agree with Narducci et al that close follow-up is preferable to reoperation, except in cases of microinvasion at the margins, adenocarcinoma in situ, poor compliance with follow-up, or women who have completed childbearing and who desire definitive surgery. ❖

Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer's Disease

ABSTRACT & COMMENTARY

Synopsis: *When given to symptomatic women, conjugated equine estrogens did not slow the progression of Alzheimer's disease.*

Source: Mulnard RA, et al. *JAMA* 2000;283: 1007-1015.

This double-blind, placebo-controlled, randomized, prospective multicenter trial was designed to determine if oral estrogen therapy would slow the progression of dementia in women with established Alzheimer's disease. To better test this hypothesis, the study population was confined to women who had undergone a hysterectomy and could therefore take unopposed estrogen and to those who did not meet criteria for depression (n = 120). Eligible women were randomized to one of three arms: placebo, conjugated equine estrogen (CEE) 0.625 mg daily, and CEE 1.25 mg orally daily for one year. Several psychometric inventories were used to monitor response to interventions.

The results showed that estrogen did not retard the progression of dementia at any of the time points (2, 6, 12, and 15 months) except for a transient benefit seen in a low-dose CEE-treated group at two months. This benefit did not persist. Women on antidementia therapies (donepezil or tacrine) showed the same response as those not taking them. The rate of adverse events was statistically comparable in all groups, although two women in each CEE arm had a deep vein thrombosis (DVT), while none in the placebo arm did. Mulnard and colleagues conclude that estrogen is not effective for slowing the progression of established Alzheimer's dementia.

COMMENT BY SARAH L. BERGA, MD

The most important message of this study is that estrogen therapy is not indicated as an intervention with established dementia. However, it is critical to emphasize that this does not mean that it is ineffective in preventing dementia or enhancing cognitive functioning in symptomatic, recently menopausal women. Estrogen therapy for menopausal women has only recently been touted as a potential cure for established disease. Previously, the mindset was that estrogen therapy was to be taken as a prophylactic against a variety of age-related diseases such as cardiovascular disease, osteoporosis, and urogenital atrophy. Why the switch in emphasis from prophylaxis to intervention? It is theoretically easier to determine if a given agent reverses or retards an established process. However, intervening once a pathologic process is well under way also raises the bar in terms of required potency. It seems too much to expect a prophylactic to undo neurofibrillary tangles and restore dead glia, melt away vessel occlusions in coronary arteries, tighten sagging pelvic ligaments, or rebuild broken cytoarchitectural struts in bone. As the addage says, "An ounce of prevention is worth a pound of cure." To my way of thinking, in the rush to show the power of estrogens, several investigative groups undertook clinical challenges of unrealistic proportions. These null studies in no way invalidate the prior mindset that estrogen therapy may help to retard disease development. However, to determine the magnitude of prophylactic benefits demands that a larger population be followed for a much longer duration. Such studies not only take a long time, but they are expensive and may not lead to much academic reward for the investigators. Sadly, the only long-term prospective, randomized, double-blind trial that is likely to yield interpretable data about multiple simultaneous end points is the Women's Health Initiative. And that study will only be a test of CEE taken orally with and without medroxyprogesterone acetate. In the interim, the burden of proof is likely to be shifted. We previously supposed that the benefits of postmenopausal hormone therapy were likely to outweigh the risks of venous thrombolic events and breast cancer. I suspect that most women will now want more evidence that this is the case and we simply do not have concrete proof that this is so. Dialogues with patients regarding the pros and cons of postmenopausal hormone use are likely to take even longer.

About three weeks after the present report, another

regarding Alzheimer's dementia (AD) appeared in the *Journal of the American Medical Association* (Naslund J, et al. *JAMA* 2000;283:1571-1577). This report presented new data regarding the pathogenesis of AD. The report showed amyloid plaque accumulation (rather than tangles) upon autopsy correlated quantitatively with degree of dementia. In the accompanying editorial (Selkoe DJ. *JAMA* 2000;283:1615-1617), an analogy was made between diffuse plaques in AD and early fatty streaks in the genesis of atherosclerosis. Based on this report and other supporting evidence, the therapeutic target for preventing AD is now established to be amyloid b-peptide (Ab). Mulnard et al suggest that in the future, we will be screening for AD with blood tests for relevant gene defects, measurement of plasma Ab, and possibly cerebrospinal fluid levels of Ab and other key markers if neuropathology is suspected. Those at high risk or with early but clinically silent disease will then receive targeted aggressive therapies directed at the key pathophysiologic steps in much the same way that those with elevated low-density lipoprotein (LDL) are supposed to receive statins before their first myocardial infarction (MI). In all likelihood, estrogen will resume its role as a preventive rather than interventive for dementia and many other pathologic processes. The key questions will then be: which estrogen, by which route, for what duration, at what dose, and how to monitor? ❖

The Effect of Weight Loss in Overweight, Lactating Women on the Growth of Their Infants

ABSTRACT & COMMENTARY

Synopsis: *Weight loss of approximately 1 lb per week in lactating women does not affect infant growth during the first three months.*

Source: Lovelady CA, et al. *N Engl J Med* 2000;342: 449-453.

For many years, it has been suggested that planned weight loss can occur during lactation without fear of injury to the mother or infant. Despite the fact that this recommendation is made by many clinicians and various bodies that make policy statements, no randomized trial has previously been conducted.

Lovelady and colleagues recruited postpartum, lactating women into this study who were generally healthy except for a body mass index (BMI) of 25-30. In addition, the women were required to have a sedentary lifestyle, be nonsmoking, and exclusively breastfeeding. The offspring had to have been delivered vaginally at term, with a weight of at least 2500 g. Women who agreed to participate in the study had extensive baseline measurements before random assignment to either a diet and exercise group or a control group. Baseline measurements included standard height and weight, skinfold thickness measurements at six body sites, residual lung/volume measurement, and body density calculations. In addition, the women were required to use portable digital scales to measure all solid and liquid intake for three consecutive days at baseline (4 weeks postpartum), at midstudy (9 weeks postpartum), and at study conclusion (14 weeks postpartum). The cardiovascular fitness of each woman was estimated using a standard methodology. Caloric intake during the study was individually assigned, with the study group receiving 500 kcal less intake per day than the control group. The exercise program required four 45-minute sessions of aerobic exercise. Those women who were not fit at the beginning of the study exercised 15 minutes initially and increased the length by two minutes each day until they could safely exercise for 45 minutes.

Forty-eight women enrolled in the study. Twenty-seven were assigned to the diet and exercise program, and 21 to the control group. Eight women dropped out of the study—six in the diet and exercise group and two in the control group. The control and study groups were similar based on a number of demographic factors. However, the women who dropped out of the study were significantly heavier than those women who remained in the study.

During the 10 weeks of the study, the diet and exercise group lost an average of 4.8 kg (10.5 lb). The control group lost an average of 0.8 kg (1.8 lb). This difference was significant. There were no differences in the weight gain of the infants in either group. The average weight gain in both groups was similar to that recorded in other studies.

Lovelady et al conclude that "moderate weight loss" (approximately 1 lb/wk) in lactating women has no effect on infant growth.

COMMENT BY KENNETH L. NOLLER, MD

Obesity remains one of the major challenges in health care today. While cardiovascular disease has been reduced in the population overall, the percentage

of individuals who are overweight continues to rise. According to a recent study quoted by Lovelady et al, 51% of women in the United States have a BMI greater than 25.

There are a few times in our lives when losing weight seems easier than others. For many women, the period of lactation is such an opportunity. Milk production requires 500-800 kcal per day. In addition, the new mother is usually extremely active, particularly if she has other young children to care for. Even moderate calorie restriction during lactation can result in impressive weight loss.

But how safe is it for a lactating woman to attempt to lose weight? This study suggests that such attempts are safe both for the mother and for her infant. However, there are some problems with generalizing this study. The study groups were extremely small. Heavier patients tended to drop out of the study. Lovelady et al did not determine whether weight loss of 1 lb/wk achieved purely by calorie restriction without exercise was similarly safe for mother and infant. Nonetheless, we can be relatively reassured when we suggest to our patients that lactation is an excellent time for weight loss.

As an aside, you might have noticed that I detailed the study methodology in my summary of the article more than usual. I did this on purpose to emphasize the fact that performance of weight loss studies has become an extremely complicated task. Simple measurement of weekly weight is no longer considered to be a valid study design. ❖

Special Feature

Mitral Valve Prolapse in Pregnancy

By Steven G. Gabbe, MD

Mitral valve prolapse (mvp) is the most common abnormality of the cardiac valves and the most common cause of severe mitral regurgitation in the United States.[1] However, there is considerable controversy about its prevalence, diagnosis, and management in pregnancy. This review describes the anatomic and physiologic changes associated with MVP in pregnancy, including echocardiographic characteristics and the differences in risk associated with anatomic vs. functional. A plan for the care of the pregnant woman with MVP will be suggested.

MVP has been defined as billowing of the mitral leaflets into the left atrium during systole.[2] The mitral leaflets do not close completely and regurgitation develops. Two phenotypic patterns have been described—an anatomic form with thickened leaflets, which may lead to progressive valvular pathology that is seen in 15-20% of patients, and a functional form characterized by a dynamic expansion or enlargement of the mitral annulus during systole. On auscultation, MVP is characterized by a nonejection systolic click that corresponds to filling of the relaxed mitral valve leaflets.[1] A late systolic murmur of mitral regurgitation may be heard. With progression to severe mitral regurgitation, the click may disappear and an S3 gallop and rales and dyspnea may be observed.

The diagnosis of MVP must be made with two-dimensional echocardiography. Classic MVP, which corresponds to the anatomic form, is characterized by displacement of the mitral valve leaflets into the left atrium by more than 2 mm and a maximum thickness of the leaflets of at least 5 mm. In contrast, the nonclassic form of MVP, which corresponds to the functional form, reveals displacement of the leaflets by at least 2 mm into the left atrium but without leaflet thickening.[2] Functional MVP is observed in 80% of patients and usually resolves with age. It is characterized by reduction in left ventricular size with a relatively larger mitral valve annulus and mitral leaflets. In contrast, the anatomic or classic form is most often seen in men after the age of 45 and is often associated with connective tissue disorders such as Marfan syndrome. It is this form of MVP that leads to elongation and rupture of the valvular chordae tendinae and is associated with atrial fibrillation, infective endocarditis, and embolic complications. A variety of symptoms have been associated with the functional form of MVP, including chest pain, palpitations, arrhythmias, fatigue, dyspnea, and syncope. However, recent studies have shown that these symptoms are not specific for or increase in individuals with MVP. In fact, echocardiography has not been recommended in individuals with these noncardiac symptoms.[3]

The prevalence of MVP was reported to be as high as 17% among young women. However, more recent studies, using carefully defined echocardiographic characteristics, have documented this valvular abnormality in approximately 3% of women.[2] Should a patient report a history of MVP, it is important to confirm the diagnosis by two-dimensional echocardiography if that study has not been performed in the past.

During pregnancy, the auscultatory findings of MVP are usually less prominent. The increased intravascular volume of pregnancy and decreased systemic vascular resistance lead to an increase in the dimensions of the left

ventricle and mitral valve annulus with a reduction in prolapse.[1] Patients with MVP can be reassured that pregnancy will not increase the risk for antepartum or intrapartum complications. Establishing the diagnosis of MVP will again require a careful clinical examination and echocardiography. During labor, epidural anesthesia can be used safely. Antibiotic prophylaxis during labor remains controversial.[4] The American Heart Association does not recommend endocarditis prophylaxis for vaginal delivery or for cesarean section in patients with MVP, either with or without mitral regurgitation. On the other hand, some cardiologists and obstetricians believe the benefit of antibiotic prophylaxis outweighs the potential risks. I prefer to use antibiotics for patients with a diagnosis of MVP established by echocardiography, administering ampicillin (2 g IV or IM) and gentamicin (1.5 mg/kg IV or IM) in the active phase of labor followed by a second dose 8 hours after the initial dose. For those allergic to ampicillin, vancomycin is used (1 g IV over 1 hour with gentamicin, 1.5 mg/kg IV or IM) in the active phase of labor, with the second dose eight hours later.

In summary, MVP is a common valvular abnormality in women, although the prevalence is lower than originally thought. Most patients will have the functional form of MVP, which is not associated with serious complications and will improve with age. Pregnancy in the patient with MVP is not associated with an increase in antepartum or intrapartum complications. The use of antibiotic prophylaxis to prevent infective endocarditis in these patients remains controversial. ❖

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CME Questions

18. The following statements are true regarding postmenopausal hormone therapy and coronary artery disease *except*:

a. The only primary prevention randomized clinical trial data are thus far limited to two years of treatment.
b. Randomized clinical trial data indicate that short-term (< 3 years) hormone treatment had no beneficial effects on already present coronary artery disease.
c. Postmenopausal women who have had a heart attack should be offered hormone therapy as part of an effort to prevent a subsequent cardiac event.
d. Almost all of the biological studies examining the effects of estrogen on the cardiovascular system are consistent with responses that should protect against coronary artery disease.

19. Which of the following circumstances would be the *least* indicative for reoperation (repeat conization or hysterectomy) rather than follow-up after conization with positive margins?

a. Microinvasion at the margin.
b. Poor compliance with follow-up.
c. Adenocarcinoma in situ at the margin.
d. CIN 3 at the margin.
e. Completion of childbearing.

20. Which of the following statements regarding Alzheimer's dementia is true?

a. Disease severity of AD correlates with neurofibrillary tangles.
b. Postmenopausal estrogen therapy retards disease progression in women with moderate Alzheimer's disease.
c. In general, it is harder to reverse an established disease process than to prevent it.
d. Estrogen therapy will prevent AD only if started early and continued indefinitely.
e. Vitamin E therapy has been shown to be more efficacious than estrogen therapy for the prevention of AD in women.

21. The prevalence of mitral valve prolapse in women is:

a. 1%.
b. 3%.
c. 10%.
d. 15%.
e. 20%.

22. According to the study by Lovelady et al, which of the following is true concerning lactating women?

a. Weight loss of approximately 1 lb/wk is safe for mother and infant.
b. Weight loss of 1 lb/wk is safe for the mother but results in poor infant growth.
c. Postpartum weight loss is safe for women who have delivered vaginally but not for women who have undergone cesarean delivery.
d. Maternal weight loss of 1 lb/wk is safe only for infants weighing more than 2500 g at birth.

In Future Issues:

Colonization by *Candida* in Asymptomatic Women