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INSIDE

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OCs and Endometriosis

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *A low-dose oral contraceptive effectively treats dysmenorrhea associated with endometriosis.*

Source: Harada T, et al. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. *Fertil Steril.* December 26, 2007, ePub.

Harada and colleagues from Japan conducted a double-blind, placebo-controlled, randomized multicenter trial of a low-dose oral contraceptive for the treatment of dysmenorrhea associated with endometriosis.[1] The oral contraceptive, given for 3 out of 4 weeks for 4 cycles, consisted of 35 µg ethinyl estradiol and 1 mg norethindrone. One hundred patients were randomized to treatment, 3 were lost to follow-up, and 14 discontinued the study. Dysmenorrhea pain interestingly decreased in the placebo group, but the decrease in the OC group was about twice as great. The treatment group demonstrated a decrease in pelvic induration that did not achieve statistical significance. Only the OC group demonstrated a reduction in the size of ovarian endometriomas that were larger than 3 cm diameter at baseline.

COMMENTARY

Progestational drugs have been used to treat the pain of endometriosis for a long time. In fact, norethindrone and norethynodrel were approved by the FDA for this purpose in 1957, 3 years before approval of the first oral contraceptive. By 1960, 500,000 women were using these agents, although it is unlikely that all had endometriosis or even dysmenorrhea. Therefore there is an enormous clinical history supporting the use of oral contraceptives for the treatment of endometriosis. Randomized trial data, however, have been lacking.

The Cochrane Collaboration meta-analysis in 2002 (CD002120) supported the use of OCs for the treatment of dysmenorrhea but emphasized that the supporting data were derived from very old studies of high-dose products. The current Japanese study, therefore,

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is valuable in that it is a placebo-controlled trial of dysmenorrhea associated with endometriosis and it provides data for a low-dose OC, confirming years of experience. It is worth noting that a randomized, placebo-controlled trial using a 20 µg estrogen OC has documented effective treatment of primary dysmenorrhea in adolescents.[2]

For years, many clinicians have believed that the daily use of an OC without a break is more effective for the treatment of endometriosis. Clinicians have also believed that monophasic products are superior to multiphasic products. Unfortunately, these two beliefs are derived from historical experience and reported in the literature as uncontrolled studies. But it is unlikely that randomized trials will address these two points, and until such studies are available, there is no valid reason to discount many years of clinical experience. In an Italian prospective study (but not a randomized trial), women experiencing recurrent dysmenorrhea associated with endometriosis while being treated with a cyclic OC regimen improved when switched to daily, continuous treatment with a 20 µg OC.[3]

Low-dose estrogen-progestin contraception is a good choice to treat pain associated with endometriosis. It is a less expensive option than GnRH analogues, side effects are not a major problem, and treatment can be maintained for long durations. This is also a good option to maintain suppression of endometriosis after surgical or GnRH analogue treatment; remember that treatments only suppress and don't cure or eliminate endometriosis. Another advantage of OC treatment is that endometriosis may be associated with a slight increase in ovarian cancer (as well as adenocarcinoma in endometriosis tissue), and the profound reduction in the risks of ovarian and endometrial cancer well-demonstrated in women without endometriosis is observed equally in women with endometriosis.[4] ■

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Prevention of Preeclampsia through Administration of Antioxidants

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: *Use of calcium, vitamin E, and vitamin C show no significant reduction in the rate of preeclampsia.*

Source: Spinnato JA, et al. Antioxidant therapy to prevent preeclampsia. *Obstet Gynecol.* 2007;110:1311-1318.

Among various agents that have been used to prevent preeclampsia, the ones that have attracted the greatest attention have been low-dose aspirin, calcium, and vitamins C and E. In December, a study emerged in *Obstetrics and Gynecology* that tested the latter two antioxidants' abilities to decrease the incidence of preeclampsia in at-risk patients.

Spinnato et al initiated a randomized trial in 4 Brazilian centers in which patients who had preeclampsia in a previous pregnancy or who had the diagnosis of chronic hypertension were given either vitamin E and C (combined) in standard dosage or a placebo. Of the 753 fulfilling the admission criteria the authors had follow-up on 705 patients (355 in the treatment arm and 352 in the placebo arm). The average time of entry and initiation of treatment was 15 weeks.

The rate of preeclampsia in the treatment group was 13.8% vs 15.6% in the control group (OR=0.87; 95% CI 0.61-1.25). Interestingly, although the above figures showed no difference in preeclampsia in the vitamin group, there was a concerning, but statistically insignificant, trend towards a higher rate of severe preeclampsia in chronic hypertensives on the study medication (6.5% vs 2.8%). The authors concluded simply that antioxidants did not seem to work to prevent preeclampsia in those predisposed to this condition.

COMMENTARY

The authors indicated that they were stimulated by a paper by Chappell et al in 1999 that showed a decrease in preeclampsia by giving vitamin E and C to patients with abnormal uterine artery waveforms. However, more recent studies using criteria other than uterine artery findings have failed to show a difference in the incidence of preeclampsia when using these agents. It seems that the ideal study would be to combine a history of preeclampsia, chronic hypertension, and uterine artery waveform analysis in the same time type of randomized trial. Unfortunately, the latter test has not caught on in the United States, as it has in Europe. Although the numbers were insufficient in the chronic hypertensive group in the above study to tell a difference in outcome, the trend towards a higher rate of severe preeclampsia in the treated group should get our attention and needs to be further explored.

It is intriguing that the trials using uterine artery waveform to predict preeclampsia demonstrate that this method seems to work best in identifying those at greatest risk for severe preeclampsia. Also, as indicated in a meta-analysis by Coomarasamy assessing the prowess of low-dose aspirin in the prevention of preeclampsia, this agent seemed to perform quite well in those with abnormal uterine artery waveform, halving the rate of severe preeclampsia.

The point here is that, so far, calcium, vitamin E, and vitamin C do not seem to represent the great hope for prevention of preeclampsia, but low-dose aspirin may provide some benefit, especially in those at greatest risk.

Although this may seem an "apples and oranges" issue, our colleagues in other specialties may now be moving to a higher dose of aspirin to prevent strokes (168 mg vs the commonly used baby aspirin dose of 84 mg). Since the aim is the same—eg, to prevent micro clotting in the peripheral circulation (as well as macro clotting), this may represent a better approach to preeclampsia prevention with, expectedly, the same low risk to mother and fetus.

The old adage that prevention of stroke would require one simply to "lick an aspirin once a day" now needs to be amended. The same may be true for preeclampsia. ■

The Value of Expert Ultrasonography

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: *Gynecologic sonographic expertise, represented as Level III scans, led to fewer major staging procedures in this first randomized clinical study of ovarian masses referred for further investigation.*

Source: Yazbek J, et al. Effect of quality of gynaecological ultrasonography on management of patients with suspected ovarian cancer: a randomised controlled trial. *Lancet Oncol.* 2008;9:124-131.

Diagnostic ultrasonography is one of the most frequently utilized adjuvant tools clinicians rely upon to make treatment recommendations for suspect adnexal pathology. Intuitively and bolstered by some clinical information, studies conducted by experienced gynecological sonographers appear to provide better diagnostic accuracy in identifying significant pathology. However, proof of this observation has not been rigorously investigated. To address whether more sophisticated (Level III) ultrasonography could reduce the number of major surgical staging procedures over routine (Level II) ultrasonography, a randomized clinical trial of women referred with adnexal masses was conducted. One hundred fifty women were randomized on referral to either of the two procedures. A Level II sonogram is a routine morphological abdominal and transvaginal study per-

formed by a technician trained in gynecologic sonography; a Level III sonogram is a similar procedure performed by a gynecologist with more than 10 years experience in gynecologic sonography. These clinicians often served as trainee preceptors in tertiary referral centers. Addressing the primary endpoint, significantly fewer major surgical staging procedures were performed in women getting Level III scans (37% vs 22%, $p = 0.049$). The total number of surgical procedures was similar between the two groups; however, the median number of hospital days was shorter for those receiving Level III scans due in large part to the more frequent use of laparoscopy. Ovarian cancer was ultimately diagnosed in 18 (12%) women. A likely histological diagnosis was opined significantly more often following Level III scans (99% vs 52%, $P < 0.0001$). Both sensitivity and specificity was improved with Level III scans. The authors conclude that improved quality of ultrasonography has a measurable effect on the management of suspected ovarian cancer in tertiary referral gynecologic cancer centers.

Gynecologic sonographic expertise, represented as Level III scans, led to fewer major staging procedures in this first randomized clinical study of ovarian masses referred for further investigation.

COMMENTARY

The value of ultrasonography in gynecology is hard to overstate. It is used as a diagnostic tool, a surveillance tool, a therapeutic adjuvant for tissue acquisition and is the foundation in many treatment and screening algorithms. The popularity of the imaging tool is rooted in both its availability and its technological features providing ever more detail to the uterus and adnexa. An unprecedented level of improved imagery in this regard is an annual occurrence and improvement is the continual goal of investigators and device makers. Nevertheless, its utility is operator dependent. The level of skill clearly impacts the inference potential; however, the degree to which this occurs has, heretofore, not been formally evaluated. The study, in the context of the UK health system, demonstrates the utility of more expert sonographers in evaluating referrals for adnexal abnormalities. An important economical impact was not reported in this current study but is planned in a future report. Based on this Level I evidence data, a review of the programmatic referral system is underway—a remarkable feat. The impact on the US health system is harder to ascertain as physician sonographic experts are a mixture of gynecologists and radiologists with special expertise in gynecologic imaging, extending beyond sonography to other modalities such as CT, FDG-PET, and MR. Nevertheless, on an individual basis our trust is naturally linked to those in whom confirmation of pathological outcomes is made. This study provides real evidence to support that bias. ■

Additional reading:

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Therapeutic Vaccination for Dysplasia: Early Efficacy

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Source: Einstein MH, et al. *Gynecol Oncol.* 2007;106: 453-460.

Synopsis: *SGN-0010, a novel heat shock fusion protein-based immunotherapeutic, demonstrates clinical efficacy in regressing cervix dysplasia in women with biopsy-proven CIN III.*

HEAT SHOCK PROTEINS HAVE BEEN OF CLINICAL interest in therapeutic vaccination based on their ability to induce significant T- and B-cell responses against microbial pathogens and tumor antigens. SGN-0010 (HspE7) is a novel therapeutic vaccine consisting of a fusion protein containing *M. bovis* BCG heat shock protein (Hsp65) covalently linked to the entire sequence of HPV 16 E7. Given observations of response of HPV-induced lesions in other disease sites to HspE7, the authors of the current study set out to examine the efficacy and toxicity of SGN-0010 in women with CIN III. Two cohorts were accrued. The

first consisted of 31 patients with CIN III who were vaccinated (1 subcutaneous injection every month for 3 months) and observed for a total of 5 months upon which they underwent LEEP; cohort 2 were those with similar lesions (N=27) in whom following vaccination underwent LEEP at 7 months. Cervix lavage for HPV type (assessed by PCR) was done monthly until LEEP and at 12 months following vaccination. Overall, 13 (23%) of 58 evaluable patients achieved a complete resolution of their CIN III disease; an additional 55% had a partial resolution defined as a 50% or more reduction of the lesion size. Two patients were classified as having progression documented as microscopic invasive disease at LEEP. Patients in whom previous ablative or extirpative surgery was done for a history of dysplasia appeared more likely (not statistically significant) to have a complete response following vaccination. In addition, lower grade lesional inflammation was associated with response. Toxicity was minimal and limited to injection site reactions; the vast majority of which resolved at 7 days post injection. The authors report that the clinical activity of this novel fusion protein met predetermined efficacy benchmarks and suggest further randomized trials are warranted.

COMMENTARY

Vaccination success for the prevention of HPV infection has been documented and has led to the current availability of one, soon to be two, commercial products. The ultimate endpoint of these agents and their associated public health programs is prevention of cervix cancer development. Much about the long-term impact of these vaccines is currently unknown. However, it is clear that successful vaccination programs will depend upon population-wide vaccination and expansion of the current type-specific focus of the available agents. In addition, vaccination of infected individuals is less efficacious than HPV-naïve, and it is likely that any real benefit from these programs are decades off to fruition. Herein lies the clinical need for therapeutic vaccination of those with established infection manifested by high-grade dysplasia. Fortunately, a number of new vaccines and vaccine strategies are under development to address this cohort of women. The need is particularly evident given the association of pregnancy complications associated with repeated extirpative procedures on the cervix, the limited scope of HPV prevention vaccination and the difficulties effecting public health care policy mandating vaccination. The current trial is of interest because of its efficacy but highlights the difficulty in doing intervention/observation trials. Remarkably, nearly 1 in 4 patients with high grade biopsy-proven CIN III achieved pathologic complete response; over half had decrease in the size of their documented lesion. However, complete remission in this study was defined as resolution of the lesion or regression to CIN I/HPV and partial regression is denoted as 50% reduction in lesion size, but it is not clear what this means (area, largest dimension, quadrants involved, etc.). Additionally, while 2 of the pCR's had resolution of HPV infection following vaccination, very little other information is presented on the viral status of the other patients or the serial observations of HPV status over the treatment interval. Finally, the lack of a control group and the non-blinded nature of the design makes it difficult to interpret whether these results, while better than historical data, represent true measures of efficacy. Nevertheless, the potential benefit, particularly to young women with high-grade cervix dysplasia, is vast and does warrant further controlled clinical investigation. ■

Special Feature

Opposition to the Timing Hypothesis

By Leon Speroff, MD, Editor

The Timing Hypothesis argues that estrogen can reduce the risk of coronary heart disease when administered to relatively young postmenopausal women before atherosclerosis has developed to the stage of unstable plaques (plaques with necrosis and inflammation). Elizabeth Barrett-Connor from the Division of Epidemiology at the University of California School of Medicine in San Diego concludes that the hypothesis is stronger than the evidence.[1]

Barrett-Connor first reviews 3 clinical trials—the HERS trial and the two canceled arms of the WHI—that failed to find an overall beneficial impact of hormone therapy on cardiac events. She further points out that subgroup analyses of HERS and WHI were problematic. In the HERS secondary prevention trial, multiple tests for interactions failed to definitely explain the results. Barrett-Connor argues that the power of the WHI to examine the timing hypothesis was limited by a relatively small number of women under age 60 and rare cardiac events in the young age group. She emphasizes that the tests for interaction with age or years since menopause

in the initial publications failed to find any significant relationships. The basic problem was that clinical trials are powered to test primary outcomes, not secondary results in subgroups.

Barrett-Connor dismisses the WHI coronary-artery calcium study[2] because coronary artery calcium was measured only in women under age 60 and not measured in older women for comparison. You will recall that the calcification in the coronary arteries is located in atheromas and is correlated with the degree of atherosclerosis. The average calcium score in the women treated with estrogen in the WHI estrogen-only arm was lower than that in the placebo arm, consistent with a lower prevalence of coronary artery disease. Barrett-Connor argues that this result does not test the timing hypothesis because it could not be compared to calcium scores in women over age 60.

Barrett-Connor claims that the timing hypothesis is being marketed, and that the hypothesis remains unproven until evidence becomes available from randomized, controlled clinical trials. She concludes that those who have been seeking "flaws" in the WHI are motivated by a reluctance to give up old ideas about the long-term benefits of hormone therapy.

One might turn Barrett-Connor's conclusion around and argue that her rebuttal represents a reluctance to accept a new idea that explains the limitations of the HERS and WHI trials. Her commentary was accepted for publication on December 21, 2006. Thus she did not have available the WHI analysis of cardiovascular risk by age and years since menopause which was published in April 2007.[3] The WHI conducted a secondary analysis combining the two canceled arms that revealed an increased risk for coronary heart disease only in the oldest women in the trials. Furthermore, when women with prior cardiovascular disease or those older than 60 years were excluded, there was no increase in the risk of stroke. But Barrett-Connor is correct in saying that the number of women and the number of cardiac events under age 60 were too small to help us answer the question: can hormone therapy given to young postmenopausal women prevent coronary heart disease?

A meta-analysis of 23 randomized hormone therapy trials concluded that hormone treatment reduced the risk of coronary heart disease in younger postmenopausal women compared to older women (OD-0.68; CI=0.48-0.96).[4] Another meta-analysis by the same authors concluded that hormone therapy reduced overall mortality in women under the age of 60.[5] But I hasten to add, most of these trials were not designed to measure a cardiovascular endpoint. The meta-analyses are reassuring but they surely do not meet Barrett-Connor's plea for evidence.

The timing hypothesis originated in the hormone trials conducted in monkeys by the Wake-Forest group headed by Tom Clarkson. This is randomized trial evidence, albeit in monkeys, and we should place the results at the head of the list of observations that support the timing hypothesis:

1. Estrogen treatment initiated immediately after menopause in monkeys inhibits progression of coronary artery atherosclerosis by about 70%. When treatment is delayed by 2 years (equivalent to about 6 years in women), there is no effect.[6]

2. Next in line, according to strength of evidence in my view, would be the recent WHI reports of reduced coronary artery calcium in estrogen-treated women and an increase in cardiac events only in the oldest women in the trials.[2,3] In the last report from the WHI estrogen-only arm, the problem of low event rates in younger women was addressed by lumping together, in one hazard ratio, myocardial infarction, coronary death, coronary revascularization, and confirmed angina—the risk in women aged 50 to 59 years for all of these events was significantly reduced (HR-0.66; CI=0.45-0.96).[7]

3. Every woman has a trajectory of atherosclerosis development, the slope of which determines the age of onset for clinical events. Premenopausal women with lower estrogen levels have higher cardiovascular risk factors and develop more coronary heart disease.[8] This includes suppressed ovarian function associated with stress, depression, or athletic activity. The importance of premenopausal estrogen is also supported by Clarkson's monkey studies. Premenopausal monkeys with normal ovarian function have less progression of coronary artery atherosclerosis as compared with monkeys with impaired ovarian function.[8]

4. The results in observational studies strongly indicate that hormone treatment of young postmenopausal women reduces the risk of coronary heart disease. In the Nurses' Health Study, the reduction was approximately 50%.[9] The women in the Nurses' Health Study who were under age 60 when hormone treatment was initiated had a significant reduction in coronary heart disease risk compared with no effect in women over age 60.[10] A similar reduction was present in the observational arm of the WHI.[11] In fact, after adjustment for confounding influences such as behavioral, dietary, physical activity, and cardiovascular risk factors, the relative risks for cardiovascular events were 30% to 38% lower than in the clinical trials. These data were derived

from populations of women usually treated with postmenopausal hormone therapy, women close to their age of menopause.

5. In a primary prevention trial using ultrasound measurement of carotid artery intima-media thickness, estradiol-treated women had slower progression of atherosclerosis.[12] These same investigators demonstrated no effect of estrogen treatment in older women who had angiographic evidence of coronary atherosclerosis.[13]

The message from multiple secondary prevention trials is clear: we should not prescribe estrogen to women with coronary heart disease in the expectation that treatment will reduce subsequent cardiac events. The evidence is also convincing that progestational agents do not produce adverse cardiovascular effects. It remains very possible, indeed likely, that primary prevention of coronary heart disease can be achieved with estrogen administered at the right time of life. We await the results of two ongoing primary prevention trials, measuring carotid intima-media thickness with ultrasound, the KEEPS trial (www.kronosinstitute.org/keeps.html) and the ELITE trial (http://clinicaltrials.gov/show/NCT00114517).

A reasonable goal is to maintain a healthy level of estrogen during the premenopausal years and in the early postmenopausal period. Although as Barrett-Connor points out, the timing hypothesis has not been proven by randomized, clinical trials, the overall evidence is impressive, and in my view, sufficient to conclude that hormone therapy in the early postmenopausal years can provide primary prevention of clinical coronary disease. Clinical decisions reflect all of our knowledge (our education, the medical literature, and our experience), not just the data from randomized, clinical trials.

The most important message is that 6 years after the initial WHI publications, it is increasingly apparent that the WHI results agree with over 20 years of research, contrary to the WHI communications first presented to the public. It is time to convince our colleagues of this conclusion and present this story to our patients. ■

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CME Questions

43. The following statements are true regarding dysmenorrhea, endometriosis, and OCs except:

a. Low-dose OCs are not less effective in treating dysmenorrhea.
b. Many women with endometriosis require long-term treatment to avoid recurrent problems.
c. Cyclic OCs are not effective for the treatment of dysmenorrhea.
d. There is no need to use higher estrogen dose OCs to treat dysmenorrhea.

44. Which of the following is correct?

a. Calcium is a deterrent to the development of preeclampsia.
b. Vitamin E can prevent preeclampsia.
c. Vitamin C can prevent preeclampsia.
d. Low-dose aspirin has been shown in some studies to decrease the incidence of preeclampsia.

45. Which answer does not fit regarding the studies currently in the literature?

a. The above index study was carried out in the United States.
b. In the above study there was a higher rate of preeclampsia in the chronic hypertensives who were taking vitamins C and E.
c. In general, vitamins C and E did not decrease the rate of preeclampsia.
d. The most common dosage of prevention of preeclampsia has been one tablet of baby aspirin per day (84mg).

46. Which of the following differences between Level II and Level III scans was reported by the authors?

a. The total number of surgical procedures was higher in Level II scans.
b. The number of invasive malignancies was higher in Level III scans.
c. The number of follow-up scans was higher in Level II scans.
d. The stage distribution for cancer identified with Level III scans was earlier.

47. What percent of the treatment population who underwent colposcopic evaluation and biopsy at 12 months following vaccination suffered recurrence of dysplasia?

a. none
b. 4%
c. 12%
d, 16%

Answers: 43 (c); 44 (d); 45 (a); 46 (c); 47 (b)

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
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FDA Heightens Warnings on Chantix

In this issue: *Stop smoking drug Chantix rates stronger warning from FDA; Type 2 diabetes surgery on the way?; Vytorin study inconclusive; Influenza A virus found resistant to Tamiflu; FDA actions.*

The FDA has strengthened its warning on the stop smoking drug varenicline (Chantix). Last November the agency issued an Early Communication regarding reports of changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior in patients taking the drug. After review of recent reports, the agency now says that it appears increasingly likely that there may be an association between varenicline and neuropsychiatric symptoms. The FDA has asked Pfizer, the manufacturer of the drug, to elevate the prominence of these warnings on the package label, and the company along with the FDA is working on a Medication Guide for patients. The FDA is recommending that patients should tell their health-care providers about any history of psychiatric illness prior to starting varenicline. There is evidence that the drug may cause worsening of current psychiatric illness, and cause old psychiatric illness to reoccur. Moreover health-care professionals, patients, patients' families, and caregivers should be alert to monitor for changes in mood and behavior in patients treated with varenicline. The FDA warning also states that vivid, unusual, or strange dreams may occur while taking the drug and that patients may experience impairment of the ability to drive or operate heavy machinery. Varenicline was approved in May 2006 under the trade name Chantix by Pfizer Pharmaceuticals to ease withdrawal symptoms associated with smoking cessation.

Weight-loss Surgery Answer for Type 2 Diabetics?

Could surgery be the answer for type 2 diabetes? In a new study from Australia, 60 patients with type 2 diabetes and a BMI of 30-40 were randomized to adjustable gastric banding surgery or conventional therapy. Conventional therapy focused on weight loss by lifestyle changes. The main outcome measure was remission of type 2 diabetes and secondary measures included weight and components of the metabolic syndrome. Remission of type 2 diabetes was achieved by 22 patients in the surgical group (73%) vs 4 patients in the conventional therapy group (13%). Relative risk for remission in the surgical group was 5.5 (95% CI, 2.2-14.0). Surgical patients lost more weight, mean (SD) 20.7% (8.6%) vs 1.7% (5.2%) for the nonsurgical group at two years (P <.001). There were no serious complications in either group. The average weight loss to achieve remission of type 2 diabetes was 10%, which was achieved in 86% of the surgical patients and only 1% of the medical therapy patients. The authors conclude that for patients with type 2 diabetes, surgical therapy was more likely to achieve remission through greater weight loss. These results should be confirmed through larger, more diverse population and have long-term efficacy assessed (*JAMA* 2008;299:316-323). An accompanying editorial suggests that gastrointestinal tract surgery may offer a new goal in diabetes management—remission rather than just treatment. The editorialists also suggest that the cost and risks of such surgery must be balanced

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with the costs and risks of long-term diabetes management (*JAMA* 2008; 299:341-343).

Vytorin Needs More Study

Vytorin has been in the news recently after Merck/Schering-Plough released the preliminary results of the Effect of Combined Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) study. Vytorin is a combination of the statin simvastatin (Zocor) and ezetimibe (Zetia), a medication that blocks cholesterol absorption through the gut. The combination drug is better at lowering LDL than either drug alone, and it was hoped that this would translate to improved cardiovascular outcomes. ENHANCE randomized 720 patients with heterozygous familial hypercholesterolemia to treatment with either simvastatin 80 mg daily or Vytorin (simvastatin 80 mg plus ezetimibe 10 mg). Mean LDL cholesterol levels at baseline were 320 mg/dl. Simvastatin alone lowered LDL by 41% while Vytorin lowered LDL by 58%. The primary endpoint was change in mean carotid intima media thickness after two years of treatment. There was no difference in this primary endpoint or in the incidence of any adverse effects between the two treatment arms. ENHANCE was widely reported as a failure for Vytorin, and there were even reports that Vytorin increased the rate of plaque production, which was not the case. The study has been criticized because of its small size, atypical patient population, and primary outcome (carotid intimal media thickness) which is not a clinical outcome. The American College of Cardiology issued a statement on January 15 suggesting that "major clinical decisions not be made on the basis of the ENHANCE study alone." The FDA issued a statement on January 25 stating that it will conduct a review of Merck and Schering-Plough's trial once the final results of the study are available. Data from the ENHANCE study is due to be presented at the American College of Cardiology meeting in March.

Virus Resistant to Tamiflu Causing Concern

A small percentage of the influenza A virus causing illness worldwide this winter is resistant to oseltamivir (Tamiflu), according to the World Health Organization. Tamiflu-resistant forms have been found in European countries, Canada, and the US. Generally mutations of this sort attenuate the virus, making it less infectious; however this is not found be the case with the resistant strain of A/N1H1 known as A(H1N1 H274Y). The highest rate of resistance was found in Norway with 75% of isolated viruses showing resistance. The rate of resistance in the US was 3.8%. There are currently no plans to change recommendations for use of Tamiflu; however, WHO officials are "troubled by the discovery" according to the *New York Times*.

Choice of Antivirals for Flu

In other flu-related news, the CDC reports that primary care physicians frequently used inappropriate flu drugs during last year's flu season. A survey published in *MMWR* found that of 730 respondents, 54% prescribed anti-viral agents and of those, one quarter prescribed amantadine or rimantadine. These drugs are no longer recommended because of a high rate of viral resistance (MMWR 1/25/08:57(03); 61-65). Finally, the FDA has approved a real-time test for influenza A and B and RSV. The test, called ProFlu+ Assay produces results within about three hours, and has a 98% sensitivity, and 83% specificity. The assay is marketed by Prodesse Inc.

FDA Actions:

The FDA has strengthened its warning on the contraceptive patch Ortho Evra regarding the risk of venous thromboembolism. The warning is based on a study conducted by the Boston Collaborative Drug Surveillance Program that showed that the patch was associated with a higher risk of venous thromboembolism than oral contraceptive pills.

The FDA has taken the strongest stance yet against the use of over-the-counter cough and cold products for children younger than two years of age. On January 17 the agency issued a Public Health Advisory for parents and caregivers recommending that the products should not be used to treat infants and children because of reports of serious adverse events including death, convulsions, rapid heart rates, and decreased levels of consciousness. The agency continues to review use of these medications on children aged two to 11.

The FDA has warned seven pharmacy operations that produce "bio-identical hormone replacement therapy" that claims of their products' effectiveness may be false and misleading because they are not supported by medical evidence. These products are frequently compounded by large pharmacy operations and contain estrogen, progesterone, and estriol. Claims range from reduced risk of stroke, cancer, and lower rates of Alzheimer's disease associated with products. Compounded drugs are not reviewed by the FDA for safety and effectiveness however misleading claims violate federal laws. The FDA considers the term "bio-identical" a marketing term which implies benefit for which there's no medical or scientific basis. Compounding pharmacy that do not address these violations are subject to further enforcement according to the FDA press release. ■