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INSIDE

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Postmenopausal Hormone Therapy and Ovarian Cancer

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *The Million Women Study reported a small increase in the risk of ovarian cancer in current users of postmenopausal hormone therapy.*

Source: Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet.* (Online). April 19, 2007.

THE MILLION WOMEN STUDY REPORTED A SMALL INCREASE IN the incidence of ovarian cancer and ovarian cancer mortality in current users of postmenopausal hormone therapy.[1] Overall the relative risk of ovarian cancer in current users was 1.20 (CI = 1.09-1.32) and in past users 0.98 (CI = 0.88-1.11). There was a trend for increasing risk with increasing duration of use. The increase was observed only with epithelial tumors, and only serous cancers had a significant increase. There were no significant differences with different estrogens or different progestins, or between oral and transdermal administration. Adjustment for various confounding factors detected no influences.

If the results of the Million Women Study are accurate, the relative risks translate into the following absolute risks:

	Incidence	Fatal Ovarian Cancer
U.K. population	2.2/1000 women /5 years	1.3/1000 women/ 5 years
Never users	2.2	1.3
Current users	2.6	1.6

All tables adapted by L. Speroff

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COMMENTARY

There have been over 20 case-control and cohort studies assessing the relationship between postmenopausal hormone therapy and the risk of ovarian cancer. The relative risks have encompassed a wide range from below 1.0 to greater than 1.0. Because this is a relatively infrequent cancer, all studies have been hampered by relatively small numbers.

The canceled estrogen-progestin arm of the Women's Health Initiative reported an increase in ovarian cancer that was not statistically significant (Hazard ratio = 1.58, CI = 0.77-3.24), prompting the authors to say: "The possibility of an increased risk of ovarian cancer incidence and mortality remains worrisome and needs confirmation."[2] The Kaplan-Meier curves suggested an increasing effect over time, but this, too, was not statistically significant. There were no differences reported in histologic type, stage, or grade (but the small numbers made it essentially impossible to assess subcategories).

The studies have found it difficult to control for all of the factors that influence the risk of ovarian cancer. This is because there are multiple factors and information regarding each factor is not readily available.

Factors That Decrease the Risk of Ovarian Cancer

- Use of steroid hormone contraceptives.
- Pregnancy and parity; a greater effect with a recent pregnancy and pregnancy at older age.[3,4]
- Breastfeeding.[5]
- Hysterectomy and tubal ligation.[6]
- NSAIDs.[7]

Factors That Increase the Risk of Ovarian Cancer

- Increasing BMI[8,9]
- Infertility[10]
- Caffeine intake[11]
- Two or more eggs per week[12]
- Family history of ovarian and breast cancer.
- Sedentary lifestyle.[13]
- Cigarette smoking[14, 15]

Mixed Reports on Decreased Risk

- Alcohol intake[16]

Because of the many factors that influence the risk of ovarian cancer, it has been essentially impossible in case-control and cohort studies to match cases and controls. Hormone users typically have used more oral contraceptives, have had fewer children, and are more educated and thinner. Adjustments have been made only for major factors, such as oral contraceptive use. The technique of meta-analysis is especially hampered by these confounding issues. The authors of the published meta-analyses[17-19] have inappropriately assumed that controlling for risk factors was uniformly accomplished in all studies.

The Million Women Study is a cohort of 948,576 women who have provided information through a baseline questionnaire and a follow-up questionnaire about 3 years later (64% responded to the request for follow-up information; thus, the accuracy of the data can legitimately be questioned). The current report, however, is impressive in the relatively large number of cases (obtained by assessing the National Health Service Central Registers in the U.K.) and the multiple adjustments for confounding factors. The investigators adjusted their analyses for the following:

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Questions & Comments

Please call **Iris Young**, Managing Editor at (404) 262-5413 between 8:00 a.m. and 4:30 p.m. ET, Monday-Friday.

- Age
- Hysterectomy status
- Region of residence (the 20 areas covered by cancer registries)
- Socioeconomic status
- Time since menopause
- Parity
- Body-mass index
- Alcohol consumption
- Physical activity
- Smoking
- Age at first birth
- Oral contraceptive use

But remember this information was derived from 2 questionnaires, and 36% of the women did not return the follow-up questionnaire. When relative risks are in the range as reported from this Million Women Study, a shift of a small number of cases can change the statistical conclusions. And although this report covers more confounding factors than any other previous study, nevertheless, some influencing factors remained unadjusted.

A major problem in previous studies has been the impact of endometrioid cancers, an ovarian cancer that logically can be expected to be influenced by estrogen therapy. In many of the studies, the overall results are swayed by the increase in endometrioid cancers, a cancer that could originate in hormonally-stimulated endometriosis. An accurate analysis requires a separate consideration of endometrioid cancers, but this is difficult because the small numbers do not allow effective sub-categorization. The number of endometrioid cancers in the Million Women Study totaled 72 cases in current users and 114 in never users for a relative risk of 1.05 (CI = 0.77-1.43). An important finding in the Million Women Study, if it is accurate, is that the increase was in serous cancers, not endometrioid cancers.

Why might postmenopausal hormone therapy increase the risk of ovarian cancer whereas steroid contraception reduces the risk? One can only speculate, but the most obvious explanation is inhibition of multiple ovulations (which increase the possibility of harmful mutations), an effect only present in premenopausal ovaries.

The authors present in their discussion an appropriate warning that comparing various reports on this subject is difficult because of differing populations, small numbers, and variances in classifications and adjustments. This doesn't stop them, however, from adding a meta-analysis of 9 studies (theirs included) with an overall increased relative risk. They further dramatize their report by producing a figure that combines ovarian, endometrial, and breast cancer. Of course the impact of hormone therapy is impressive because of the much greater prevalence of breast cancer. But a similarity between ovarian cancer and breast cancer is apparent in the data from the Million Women Study. The risk of the two cancers is reported to be increased only in current users. The risk returns to that of never users rapidly after discontinuation. Women in the Million Women Study who developed ovarian cancer were diagnosed from 0.8 to 4 years after an average use of hormone therapy for 7.7 years was last reported. As with breast cancer, the data suggest that hormone therapy is influencing pre-existing tumors. In other words, it is not certain these are new cancers. Cancers originate in mutations, a point of origin not known to be influenced by hormones. ■

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Special Feature

Understanding Hormone Action: Does Route of Administration Matter?

By Sarah L. Berga, MD

James Robert McCord Professor and Chairman, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta

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

UNTIL RECENTLY, AVAILABLE INFORMATION SUPported the notion that the transdermal route of administration of estradiol has less hepatic impact than the oral route. The basis of this contention was that the oral route of estradiol administration gave levels in the liver sinusoids that are 4-5 times higher than those found in the systemic circulation. Because the liver makes coagulation factors, an oral route of administration would elevate the risk of venous thromboembolism more than a transdermal route of administration. Indeed, the ESTHER (Estrogen and Thromboembolism Risk) Study Group found that the odds ratio (OR) for oral vs transdermal estrogen was 4.2 (confidence interval 1.5-11.6). Because the ESTHER Study was conducted in France, of 271 cases and 610 controls, only 2 cases and no controls took conjugated equine estrogen (Scarabin 2003, Canonico 2007). Most of the oral estrogen users took estradiol in doses ranging from 0.5 to 2.0 mg daily. Further, the mechanistic data on the impact of transdermal vs oral estradiol on hemostatic variables associated with venous thrombosis (Post 2003) support the observational epidemiological data. Women with prothrombotic mutations also display fewer thrombotic events when given transdermal vs oral estradiol (Straczek 2005). In aggregate, the data are consistent and supported the conclusion that the transdermal route of administration of estradiol minimizes the risk of venous thromboembolism when compared to the oral route.

Given the above considerations, the recent data showing that there was a more than two-fold increase in the venous thromboembolism rate (incidence rate ratio 2.2, CI 1.3-3.8) among women using transdermal ethinyl estradiol in a contraceptive patch as compared to women using an oral contraceptive containing 35 mcg of ethinyl estradiol are surprising (Cole 2007). Suffice it to say that this study has generated a lot of confusion over principles, particularly the understanding that route of administration of estrogen matters. However, the authors did not discuss the mechanisms that might explain this finding in the discussion. Should we abandon the notion that transdermal estrogen reduces the risk of venous thromboembolism when compared to the oral route of administration? How do we reconcile the observations in menopausal women with those obtained in younger women using contraceptives? Some have suggested that the contraceptive patch delivers a higher dose of ethinyl estradiol. But this explanation would only explain the higher risk of VTE in contraceptive patch users if route of administration did not matter for ethinyl estradiol. For the moment, the provisional conclusion has to be, then, that route of administration does not minimize the risk of VTE when the estrogen is ethinyl estradiol. This conclusion however only begs the next question.

Why would route of administration matter for estradiol and not ethinyl estradiol? Since ethinyl estradiol (EE) differs from estradiol only in the placement of an ethinyl group at carbon position 16, it is not immediately obvious that the route of administration should matter for estradiol and not for EE. However, one of the attributes that the addition of the ethinyl group confers is stability to degradation. This stability is partly conferred by the triple bond in the ethinyl group. Since the main site of degradation and metabolism is the liver, it stands to reason that both routes of administration maximally challenge the liver when the compound is EE. On a molar basis, EE has been estimated to be 400 fold more potent at the level of liver and only 100 fold more potent at the pituitary. There may be more to it than these considerations, but long story short, route of administration does appear to matter when the estrogen is the cognate ligand estradiol but not when the estrogen is ethinyl estradiol. ■

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The FUTURE of Cervix Cancer Prevention?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *A phase 3 trial was conducted to evaluate the efficacy of a prophylactic quadrivalent vaccine in preventing anogenital diseases associated with human papillomavirus (HPV) types 6, 11, 16, and 18.*

Source: Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases. Garland S, on Behalf of the FUTURE I investigators. *New Engl J Med.* 2007;356:1928-1943.

Human papilloma virus (HPV) is recognized worldwide as the principal culprit in the development of cervix cancer and its precursor dysplastic lesions. Also increasingly recognized is its role in other anogenital disease such as vulvar, vaginal and perianal warts, dysplasia and cancer. The purpose of the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I study was to assess the efficacy of the quadrivalent HPV vaccine (Gardasil, Merck) against the development of anogenital disease. Two primary hypotheses were considered: first, that HPV vaccination will reduce the incidence of a composite endpoint of anogenital warts, vulvar (VIN) or vaginal (VAIN) intraepithelial neoplasia grades 1 to 3 or cancer associated with vaccine-type HPV (types 6, 11, 16, 18) and second, that HPV vaccination will reduce the incidence of cervical (CIN) intraepithelial neoplasia, grades 1 to 3, adenocarcinoma in-situ (AIS) or cancer associated with vaccine-type HPV. To evaluate these endpoints, 5455 women aged 16 to 24, without a prior history of HPV infection or associated pathology and no more than 4 lifetime sexual partners were randomized to the 3 planned injections of the quadrivalent vaccine or an aluminum-based placebo. Three analysis populations were considered: those that followed the protocol strictly and were sero-negative on day 1 for vaccine-specific HPV (per protocol population), those that had protocol violations but were sero-negative on day 1 for vaccine specific HPV (unrestricted population) and those who were not sero-negative at baseline or had prevalent disease (intent-to-treat [ITT] population). The table summarizes the study's findings against the 2 primary endpoints and the populations considered:

	Composite Endpoint	
Population	1 (anogenital)	2 (cervical)
Per Protocol	100%	100%
Unrestricted	95%	98%
ITT	73%	55%
ITT + prevalent disease (not type specific)	34%	20%

Table provided by R. Coleman

Adverse affects were more common in the vaccine cohort with injection site pain, erythema, pruritus and swelling being reported most commonly (~87%). Systemic effects were less frequent (~13%) but were also more common in the vaccine cohort. The authors conclude the vaccine is extremely effective in preventing type-specific HPV disease in this cohort of women.

COMMENTARY

On June 8, 2006, these and data from the FUTURE II trial (also published with the current trial in the same issue of the New England Journal of Medicine) were presented as part of the FDA submission leading to regulatory approval of this vaccine. The current reports add another year of follow-up (now an average 3 years from the injection #1 time point) and continues to demonstrate the favorable findings presented at that pivotal registration meeting. Since that time, significant dialogue, largely spurred by political mandates and advocacy groups, have raised the topic of HPV vaccination to the level of "water-cooler" or dinner conversation. While this development, for the most part, is good, there are many challenges that await what few would argue is the ultimate endpoint of this intervention—the elimination of anogenital cancer due to HPV infection.

The current report and availability of vaccination should serve not necessarily as the means to an end but a demonstration of what may be an effective strategy to define the ends and to establish a road map to get there. Clearly, there is suboptimal protection against incident disease not specifically vaccinated against highlighting the importance of continued vaccine research. Indeed, a bivalent HPV-16/18 vaccine with a different adjuvant is near FDA-filing and multivalent and non-virus like particle (VLP) vaccines are under investigation. In addition, these observations highlight the danger in complacency of gynecologic screening, which is recommended even in vaccinated subjects. There are also continued concerns as to the duration of protection in type-specific HPV disease even though re-challenge with antigen at 5 years evokes a type-spe-

cific immune response similar to acute infection. Add to this concerns of cost, uni-gender vaccination practice, reduced utility in HPV-positive (prevalent) subjects, limited experience in pre-teens and older women, potential underestimation of side-effects (control group received aluminum-adjuvant placebo instead of saline), absence of long-term follow-up to evaluate late-effects, strategies for vaccine implementation in the US (as well as worldwide) and time to see an impact (likely 30 to 50 years) and one can appreciate we are at the start of this race. However, we are moving and there is hope we can overcome these challenges with continued research. ■

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Cervical Length Changes During Preterm Cervical Ripening: Effect of 17-a-Hydroxyprogesterone Caproate

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

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

Synopsis: *The purpose of this study was to evaluate whether 17-alpha-hydroxyprogesterone caproate (17P) treatment affect changes in cervical length.*

Source: Facchinetti F, et al. *Am J Obstet Gynecol.* 2007 May;196(5):453.e1-4; discussion 421.

In previous Clinical Alerts, much attention has been given to preterm labor (PTL), perhaps to a point where the readers might prefer that another subject be covered this month. For those, I have an addendum to follow.

In the May issue of the *American Journal of Obstetrics and Gynecology*, there was a report of a small randomized trial that might generate some cautious optimism regarding the treatment of PTL. The Italian authors studied 60 patients who were admitted in PTL, defined as having contractions 6 or more times in 30 minutes, and demonstrating cervical change by digital examination. Thirty patients were randomized to treatment with 17-a-hydroxyprogesterone caproate (17P) and the remaining 30 controls were not given the medication. All 60 patients received "standard tocolysis." Two of the authors, blinded to which group the patients were in, performed cervical length (CL) examinations by transvaginal ultrasound on admission, and then at 1 and 3 weeks later.

Frankly, the results were surprising. Fifty-seven percent (57%) of controls delivered prior to the 37 weeks vs 16% treated with 17P. The average birth weight in the control group was 2809 gm vs 3193 gm in the 17P patients. There was a statistically insignificant difference between groups with regard to delivery prior to 35 weeks, but the same trend persisted (23% in the placebo group vs 10% in the 17P group). What was intriguing were the changes in the CL over time between groups. At 7 days, the average decrease in CL between controls and treated patients, respectively, was 2.37 mm vs 0.83 mm; and at 21 days was 4.60 mm vs 2.40 mm.

COMMENTARY

After years of evidence that tocolytics do not seem to work in preventing preterm birth, along came two studies to show that we should not give up in patients who are truly in PTL. These authors used progesterone as a last ditch effort in those patients already demonstrating strong evidence of labor, rather than as a prophylactic tactic, as first published by Meis et al (using IM 17P) or da Fronseca et al, using daily progesterone suppositories. Also, in the January issue of the same journal an article appeared suggesting that transdermal nitroglycerine patches prolong pregnancy by 10 days, on average, and can decrease neonatal morbidity significantly. They were particularly effective in those pregnancies below 28 weeks.

For a variety of reasons, I have been very skeptical about the efficacy of weekly IM progesterone in the prevention of PTL. However, it is clear from in vitro animal and human investigation, the role that progesterone plays to quiet smooth muscle, and here now is evidence to suggest that, even once the hormonal cas-

cade of labor has been triggered, progesterone may work when given every 4 hours in patients presumably in preterm labor by the most stringent criteria.

Maybe there is light at the end of the tunnel?

On another note, the very next study in the above issue of the *American Journal* caught my eye. For years it has been common practice to administer antibiotics during cesarean sections after the cord has been clamped. The idea is that one would circumvent the fetus/infant from getting an unneeded, and potentially problematic, dose of antibiotics. Sullivan et al randomized 357 patients to be given one dose of cefazolin 15 to 60 minutes before skin incision or, alternatively, to have this given at the time of cord clamping (controls). The "early" group had less endometritis (1% vs 5%), fewer wound infections (2% vs 5%), and less "total infectious morbidity" (4.5% vs 11.5%). Yet, there were no differences in any types of neonatal morbidity between groups. Interestingly, there were fewer days in the nursery for infants born to the "early" mothers.

Like voting in Chicago, "early" may make sense, but not "often"—only once is recommended. ■

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Hepatitis C and Menopause

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Liver fibrosis from chronic hepatitis C is worse after menopause and less severe in women receiving hormone therapy.*

Source: Codes L, et al. Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormone replacement therapy. *Gut.* 2007;56:390-395.

Codes and colleagues from France followed a cohort of 251 women with chronic hepatitis C, and report data associating the severity of fibrosis established by liver biopsies with menopause and hormone therapy. There were 4 principal factors influencing the severity of fibrosis: duration of infection (> 15 years), excess body weight, presence of steatosis (fatty degeneration of the liver), and menopause. In those women receiving hormone therapy, fibrosis was predominantly mild. Fatty degeneration of the liver was seldom present in women younger than age 55. The authors concluded that estrogen protects against progression of fibrosis.

■ COMMENTARY

Most individuals with hepatitis C virus infection develop chronic disease, a major cause of worldwide morbidity and mortality from liver fibrosis. The time course is relatively slow, taking years to progress from infection to cirrhosis. Progression is increased by consumption of alcohol, excess body weight, diabetes, and degree of fatty degeneration in the liver. The severity of liver fibrosis is greater in men, and progression in women accelerates at around age 60. In vitro and animal experiments have documented a beneficial effect of estrogen on the development of fibrosis, an effect that is consistent with the data in this study finding greater progression of fibrosis after menopause and amelioration with hormone therapy. Another French study, a retrospective survey, reported a greater rate of fibrosis progression with hepatitis C in postmenopausal and nulliparous women, and a lower rate in postmenopausal women treated with hormone therapy compared with nontreated women. (*Hepatology.* 2004;40:1426-1433).

Liver fibrosis from hepatitis C infection is not the result of viral destruction of hepatic cells. Fibrosis is a response to the inflammatory activity incited by the virus. By now it is well known that estrogen can suppress the secretion of proinflammatory cytokines. Because of the prevalence of hepatitis C infection, these French reports are very important. Many clinicians are reluctant to prescribe hormone therapy to women with a history of liver disease. However, as long as liver enzymes are normal, there is no reason to withhold treatment, and these French studies indicate that estrogen therapy is beneficial. Postmenopausal hormone therapy should be discussed when women present with a history of hepatitis C infection. ■

CME Questions

11. The following statements regarding hormone therapy and ovarian cancer are true except:

a. Actions that reduce the number of premenopausal ovulations reduce the risk of ovarian cancer.
b. Epidemiologic studies of ovarian cancer are hampered by the infrequency of the disease and the large number of factors that influence risk.
c. Oral hormone therapy has a greater risk of ovarian cancer than transdermal treatment.
d. The strength of the Million Women Study is its size; its weakness is the method of obtaining data.

12. In the FUTURE I study, vaccinated women who were seropositive for HPV at baseline but received all 3 vaccine injections were considered in which population for analysis:

a. per-protocol population
b. unrestricted population
c. intent to treat population

13. Which one is correct? 17 P seems to:

a. decrease the incidence of PTB prior to 37 weeks
b. cause no appreciable change in cervical length at 7 and 21 days post treatment
c. be associated with a non-significant, but beneficial, trend away from PTB prior to 35 weeks
d. cause less intervals shortening and cervical length than placebo up 21 days

14. The following statements are true regarding hypothyroidism and pregnancy except:

a. because of the hormonal changes in pregnancy, laboratory tests of thyroid function are unreliable.
b. subclinical hypothyroidism has been associated with an increase in early pregnancy losses.
c. subclinical hypothyroidism has been associated with an increase in premature births.
d. thyroid requirements change during pregnancy.

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.

Answers: 11(c); 12(c); 13(b); 14(a)

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Avandia, Risk of Congestive Heart Failure Significant Safety Risk

GlaxoSmithKline's rosiglitazone (Avandia) will receive a black box warning by the FDA because of concerns over heart failure associated with use of the drug. Pioglitazone (Actos) will also be subject to a black box warning for the same reason. The drugs, used for treatment of type 2 diabetes, have been scrutinized because of a recent meta-analysis that suggested that rosiglitazone was associated with a significant- increase risk of myocardial infarction and a borderline significant-increase risk of death from cardiovascular causes. (published www.NEJM. org on June 21, 2007 [10.1056/NEJMoa 072761]). Soon on the heels of the publication of this study, Glaxo rushed an interim analysis of its own trial to press. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was published online in the *New England Journal of Medicine* on June 5, 2007. In the RECORD study, 4,447 patients with type 2 diabetes who had inadequate control with metformin or a sulfonylurea were randomized to receive add-on rosiglitazone or a combination of metformin and a sulfonylurea. The primary endpoint was hospitalization or death from cardiovascular causes. After mean follow-up of 3.75 years, 217 patients in the rosiglitazone group and 202 patients in the control group had the primary endpoint (hazard ratio 1.08), and after adding in pending primary end points the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There was no statistically significant difference between either group with regard to myocardial infarction or death from cardiovascular causes or any cause. There was a significantly higher rate of heart failure in rosiglitazone group (HR 2.15; 95% CI, 1.30 to 3.57). The authors conclude that the study was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes, as there was no evidence of an increased death rate of cardiovascular causes or all causes associated with the drug, but there was a significantly higher rate of heart failure. There was insufficient data to determine if there was an increase risk of myocardial infarction (published at www.NEJM.org June 5, 2007 [10.1056/NEJMoa 073394]). The study was accompanied by 3 editorials that recommended caution in use of rosiglitazone and similar drugs especially in patients at risk for congestive heart failure. And while GlaxoSmithKline sees the study as vindication of the safety the drug, others, including the FDA, see the risk of congestive heart failure as a significant safety risk. Soon after publication of the RECORD study, a congressional hearing was held to discuss the safety of rosiglitazone and within days the FDA issued the black box requirement for rosiglitazone and pioglitazone. During the hearing, it came to

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light that at least one official at the FDA had suggested stronger warnings on rosiglitazone nearly a year ago, but her recommendation was ignored; she was reassigned and subsequently left the agency. Within several days of the rosiglitazone hearing, legislation was introduced to bolster the FDA's ability to monitor prescription drug side effects, a bill which also includes many of the Institute of Medicines recent recommendations on drug safety, and also included limiting direct-to-consumer advertising for newly approved medications.

Aspirin, Higher Doses No More Effective, Risky

What is the best dose of aspirin for prevention of cardiovascular disease? More than 50 million people take aspirin regularly in doses that range from 50 mg to over 1000 mg per day. The most commonly used doses are 81 mg and 325 mg per day. A recent systematic review of the English-language literature revealed that doses as low as 30 mg/day are effective at fully inhibiting platelet thromboxane production and preventing platelet aggregation. Despite this, higher doses are frequently used. The available evidence, primarily from secondary prevention trials, suggest that doses greater than 81 mg do not enhance efficacy, but do increase risk of GI bleeding and other toxicities. The authors conclude that aspirin doses of 75 mg to 81 mg/day are optimal for the indication of cardiovascular disease prevention, and higher doses are no more effective but are associated with higher risk (*JAMA* 2007; 297:2018-2024).

Subclinical Hypothyroidism Treatment Benefits

Subclinical hypothyroidism is defined as raised TSH levels with circulating thyroid hormones within the normal range. A new study suggests that treatment of subclinical hypothyroidism improves cardiovascular risk factors and quality of life. One hundred patients with a mean TSH of 6.6 mIU/l who had never received thyroid treatment and did not have cardiovascular disease were enrolled in a randomized, double-blinded crossover study of 100 µg of l-thyroxine or placebo daily for 12 weeks. Treatment with L-thyroxine reduced total cholesterol from an average of 231.6 to 220 mg/dl (P <0.001), LDL cholesterol from 142.9 to 131.3 mg/dl (P < 0.05), and waist to hip ratio from 0.83 to 0.81 (P < 0.006). Treatment also significantly improved endothelial function based on brachial artery flow mediated dilation, an early marker of atherosclerosis. Patients also reported decreased tiredness in the active treatment group, and there was a trend towards improvement in the perceived negative impact of hypothyroidism on sexual function. The authors conclude that treating subclinical hypothyroidism with l-thyroxine lead to significant improvements of cardiovascular risk factors and symptoms of tiredness (*J Clin Endocrinol Metab* 2007; 92:1715-1723).

FDA approvals

The FDA has approved a new transdermal patch for the treatment of early stage idiopathic Parkinson's disease. Rotigotine transdermal is a once-daily patch that is available in 2, 4 and 6 mg strengths. The drug is a dopamine agonist that affects D3/D2/D1 receptors and is thought to exert its effect via stimulation of dopamine D2 receptors. In clinical trials the patch was shown to improve scores on standardized rating scales for daily living and motor components in Parkinson's disease. The most common side effects are site reactions, dizziness, nausea, vomiting, somnolence and insomnia. Rotigotine transdermal will be available by the end of 2007 and will be marketed by Schwartz Pharma under the trade name Neupro.

The FDA has approved a new continuous contraceptive for women that is designed to eliminate menstruation. Wyeth pharmaceuticals Lybrel is a 28-day pill pack of levonorgestrel and ethinyl estradiol (90 µg/20 µg) that does not contain a placebo or pill-free interval. In clinical trials 59% of women achieved amenorrhea without bleeding or spotting, while 20% experienced spotting but did not require sanitary protection, and 21% required sanitary protection due to breakthrough bleeding. There was also no delay to return of menses after discontinuing the product nor any significant delay in fertility. Lybrel is scheduled to be available by July 2007.

Risedronate (Actonel) has received approval for a new once-a-month dosing schedule for the treatment of osteoporosis. The dose regimen requires patients to take 75 mg tablets on 2 consecutive days each month. The approval was based on a study that compared the monthly regimen with a daily regimen of 5 mg per day and showed no significant difference in efficacy for increasing bone mineral density at the lumbar spine, total hip, and hip trochanter. Risedronate is marketed by Procter & Gamble pharmaceuticals. ■