

Primary Care Reports



Volume 8, Number 25

December 9, 2002

Editor's Note—Suppose your patient schedule today includes SJ, a 29-year-old woman coming in for her annual gynecologic exam. She is married, without children, and wanting to stop her oral contraceptives so she can become pregnant. She asks, "Doctor, is there anything I can do to make sure I have a normal, healthy pregnancy?" What would you advise? Also on your schedule today is TC, a 30-year-old woman being worked in for "bronchitis." She smokes a package of cigarettes each day, is mildly obese, and has had mildly elevated blood pressure during the last several visits. You ask her if she might be currently pregnant, she says no, but has been "thinking about getting pregnant." What would you do?

The primary care physician who cares for couples in their childbearing years should encourage women and their partners to receive preconception care. The physician can enhance this opportunity by adopting a preconception focus during annual medical exams and asking the patients about their conception plans. Preconception care includes screening for infectious diseases, reviewing the genetic history and exposure risks, updating immunizations, and optimizing health status. There is good evidence that women should consume a healthy diet, limit consumption of certain fish, and supplement their diet with folic acid (0.4 mg daily). Finally, women should be encouraged to seek early prenatal care when a pregnancy is confirmed or an early evaluation if there is infertility, especially in women older than 35 years.

Preconception Care

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Why Preconception Care?

Preconception care is the promotion of the health and well-being of a woman and her partner before pregnancy. The optimal time to identify, manage, and treat many pregnancy conditions and complications is before pregnancy

occurs. The goal of a preconception office visit is to identify and assess those medical and social conditions that may put the mother or fetus at risk.¹ The benefits of intentionally preparing for a

pregnancy relate to the important and critical period of cell differentiation and organogenesis, which occurs between days 17 and 56 postfertilization.² The traditional first prenatal visit, usually 8 weeks after the last menstrual period, is too late to have an effect on reproductive outcomes associated with abnormal organogenesis secondary to drugs, alcohol, and poor diet. The benefits of optimal medical treatment for disease prior to pregnancy seem apparent, yet there is little evidence to support improved outcomes except in certain conditions. These conditions include diabetes mellitus, phenylketonuria, and a previous pregnancy with a fetus with a neural tube defect.^{1,3}

The Preconception History

The primary care physician should approach the preconception evaluation systematically. There are 7 broad categories that should be addressed:¹⁵

1. medications and teratogenic agents;

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2. environmental toxins;
3. age, family history, and genetic disorders;
4. infections and immunizations;
5. social habits and risk factors;
6. diet and exercise; and
7. chronic illnesses.

Medications and Teratogenic Agents

A key challenge is to identify those medications and chemicals that are potentially teratogenic before conception and discourage their use during the preconception and early pregnancy periods. All current prescription and nonprescription medications, as well as herbal supplements, must be reviewed. All primary care physicians should have ready access to references that include reviews of reproductive literature relevant to drugs, such as *Drugs in Pregnancy and Lactation*.⁴ These references also provide the classifications of safety in pregnancy as outlined by the Food and Drug Administration (FDA). The FDA has defined risk factor designations A, B, C, D, and X to classify drugs used in pregnancy. Category X drugs, which are commonly used by women of childbearing age, include ergotamines, flurazepam, temazepam, misoprostol, nicotine gum, HMG-CoA reductase inhibitors, warfarin, isotretinoin, and oral contraceptives.^{5,14} Additionally, the American College of Obstetrics and Gynecology (ACOG) recommends that pregnant and preconceptional women avoid taking more than 5000 IU of vitamin A daily.

Primary Care Reports™, ISSN 1040-2497, is published biweekly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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Periodicals postage paid at Atlanta, GA.

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In order to reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief) serves as a consultant to Aventis and Sanofi and does research for AstraZeneca. The peer reviewer is a consultant for Women First Healthcare and is involved in research with Pfizer and the NIH. Dr. Frey (author) reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Environmental Toxins

Many toxic exposures are teratogenic, including occupational exposure to organic solvents, anesthetic gases, and antineoplastic agents.⁶ A detailed occupational history, including household and hobby activities, can reveal potential teratogenic exposures. Women planning a pregnancy should minimize use of common household products such as paint and paint removal products, bleaches, lye, and oven cleaners. There is no convincing evidence of adverse pregnancy outcomes for women exposed to common sources of electromagnetic field radiation, such as office and home computer use, electric blankets, and heated waterbeds.⁷

Age, Family History, and Genetic Disorders

Many women are postponing pregnancy because of educational and career goals; therefore, advanced maternal age is becoming more common. The older woman is more likely to have concerns about chromosomal abnormalities and infertility, as well as an increased likelihood of chronic medical illness.^{14,15} Advanced maternal age contributes to the risk of chromosomal abnormalities, as does advanced paternal age older than 60. The preconception period is the perfect opportunity to educate patients about a woman's fertility "biologic time clock" (particularly a woman older than 35 years) and the purposes and techniques of prenatal diagnosis.⁵ A detailed review of the woman's family history and ethnicity for genetic disorders (for such disorders as cystic fibrosis, sickle cell anemia, and Tay-Sachs disease) and malformations (such as neural tube defects) should be accomplished during the preconception office visit. The primary care physician should consider referring the patient to a genetic counselor or maternal-fetal specialist if there is a personal or family history of a child with a potential genetic disorder or advanced maternal age.⁶

Infections and Immunizations

Hepatitis B is the most common type of hepatitis in the United States. During the preconception evaluation, a history of high-risk behavior, including multiple sexual partners, sexually transmitted diseases, blood transfusions, or intravenous drug abuse, should be obtained for both the patient and her sexual partner. All women should be screened for hepatitis B, and those patients at high risk should be tested for the presence of both HBSAg and HbeAg. Most women who could transmit HIV infection to their fetus are asymptomatic. Vertical transmission results in approximately a 25% chance of fetal infection from an untreated HIV-positive mother, a risk that can be significantly reduced with preconception or early pregnancy treatment.^{5,14} During the preconception period, women should be educated about high-risk behavior, as well as given advice on contraception. All sexually active women should be offered HIV testing.

Toxoplasma gondii is a parasite and teratogen that can cause fetal growth retardation, congenital anomalies, chori-

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oretinitis, and other sequelae. Approximately 30% of adults in the United States have serologic evidence of prior exposure. Screening is controversial because evidence that treatment prevents congenital disease is lacking. The physician should recommend that patients reduce their risk by avoiding the high-risk practices of eating raw or uncooked meat, changing cat litter, and failing to wash kitchen knives after preparing raw meats. Congenital cytomegalovirus (CMV) infection occurs in 1% of all live births in the US and causes major neonatal illness in 5 to 10% of these cases. Most congenital CMV is a result of a primary infection during pregnancy. No specific recommendations for health care and daycare workers have emerged, other than universal precautions, due to a lack of evidence for efficacy of screening and/or treatment programs to prevent infection.² However, day care workers caring for children in the 12- to 36-month age group have the highest risk of occupational CMV seroconversion and, if seronegative, may want to consider shifting their job to care for either infants or older children to reduce their exposure.⁸

The preconception visit should include an evaluation and update of standard adult immunizations. These would include tetanus, rubella, hepatitis, and varicella. Women who are varicella nonimmune are at risk for development of varicella pneumonia, which has a maternal mortality rate as high as 40%.² Finally, pregnancy is considered a high-risk condition for influenza. Women expected to be at least 3 months pregnant during the influenza season (November to April) should be vaccinated. The specific guidelines for immunizations for adults can be found under "Recommendations of the Advisory Committee on Immunization Practices" (ACIP) at their web site: <http://www.cdc.gov/nip/publications/ACIP-list.htm>.

Social Habits and Risk Factors

A woman's psychosocial and mental health can have a significant effect on a pregnancy. Ongoing use of alcohol, tobacco, and illicit drugs should be reviewed at the preconception visit and users should be counseled about both their risks and the risks to their fetus.⁷ Approximately a third of women in the United States drink alcohol during their pregnancy. Fetal alcohol syndrome occurs at a rate of 1.95 per 1000 live births in the general population and is higher (4.7 per 1000 live births) in daily drinkers. However, even modest amounts of alcohol consumption during pregnancy can cause persistent neurobehavioral deficits in children. Approximately 18% of pregnant women report smoking tobacco and will be at risk for such complications as abruptio placenta, pre-eclampsia, and preterm labor.⁶ Additionally, tobacco is associated with decreased fertility rates and increased oocyte depletion rates. The preconception visit should also be used as an opportunity to screen women at risk for domestic violence. The physician can use a simple 4-question screening tool modeled after the CAGE questionnaire for alcoholism:

- How often does your partner hurt you?
- How often does your partner insult or talk down to you?
- How often are you threatened with physical harm?
- How often does your partner scream or curse at you?

Responses of "often" or "frequent" to any of these questions place the women at risk for domestic violence. The patient should receive information about community resources for battered women and emergency shelters.^{7,14}

Diet and Exercise

A balanced diet, along with the achievement or maintenance of an ideal body weight, improves pregnancy outcomes. A target preconception body weight should be between a body mass index (BMI) of 20 and 27. Women with eating disorders should be evaluated and treated prior to pregnancy. Most general diets, including vegetarianism, will be safe during pregnancy. More restrictive diets, such as lactovegetarians (who eat no eggs) and vegans (who eat only plants), will require supplementary calcium, zinc, iron, and vitamins B and D. High-dose vitamin supplements should be avoided. Daily folic acid intake of 0.4 mg should begin at least 1 month prior to pregnancy and continued through the first trimester. For women who have had a child with a neural tube defect, a higher dose of folic acid (4.0 mg) is recommended and has been shown to decrease the recurrence rate of neural tube defects.⁷ The FDA has recently warned that women who may become pregnant and those pregnant and lactating should avoid certain fish because of methyl mercury. This form of mercury can cause harm to the developing fetal nervous system. The specific FDA recommendations are listed in the Table.⁹

The current evidence continues to demonstrate marked benefit to both the mother and fetus for women who exercise during pregnancy. The current recommendation is for women to continue their prepregnancy activity level when they become pregnant. The primary care physician should therefore encourage either the initiation or continuation of an exercise program for their preconception patients.¹⁰

Table. FDA Recommendations for Fish Consumption for Preconceptive, Pregnant, and Lactating Women

Safer fish (12 ounces of cooked fish per week)

- Shellfish
- Canned fish
- Smaller ocean fish
- Farm-raised fish
- Canned tuna

Avoid in diet

- Shark
- Swordfish
- King mackerel
- Tile fish

The Preconception Physical Examination and Laboratory Screening

A thorough physical examination, including a breast and pelvic examination, is recommended. There should be a specific focus on the clinical findings associated with the underlying diseases which may affect pregnancy (see below). From the available evidence, it is reasonable to screen all women for syphilis, gonorrhea, chlamydia, hepatitis B, HIV, and rubella immunity (or document evidence of immunization). The patient's Pap test should be up to date. Additional laboratory testing should be based on the findings of the history and physical examination.

Chronic Illnesses

The primary care physician should review the woman's personal medical history, attempt to identify subclinical illness, and optimize the health status for existing illness. The most common chronic illnesses that have preconception care implications include asthma, hypertension, cardiac disease, thromboembolic disorders, seizures, renal disease, diabetes mellitus, and autoimmune disorders.

Asthma

Asthma is one of the most common medical illnesses likely to occur in women of childbearing age, with approximately 1% of pregnancies complicated by asthma. The physician's goals include optimizing preconceptional asthma control, reviewing use of the peakflow meter and personal best surveillance, and offering influenza vaccine. Although the majority of the medications used to treat asthma appear to be safe, the fewest medications needed to control symptoms should be recommended.⁵

Hypertension

The majority of women who have chronic essential hypertension and become pregnant may anticipate uncomplicated pregnancies. Complications are most likely to occur in older women, particularly those with end-organ damage secondary to hypertension. It is important that women with hypertension be evaluated before pregnancy to determine the severity of the hypertension and to recommend potential lifestyle modifications. The secondary causes of hypertension should be ruled out during the preconception period because these patients are at higher risk for serious maternal and fetal complications during pregnancy. Specific classes of antihypertensive medications, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and thiazide diuretics should be discontinued. For those patients who require continued drug therapy, methyl dopa is preferred by many physicians as first-line therapy because of the well-established record of maternal and fetal safety and reports of stable uteroplacental blood flow and fetal hemodynamics.⁵ Alternative agents for the treatment of chronic hypertension in pregnancy include beta blockers and calcium channel blockers.^{11,14}

Cardiac Disease

The preconception evaluation should identify cardiac disease risk factors, determine the extent of disease, identify cor-

rectable problems, and provide the patient with detailed information about maternal and fetal risks. Maternal morbidity is as high as 7% in combined New York Heart Association classes III and IV heart disease, compared to only 0.5% in combined classes I and II. Certain cardiac disorders, such as primary pulmonary hypertension, place women at very high risk during pregnancy. (Maternal mortality approaches 50%).⁵ Any woman with a substantial history of cardiac disease should be seen in consultation by a cardiologist during the preconception period.

Thromboembolic Disease

Women with a history of thromboembolic disease are at increased risk for recurrent disease during pregnancy. Additionally, patients with hypercoagulable thrombophilias such as antithrombin-III deficiency, protein C and protein S deficiencies, factor V deficiency, and anticardiolipin antibody syndrome are at risk. Patients who have had recurrent thromboembolic events, recurrent pregnancy losses, or a positive family history for thromboembolic disease, should be evaluated for these disorders before pregnancy.⁵ The ACOG recently published new clinical management guidelines for prevention and management of venous thromboembolism in pregnancy.¹² Heparin prophylaxis is recommended for pregnant women with any of the following conditions: artificial heart valves, a history of rheumatic heart disease and atrial fibrillation, antithrombin-III deficiency, antiphospholipid syndrome, or a history of anticoagulation therapy. Recommended prophylactic heparin regimens in pregnancy are included in this ACOG practice bulletin. Coumadin should be avoided and the patient switched to heparin before conception or as soon as pregnancy is diagnosed.^{12,15,16}

Epilepsy

Seizure disorders are the most common serious neurologic disorders seen in women of childbearing age. The patient's history, diagnostic studies, and medication use should be reviewed during the preconception visit. The clinician's focus is to confirm the correct diagnosis of a seizure disorder, optimize seizure control, prescribe folic acid supplements (at least 1 mg daily), and aim to use the best single agent for the seizure type.¹⁴ The decision to stop medications, if the patient has been seizure-free for at least 2 years, should be made in consultation with a neurologist.⁵

Renal Disease

Women who have chronic renal disease with mild impairment of renal function, without proteinuria or hypertension, are very likely to have a successful pregnancy outcome. Those patients with more significant renal impairment will require a more thorough preconception evaluation. Additionally, many women with a renal transplant have had successful pregnancies.⁵

Autoimmune Disorders

Autoimmune disorders are common among women of childbearing age and often clinically improve during pregnancy. Women with quiescent disease or a distant history of dis-

ease should be carefully evaluated and counseled about maternal and fetal risks. Systemic lupus erythematosus is a multisystem connective tissue disorder most prevalent in women of childbearing age. Patients should be counseled that the best time to attempt conception is during periods of inactive disease. Patients with a history of immune thrombocytopenia purpura should be aware that even if their disease has been treated, circulating antiplatelet antibodies may still be present and cross the placenta.⁵ These antiplatelet antibodies may affect the fetal platelet count, thus consultation with a maternal-fetal medicine specialist is recommended.¹⁵

Diabetes Mellitus

Optimal preconception control of diabetes mellitus is essential. There is well-established evidence that congenital anomalies occur more commonly in infants of mothers with established diabetes when compared to the general obstetrical population. Poor glycemic control early in pregnancy, as evidenced by elevated maternal hemoglobin A1c levels, has been strongly correlated with significant rates of spontaneous abortion and with increased likelihood of birth defects in infants from successful pregnancies.¹⁴ Unfortunately, the majority of diabetic women do not plan their pregnancies and enter pregnancy with inadequate blood-sugar control. The diabetic woman should pursue intensive diabetic management, with optimal glycemic control, prior to attempting to conceive.^{13,14}

Preconception Health Issues in Men

There is expanding evidence of male-associated health issues and pregnancy outcomes. Both paternal smoking and alcohol consumption have been associated with low-birth-weight infants and smoking specifically with an increased incidence of fetal malformations. Other substances and chemicals may adversely affect spermatogenesis and male fertility. The primary care physician can use a general medical visit to educate men about such risks, review their family history for genetic disorders, and screen for sexually transmitted diseases and sexual dysfunction.⁷

Conclusions

Preconception care represents the very best of preventive health care. The knowledgeable primary care physician has the opportunity to positively affect the health outcomes of 2 lives—the mother and her infant. A systematic approach, as outlined above, will guide the physician in optimizing the health of a woman and her partner before a pregnancy.

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CME Questions

63. Which risk factor designation of medications does the FDA recommend be avoided in pregnancy?
 - a. A
 - b. B
 - c. C
 - d. D
 - e. X
64. When is the critical, postfertilization period of fetal cell differentiation and organogenesis?
 - a. 1 to 2 weeks
 - b. 2 to 3 months
 - c. 17 to 56 days
 - d. 4 to 6 months
 - e. Unknown

65. The recommendations for preconception women to minimize their risk of infection by toxoplasma gondii include all of the following, *except*:
- avoiding working as a daycare assistant.
 - avoiding eating raw meat.
 - avoiding changing cat litter.
 - cleaning kitchen knives after preparing raw meats.
 - eating thoroughly cook meats.
66. The preconception visit should review and update which group of immunizations?
- Pneumococcal, tetanus, diphtheria
 - Varicella, tetanus, rubella, hepatitis B
 - BCG, polio, tetanus
 - Yellow fever, rubella, cholera
 - Pertussis, tetanus, diphtheria, measles
67. Which medical condition has the best evidence supporting optimal control prior to pregnancy to improve outcomes?
- Essential hypertension
 - Seizure disorders
 - Diabetes mellitus
 - Thromboembolic disease
 - Chronic renal disease

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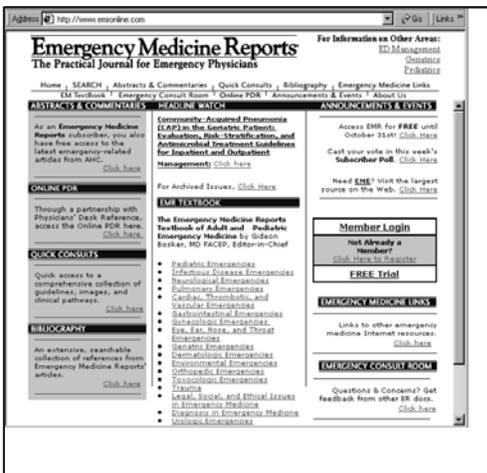
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**Syndrome X—
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PHARMACOLOGY WATCH



FDA Approves Generic Version of AstraZeneca's Prilosec

The FDA has approved the first generic version of AstraZeneca plc's blockbuster drug, omeprazole (Prilosec). KUDCO, a subsidiary of Germany's Schwartz Pharma was granted the approval in a court ruling in mid-October. The FDA has cleared a number of other generic versions of the drug; however, this is the first, in the eyes of the courts, that does not infringe on patents held by AstraZeneca. In a complicated set of deals, KUDCO is partnering with Andrix Pharmaceuticals and Genpharm Inc to bring the drug to market by early 2003. Prilosec, with worldwide sales of more than \$4 billion a year, has been the focus of intense legal wrangling as AstraZeneca has pulled all the stops to prevent marketing of generic forms of the drug. Meanwhile, consumer groups hoping to bring down the cost of prescription medications have been urging the Bush administration to speed generics, such as omeprazole, to market. The FDA has approved omeprazole for over-the-counter use but is still working with AstraZeneca on labeling language. Consumers can expect OTC Prilosec in the second quarter of next year.

Pegasys Approved To Treat Hepatitis C

A second pegylated interferon has been approved for the treatment of chronic hepatitis C infection. F. Hoffmann-La Roche Ltd's peginterferon alfa-2a (Pegasys) will compete with Schering-Plough's peginterferon alfa 2-b (Peg-Intron) for this indication. It is estimated that nearly 4 million Americans have evidence of infection with hepatitis C, of which nearly 3 million have chronic hepatitis C infection. In the last few years, standard treatment has become interferon either standard or pegylated, alone or in combination with ribavirin. Standard interferon

must be given 3 times a week. Adding polyethylene glycol (PEG) to the interferon molecule increases the elimination half-life, allowing for less-frequent dosing, generally once a week. Pegasys is approved only as monotherapy; however, Schering-Plough has applied for approval of combination therapy with Pegasys and ribavirin. The FDA has fast-tracked the application, with final approval expected before the end of year.

HRT Reduces Alzheimer's Risk, Study Says

Yet another study has weighed in on the issue of hormone replacement therapy and the risk of Alzheimer's disease (AD). This study of a population of older adults in Cache County, Utah showed that 10 years or more of HRT significantly reduced the risk of Alzheimer's disease. Importantly, the study also showed that once women are in the early stages of Alzheimer's disease, it is too late for HRT to have any benefit. The rate of AD was evaluated in 1357 men (median age, 73.2 years) and 1889 women (mean age, 74.5 years). After a 3-year follow-up, women who formerly used HRT or women who are currently using HRT for longer than 10 years had a statistically significant reduction in the rate of AD (HRT users represented 26 cases/1066 women, non

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HRT users represented 58 cases/800 women [adjusted HR, 0.59; 95% CI, 0.36-0.96]). Almost all the HRT-related reduction in the incidence of AD was among women who had formerly used HRT. A related editorial suggests that there may be a critical period soon after menopause, which is characterized by rapid estrogen depletion, where HRT may provide the most neuroprotective benefit for women (*JAMA*. 2002;288:2123-2129, 2170-2173). In mid-October officials from the National Institutes of Health announced that they would continue to study the effects of HRT or conditions such as osteoporosis and AD. This announcement was important in light of the early termination of the Women's Health Initiative study on hormone replacement in July. Currently, the National Institute on Aging is funding 3 studies that will compare how well HRT combination therapy or estrogen alone helps prevent memory loss and loss of cognitive function in women older than 65.

Heparin Plus Alteplase More Effective

Patients with submassive pulmonary emboli (PE) will fare better treated with heparin plus alteplase compared to heparin alone, according to a new study. Alteplase, a thrombolytic agent, is commonly used in the treatment of massive PE. This study seeks to define the drug's role in submassive PE in hemodynamically stable patients. Two hundred fifty-six patients with PE and pulmonary hypertension or RV dysfunction but without arterial hypertension or shock were evaluated. One hundred thirty-eight received heparin plus alteplase 100 mg and 118 received heparin plus placebo. The primary end point was in-hospital death or treatment escalation (pressors, repeat thrombolysis, intubation, CPR, or emergency embolectomy). The primary end point occurred nearly 3 times as often in the heparin plus placebo group, all due to treatment escalation. In-hospital death was nonsignificantly higher in the heparin group, 3.4%, vs 2.2% for the alteplase group ($P = .71$). However, 30-day event-free survival was higher with heparin vs alteplase ($P = .005$). The authors conclude that thrombolytic therapy with alteplase plus heparin should be considered in patients with submassive PE (*N Engl J Med*. 2002;347:1143-1150).

Digoxin Effects Differ By Sex

Digoxin should be used with caution in women with heart failure and may even be associated with an increase in mortality, according to a new study. The Digitalis Investigation Group looked at

6800 patients on digoxin therapy with the primary end point being mortality from any cause. While there was no increased mortality in men on digoxin, women on the drug had a higher rate of death compared to the placebo group (33.1% vs 28.9%, respectively; 95% CI, -0.5-8.8). The authors conclude that the effect of digoxin therapy differs between men and women. Women with congestive heart failure of a higher mortality rate associated with use of the drug, while the same is not seen with men (*N Engl J Med*. 2002;347:1403-1411).

McClellan Named FDA Commissioner

The Food and Drug Administration finally has a commissioner, after 2 years of vacancy in the position. The new commissioner, Mark McClellan, MD, was approved quickly and unanimously. He has a background in both medicine and economics, and has been an advisor to both Presidents Clinton and Bush. He has most recently been a professor of medicine and economics at Stanford University. Dr. McClellan joins the FDA at a time of unprecedented change and turmoil. There is high turnover at the agency, and criticism from consumer groups that drug approvals take too long on the one hand, and are too cursory on the other. President Bush has recently backed removing legal obstacles to the approval of generic drugs, a move meant to reduce prices for consumers, and a move that is not popular with Pharma.

FDA Actions

The FDA has approved 2 formulations of buprenorphine, a new schedule III narcotic for treatment of patients with narcotic addiction. Buprenorphine will be marketed as Subutex by Reckitt Benckiser pharmaceuticals, while the second preparation, which combines buprenorphine with naloxone, will be marketed by the same company as Suboxone. The combination with naloxone is intended for maintenance therapy since naloxone will safeguard against intravenous abuse. The FDA took the unusual step of putting buprenorphine into the schedule III category rather than schedule II to allow easier prescribing in compliance with recent congressional legislation making maintenance narcotics more available to patients.

Bristol-Myers has received approval to market Metaglip, a new combination drug for treatment type 2 diabetes. Metaglip combines gliptizide and metformin in a single tablet for initial therapy of type 2 diabetes. ■