with atrial fibrillation who are at high risk for thrombotic stroke.

Menopausal Hormone Therapy (MHT)

The most common type of MHT (previously referred to as hormone replacement therapy, or HRT) consists of the administration of estrogens together with a progestogen. Because of the risk of uterine cancer, estrogen therapy alone is used only in hysterectomized women. Initially used to counteract "hot flashes" and other symptoms of menopause, early clinical studies suggested that MHT use in postmenopausal women could prevent or slow the progression of osteoporosis (Chapter 26) and reduce the likelihood of myocardial infarction. However, subsequent randomized clinical trials have produced decidedly mixed results. In 2002, the Women's Health Initiative stunned the medical community by reporting that a large prospective placebo controlled trial failed to find support for some of the presumed beneficial effects of the therapy. This study involved approximately 17,000 women who were taking a combination of estrogen (conjugated equine estrogens) and a synthetic progestin (medroxyprogesterone acetate). Although MHT did reduce the number of fractures in women on treatment, researchers also reported that after 5 years of treatment, combination MHT increased the risk of breast cancer (Chapter 23), stroke, and venous thromboembolism and had no effect on the incidence of coronary heart disease. The shockwaves produced by these findings led to a drastic decrease in the use of MHT, from 16 million prescriptions in 2001 to 6 million in 2006, which was accompanied by an apparent drop in the incidence of newly diagnosed breast cancers. But during the past few years there has been a reappraisal of the risks and benefits of MHT. These newer analyses showed that MHT effects depend on the type of hormone therapy regimen used (combination estrogen-progestin versus estrogen alone), the age and risk factor status of the woman at the start of treatment, the duration of the treatment, and possibly the hormone dose, formulation, and route of administration. The current risk:benefit consensus can be summarized as follows:

- Combination estrogen-progestin increases the risk of breast cancer after a median time of 5 to 6 years. In contrast, estrogen alone in women with hysterectomy is associated with a borderline reduction in risk of breast cancer.
- MHT may have a protective effect on the development of atherosclerosis and coronary disease in women younger than age 60 years, but there is no protection in women who started MHT at an older age. These data support the notion that there may be a critical therapeutic window for MHT effects on the cardiovascular system. Protective effects in younger women depend in part on the response of estrogen receptors and healthy vascular endothelium. However, MHT should not be used for prevention of cardiovascular disease or other chronic diseases.
- MHT increases the risk of stroke and venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. The increase in VTE is more pronounced during the first 2 years of treatment and in women who have other risk factors such as immobilization and hypercoagulable states caused by prothrombin or factor V Leiden mutations (Chapter 4). Whether risks of VTE and stroke are lower with transdermal than oral routes of estrogen administration warrants further study.

As can be appreciated from these associations, assessment of risks and benefits when considering the use of MHT in women is complex. The current feeling is that these agents have a role in the management of menopausal symptoms in early menopause but should not be used long term for chronic disease prevention.

Oral Contraceptives (OCs)

Worldwide, more than 100 million women use hormonal contraception. OCs nearly always contain a synthetic estradiol and a variable amount of a progestin, but some preparations contain only progestins. They act by inhibiting ovulation or preventing implantation. Currently prescribed OCs contain a much smaller amount of estrogens (as little as 20 μg of ethinyl estradiol) than the earliest formulations, and are associated with fewer side effects. Transdermal and implantable formulations have also become available. Hence, the results of epidemiologic studies should be interpreted in the context of the dosage and the delivery system. Nevertheless, there is good evidence to support the following conclusions:

- *Breast carcinoma*: The prevailing opinion is that OCs *do not* increase breast cancer risk.
- *Endometrial cancer and ovarian cancers*: OCs have a protective effect against these tumors.
- *Cervical cancer*: OCs may increase risk of cervical carcinomas in women infected with human papillomavirus, although it is unclear whether the increased risk merely reflects greater sexual activity in women on OCs.
- *Thromboembolism*: Most studies indicate that OCs, including the newer low-dose (less than 50 μg of estrogen) preparations, are associated with a threefold to sixfold increased risk of venous thrombosis and pulmonary thromboembolism due to a hypercoagulable state induced by elevated hepatic synthesis of coagulation factors. This risk may be even higher with newer "third-generation" OCs that contain synthetic progestins, particularly in women who are carriers of the factor V Leiden mutation. To put this complication into context, however, the risk of thromboembolism associated with OC use is two to six times lower than the risk of thromboembolism associated with pregnancy.
- *Cardiovascular disease*: There is considerable uncertainty about the risk of atherosclerosis and myocardial infarction in users of OCs. It seems that OCs do not increase the risk of coronary artery disease in women younger than 30 years or in older women who are nonsmokers, but the risk does approximately double in women older than 35 years who smoke.
- *Hepatic adenoma*: There is a well-defined association between the use of OCs and this rare benign hepatic tumor, especially in older women who have used OCs for prolonged periods. The tumor appears as a large, solitary, and well-encapsulated mass.

Ultimately, the pros and cons of OCs must be viewed in the context of their wide applicability and acceptance as a