

# The Role of Hormones in Women's Stroke Risk

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## ABSTRACT

Although often overshadowed by breast cancer and other women's health issues, stroke is a primary cause of mortality and morbidity among women in the United States today. This article explores three major populations of women: postmenopausal women who are taking hormone-replacement therapy, women ingesting estrogen-containing oral contraceptive pills, and women who are currently pregnant. It compiles recent research and physiologic information that can aid in assessing these women's risk for stroke. This review can help healthcare providers evaluate and manage these populations, and assess the health risks and benefits of certain estrogen-containing therapies.

## INTRODUCTION

Recent studies have sought to evaluate the risk of stroke in postmenopausal women taking hormone-replacement therapy, in women of childbearing age taking oral contraceptives, and in pregnant and recently pregnant women undergoing natural shifts in hormone levels. Some of these women are already at increased risk for stroke due to genetic predispositions or other underlying risk factors. It is essential for physicians and medical practitioners to understand these women's risks before initiating hormonal therapy.

### POSTMENOPAUSAL WOMEN ON HORMONE-REPLACEMENT THERAPY

Epidemiologic and observational studies have suggested a decreased rate of coronary heart disease in postmenopausal women taking hormone-replacement therapy compared to other women in their age groups (Bush et al. 1987). The effect on stroke was less consistent. Some data showed a decreased rate of stroke (Stampfer et al. 1991), while conflicting data showed no change in stroke risk with hormone-replacement therapy (Finucane et al. 1993). Despite these inconsistencies, physicians were aware that estrogen lowers low-density lipoprotein (LDL) cholesterol, a known risk factor for atherosclerosis (PEPI 1995). This made them optimistic that they could save many women from the disabilities of heart disease and stroke by instituting a hormone-replacement therapy regimen. Randomized controlled studies were conducted to confirm these impressions. Paradoxically, researchers found that hormone-replacement therapy seemed to increase the risk of heart disease and stroke (Wassertheil-Smoller et al. 2003; Manson et al. 2003; Hendrix et al. 2006). Although women given hormones showed significant increases in high-density lipoprotein cholesterol and marked decreases in LDL cholesterol, total cholesterol, and insulin when compared to the placebo group, they also showed a 24 percent greater risk

of cardiac events, including death and myocardial infarction (Manson et al. 2003). It appears that the beneficial effects of lowering LDL levels are outweighed by a higher propensity for thrombosis, which can greatly increase a woman's risk of stroke and myocardial infarction (Grady et al. 2000). The protective effect that had been initially attributed to hormone-replacement therapy seemed to be simply the result of a selection bias. It is likely that the women who chose to take hormone-replacement therapy were leading healthier lifestyles than age-matched controls by modifying habits such as diet, exercise, and smoking. These choices decreased their stroke risk. Since early studies were nonrandomized and observational, the decreased morbidity and mortality were falsely attributed to estrogen-replacement therapy.

The Woman's Health Initiative was a large investigation composed of several clinical and observational trials. It was meant to study the most-serious illnesses affecting postmenopausal women. Among these studies was a randomized controlled trial designed to see if postmenopausal women treated with estrogen-replacement therapy would have a decreased risk of coronary artery disease and fractures. Each woman with a uterus was treated with estrogen and progestin to protect against endometrial cancer, while those with prior hysterectomies were treated with estrogen alone (Women's Health Initiative 1998). Three years before the trial was supposed to end, data showed that women in the estrogen-plus-progestin group were at a significantly increased risk of stroke compared to those given placebo. The estrogen-plus-progestin treatment group had a 31 percent increased incidence of any type of stroke and a 44 percent increased incidence of ischemic stroke. This evidence was strong enough to terminate the estrogen-plus-progestin arm of the trial (Wassertheil-Smoller et al. 2003). Two years later, the estrogen-only arm was terminated for similar reasons. There was a 37 percent increased incidence of all strokes and a 55 percent increased incidence of ischemic strokes in the treatment group after seven years of treatment. This suggests that while the increased risk of stroke is seen more quickly

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**The Role of Hormones in Women's Stroke Risk**

with estrogen plus progesterone than with estrogen alone, stroke risk over time may be greater when estrogen is used without progesterone. This further implies that estrogen, not progesterone, is the hormone responsible for the increased stroke risk (Hendrix et al. 2006).

When stroke risk with estrogen-replacement therapy was specifically explored in women who had experienced a prior cerebrovascular accident (secondary prevention), there was no increased risk for recurrent nonfatal strokes. However, the nonfatal strokes were more debilitating than those in the control group. Furthermore, the women were more likely to fall victim to fatal strokes (Viscoli et al. 2001).

It is important to note that, while some studies did not look at stroke specifically, the risk for stroke correlates well with the risk for coronary heart disease and thrombosis. Women taking hormones appear to be at increased risk for embolic strokes. Normally, systemic venous blood goes through the right heart to the lungs for oxygenation before traveling to the left heart and the systemic circulation, including the brain. This makes it more likely that a deep-vein thrombosis will cause a pulmonary embolism rather than a stroke. However, autopsy studies have shown that approximately 27% of people in the general population have a patent foramen ovale, which would allow a clot to bypass the lungs and, paradoxically, travel directly to the brain (Shah and Shindler 2002). In fact, a patent foramen ovale was noted in approximately 40% of autopsies in stroke victims (Shah and Shindler 2002). Therefore, a significant proportion of the population may be at increased risk for stroke if they have a propensity for clotting.

**THE USE OF ESTROGEN-CONTAINING CONTRACEPTION IN WOMEN OF CHILDBEARING AGE**

The evidence that hormone-replacement therapy can increase vascular events in postmenopausal women leads to concerns for the broader population of women who use related drugs. Estrogen seems to be culpable in the increase in clotting in postmenopausal women taking hormone-replacement therapy. Estrogen is also a key component of oral birth-control pills. In fact, contraceptives generally have higher levels of estrogen than the usual doses in replacement-therapy regimens (Grady et al. 2000). This raises concerns that younger women may be increasing their risk for stroke by using these agents. However, since the risk for stroke increases with age, young women who are taking oral contraceptives are at lower risk for stroke than postmenopausal women undergoing hormone-replacement therapy (Heinemann et al. 1997).

Nonetheless, women who use oral contraceptives are at a higher risk for stroke when compared to women of their age group who are not using that method of

birth control. The strokes that occur among oral-contraceptive users appear to be embolic, attributed to the hypercoagulable state of blood induced by estrogen. Atherosclerosis is usually not present in these women (Ropper and Brown 2005). The effect of the estrogen on stroke risk seems to persist long after these women discontinue the oral contraceptives. The risk in prior users, however, is not so great as in current users, whose chance of developing a stroke is double that of women who have never used oral contraceptives (Hannaford et al. 1994). The risk for stroke in women taking birth-control pills increases further if they are smokers, over the age of 35, suffer from migraine, or are hypertensive (Ropper and Brown 2005).

There appears to be a correlation between the amount of estrogen in the oral-contraceptive pill and the likelihood of falling victim to stroke. Over the years, newer oral-contraceptive pills have been developed with lower levels of estrogen. The types of progestins have changed as well; there are now first-, second-, and third-generation progestins. It is generally established that higher doses of estrogen have been associated with increased incidence of ischemic stroke (Heinemann et al. 1997). However, whether the various types of progestins have different effects on stroke risk is controversial. Some studies show an increased incidence of stroke with second-generation progestins (Lidegaard and Kreiner 2002), while other studies show no significant differences between the various progestins and stroke risk (WHO 1996; Heinemann et al. 1997).

**RISK OF STROKE DURING PREGNANCY**

During pregnancy, a woman's natural hormones change dramatically and her body is under considerable stress. With pregnancy comes an increased threat of stroke. The rate of stroke increases with age, but is found to be approximately 6.2 per 100,000 pregnancies (Ropper and Brown 2005). Right-heart pressure increases during pregnancy, as does the susceptibility to forming thromboses in the legs and pelvic veins (Ropper and Brown 2005). As noted earlier, these factors can predispose a woman to a paradoxical embolic stroke.

In order to accommodate the fetus within the mother's body, and to facilitate parturition, the mother's estrogen levels increase dramatically during pregnancy (Guyton and Hall 2006b). One might anticipate that this elevation of estrogen levels would increase the incidence of stroke in pregnant women secondary to thrombosis. Throughout the prenatal period, however, the risk level for developing stroke or a blood clot varies. Arterial thrombosis tends to occur during the last two trimesters and one week postpartum, while venous thrombosis does not tend to occur until later, at around one week to one month postdelivery (Ropper and Brown 2005). One clinical trial showed that the incidence of both isch-

## The Role of Hormones in Women's Stroke Risk

emic and hemorrhagic stroke increased dramatically in the six weeks postpartum, while it did not increase significantly during the pregnancy itself (Kittner et al. 1996).

The apparent increased risk of stroke at the end of pregnancy and the recent-postpartum period is logical when the hormone changes are examined more carefully. While estrogen increases during pregnancy, so does progesterone. Estrogens increase uterine contractility and progesterone prevents the uterus from early contractions that can cause premature parturition. It is hypothesized that at the end of pregnancy, particularly during parturition, the estrogen-to-progesterone ratio increases (Guyton and Hall 2006b). If estrogen is, in fact, responsible for blood hypercoagulability, this would explain why more strokes are seen at the end of pregnancy as well as immediately following delivery when compared to early pregnancy.

### WOMEN WITH GENETIC PREDISPOSITIONS TO STROKE

While elevated estrogen levels do increase the risk of stroke in women, the probability of having a stroke is still relatively small in young, otherwise healthy women. However, some women have genetic predispositions that can elevate their risk, especially when compounded by pharmacologic estrogen levels. Many of these genetic traits are otherwise silent and, therefore, women are often unaware of their increased risk.

Homeostatic mechanisms prevent coagulation during normal circulation, while maintaining the ability to clot after an injury. Normally, procoagulants initiate clotting after an injury, while anticoagulants prevent clotting in the normal systemic circulation. When the blood has to coalesce after injury, a prothrombin activator is formed that converts prothrombin into thrombin, which converts fibrinogen into fibrin. Fibrin forms the initial blood clot, which is later strengthened by fibrin-stabilizing factor. After a clot is initiated, factors are released to further coagulate the blood. When it is time for the clot to disseminate, protein C inactivates clotting factors V and VIII to prevent further coagulation (Guyton and Hall 2006a). In certain individuals this clotting cascade can be abnormal, leading to either increased or decreased propensity for thrombosis.

Approximately 35% of idiopathic cases of stroke are attributed to a mutation in the prothrombin gene. Women with this mutation who use oral contraceptives increase their risk of stroke twentyfold (Ropper and Brown 2005). Similarly, a mutation in coagulation factor V, known as the factor V Leiden mutation, makes this particular clotting factor resistant to breakdown by protein C (Dahlback 1994). Because of this, factor V remains active when it should not be functioning, causing excessive coagulation. According to clinical trials, women with factor V Leiden have a threefold increased risk for venous

thromboembolic events when compared to women without the mutation. This risk increases tenfold when these women are placed on hormone-replacement therapy (Herrington et al. 2002).

Some individuals also have syndromes causing them to have antibodies against phospholipids that are associated with an increase in thrombosis. One example is the lupus anticoagulant that is associated with an increase in the risk for both arterial and venous thrombosis (Brey et al. 2002). These clots can potentially lead to stroke, particularly in someone with a right-to-left shunt.

### CARING FOR OUR PATIENTS

Knowing that genetic abnormalities can put people at increased risk for stroke, particularly with concomitant oral-contraceptive use or hormone-replacement therapy, one might consider testing all women before initiating treatment with estrogen. However, given the low overall risk for stroke, even with these mutations, this probably would not be a cost-effective approach (Vandenbroucke et al. 1996).

Nonetheless, there are certain populations of women who might benefit from screening—for example, women with relatives who have had clinical events such as stroke, myocardial infarction, and deep-vein thrombosis, and were subsequently found to have a genetic predisposition to thrombosis. It is, therefore, essential for physicians to take a careful family history before prescribing estrogen-containing drugs. Women with a positive family history might benefit from screening and education about the risk of using certain contraceptives or estrogen therapies (Vandenbroucke et al. 1996).

In general, all women should be properly educated about the risks of supplemental estrogen when they are considering their options for contraception. There are other methods of birth control, including progesterone-only oral contraceptives, that are not associated with increased risk of stroke (Ropper and Brown 2005).

Regarding pregnancy, the overall risk of stroke is very low and screening does not seem to be realistic. Only women with a concerning level of risk, such as a familial trait, should consider screening.

Even in women who are not at excessive risk for stroke or thrombosis, hormone-replacement therapy should be avoided. It seems that the risks outweigh the potential benefits of such treatment. Those with disabling menopausal symptoms should take the lowest possible dose for the shortest possible amount of time. Hormone-replacement therapy should certainly not be used as a method of reducing the risk of cardiac events, as the therapies appear to have the opposite effect.

The Role of Hormones in Women's Stroke Risk

CONCLUSIONS

Women should exercise caution when considering estrogen supplements, particularly if they have other risk factors for thrombosis. As they would for any therapy, women should carefully weigh the risks and benefits of using certain drugs and should be educated about stroke, as well as heart disease, cancer, and osteoporosis.

Physicians and scientists should continue to research both the long-term and short-term effects of current birth-control methods and postmenopausal treatments, and explore newer, safer techniques. Clinicians should continue to read and critically analyze the literature in order to better serve and educate their patients.

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