# Preeclampsia Tied to Offspring's Stroke Risk

BY HEIDI SPLETE
*Senior Writer*

WASHINGTON — A maternal history of preeclampsia may identify adults who are at increased risk for stroke: Adults whose mothers had severe preeclampsia were almost twice as likely to have strokes as were adults whose mothers did not have preeclampsia, based on data from more than 6,000 singleton pregnancies in Finland.

This study is one of the first to examine the long-term health risks of the offspring of women who had preeclampsia, Dr. Eero Kajantie said at the annual congress of the International Society for the Study of Hypertension in Pregnancy. "We know surprisingly little about which pregnancy conditions are associated with increased risk for coronary heart disease and stroke" among offspring.

Previous studies have shown that these women are at increased risk for coronary heart disease and stroke later in life. Also, their children are prone to high blood pressure during childhood, said Dr. Kajantie of the National Public Health Institute in Helsinki. Dr. Kajantie and his colleagues based their conclusion on a review of data from 6,410 members of the Helsinki Birth Cohort, who were born as singletons between 1934 and 1944.

Overall, 284 pregnancies (4.4%) were complicated by preeclampsia and 1,592 (24.8%) met criteria for hypertension without proteinuria. Among the children of these pregnancies, 464 (7.2%) had a diagnosis of coronary heart disease and 272 (4.2%) had a diagnosis of stroke. Diagnoses of CHD and stroke were collected from national hospital discharge records and death registries. The risk of stroke was almost twice as likely in the 164 adults whose mothers had severe preeclampsia (hazard ratio, 1.7), after the researchers controlled for sex, low birth weight, and gestational age.

The researchers also found that hypertension was a significant predictor of stroke, but was not a significant predictor of CHD.

Dr. Kajantie stated that he had no financial conflicts to disclose.■

# Immunodrugs Compared On Pregnancy Outcomes

BY HEIDI SPLETE
*Senior Writer*

WASHINGTON — Perinatal outcomes were slightly, but not significantly, better in renal transplant recipients who were immunosuppressed with cyclosporine, compared with those given azathioprine, according to findings from a study involving 59 pregnant women at a single research center.

"There are no described rates of maternal mortality for women with renal transplants," noted Dr. Vicenç Cararach, who presented study results at the annual meeting of the International Society of Obstetric Medicine.

Dr. Cararach and colleagues at the University of Barcelona compared 27 patients who were treated with azathioprine and prednisone (1973-1991) and 32 patients who were treated with cyclosporine and prednisone (1992-2007).

Overall, 3 patients (11%) in the azathioprine group and 2 patients (6%) in the cyclosporine group delivered at less than 32 weeks' gestation. An average of 13 infants in each group had birth weights below 2500 grams.

There were no maternal deaths in either group, and the three reported perinatal deaths all occurred in the azathioprine group.

More cases of premature rupture of membranes occurred in the azathioprine group, while more cases of preeclampsia and intrauterine growth restriction were found in the cyclosporine group.

Although these differences were not significant because of the limited number of cases, "it does not mean that they were not clinically important," Dr. Cararach noted.

Creatinine levels during pregnancy were similar between the two groups, he said. However, 3 years after pregnancy, creatinine levels were higher in the cyclosporine group, which raises some concerns about renal function with long-term cyclosporine use, Dr. Cararach added.

The results support those from previous studies demonstrating that perinatal outcomes are generally positive among renal transplant recipients, he said.

However, the elevated risk of premature birth remains a concern. And there are long-term risks for hypertension and infection that deserve further study, he noted.

Dr. Cararach stated that he had no financial conflicts of interest. ■

## DRUGS, PREGNANCY, AND LACTATION

# Cigarette Smoking Cessation

BY GERALD G. BRIGGS, B.PHARM, FCCP

The rate of cigarette smoking during pregnancy has declined to about 11%, but the prevalence is higher among younger (under 20 years) and older (over 35 years) women. Smoking remains a significant cause of embryonic, fetal, neonatal, infantile, and adolescent toxicity that includes growth restriction, a small increased risk for some birth defects, functional-neurobehavioral deficits, and death. In the 8th edition of my book, "Drugs in Pregnancy and Lactation," smoking is cited as a major cause of such pregnancy complications as premature birth, placental abruption, placenta previa, and premature rupture of the membranes (Philadelphia: Lippincott Williams & Wilkins, 2008). Because there is a dose-effect relationship between smoking and these toxicities, attempts should be made to stop, or at least reduce, smoking during pregnancy. Unfortunately, cigarette smoking is heavily addictive and is a challenge to overcome for many patients.

The primary intervention strategy is nonpharmacologic (counseling, acupuncture, and hypnotherapy). A 2005 American College of Obstetricians and Gynecologists Committee Opinion detailed a counseling intervention known as the 5 A's: Ask, Advise, Assess, Assist, and Arrange (Obstet. Gynecol. 2005;106:883-8), which also provided a number of resources for smoking cessation. The few studies that have been conducted with acupuncture and hypnotherapy have not clearly shown these therapies to be more effective than placebo for smoking cessation; larger and better-designed studies are warranted (Clin. Obstet. Gynecol. 2008;51:419-35).

Pharmacologic therapy may be required if intensive counseling is not successful. Pharmacologic interventions include varenicline (Chantix); nicotine replacement therapy (NRT) with patches, gum, lozenges, inhalers, and nasal sprays); antidepressants, such as bupropion (Zyban, Wellbutrin); and nonspecific therapies.

Varenicline was approved for smoking cessation by the Food and Drug Administration in 2006. Its mechanism is unique in that it prevents nicotine from binding to nicotinic acetylcholine receptors. Although reproduction studies in animals are reassuring, there are no human pregnancy data. Nevertheless, if a woman requires this therapy to stop smoking, the risk-to-benefit ratio appears to favor use of the drug.

The use of NRT in pregnancy is controversial. Nicotine is the primary chemical derived from smoking and it is a toxin. As noted above, smoking is known to increase the risk of developmental toxicity, which could potentially occur with NRT. Although nicotine patches produce nicotine serum levels that are similar to smoking, they prevent exposure to other toxins, such as carbon monoxide, cyanide, dioxin, cadmium, thiosulfate, and the more than 3,000 additional compounds that have been identified in cigarette smoke. Removal of the patch at night before going to sleep will reduce nicotine serum levels for part of the day. Nicotine gum, lozenges, inhaler, and nasal spray produce lower maternal nicotine serum levels but they may cause adverse effects—poor taste (gum and lozenges) and throat and nasal irritation (inhaler and spray)—which might reduce compliance.

One study found a nonsignificant increase overall in birth defects in the offspring of women using NRT, compared with women who did or did not smoke (Obstet. Gynecol. 2006;107:51-7). Significant increases, though, were found in cleft lip and in defects of the digestive tract and cardiovascular system. The authors concluded that the data suggested an increased risk of defects but that their study could not prove or exclude causality.

Bupropion is approved by the FDA for smoking cessation; it seems to be effective in reducing withdrawal, weight gain, and cravings. Adverse effects, such as insomnia, dry mouth, and an increased risk of seizures, can be problems, but the drug is more effective than NRT and does not expose the mother or the embryo-fetus to nicotine. The bupropion birth defect registry (now closed) collected data from 1997 to late 2007. After reviewing 1005 prospective pregnancy outcomes, the registry was able to exclude a major teratogenic effect. However, the registry was not designed to exclude an increase in the risk of specific defects (http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf).

Nonspecific therapies include the antihypertensive/central analgesic clonidine, the narcotic antagonists naloxone and naltrexone, and melatonin. However, these therapies have not been very effective in stopping smoking. Melatonin has not been studied in pregnancy or in lactation and should be avoided.

Smoking decreases the duration of breastfeeding and exposes the nursing infant to nicotine and other toxins by both inhaled and oral routes. If the mother cannot stop smoking, she should at least be encouraged to not smoke around the infant or while nursing. There is no clear answer to the use of NRT during lactation because the risks to the infant have not been defined. Because patches can provide high levels of nicotine in milk, other forms of NRT might be preferred. Varenicline is probably excreted into milk and could potentially cause adverse effects in the nursing infant. Bupropion is excreted into milk and, in the case of one infant exposed via breast milk, no adverse effects or drug were observed or found.

Counseling is the preferred treatment for smoking cessation in pregnancy and lactation but, if not effective, bupropion would be my first choice for pharmacologic therapy, followed by varenicline and then NRT. However, I would avoid NRT in the first trimester. All these options are superior to continued cigarette smoking.

MR. BRIGGS *is a pharmacist clinical specialist, Women's Pavilion, Miller Children's Hospital, Long Beach, Calif.; a clinical professor of pharmacy, University of California, San Francisco; and an adjunct professor of pharmacy, University of Southern California, Los Angeles.*