Studies Link Preeclampsia, Cardiovascular Disease

The two disorders are thought to have a common pathogenesis that is rooted in shared risk markers.

BY JONATHAN GARDNER
London Bureau

Women who have had preeclampsia are at increased risk of cardiovascular disease later in life, suggesting that they should be targeted for primary prevention, according to a British review published online in the British Medical Journal.

Meanwhile, an accompanying population-based prospective study in Norway suggests that cardiovascular risk factors are associated with a higher risk of preeclampsia.

"The underlying link between preeclampsia and cardiovascular disease is unclear. Although preeclampsia may initiate endothelial damage, it is thought to be more likely that preeclampsia and cardiovascular disease have a common pathogenesis rooted in shared risk markers," wrote Dr. Laura Magee and Dr. Peter von Dadelszen of the University of British Columbia, Vancouver, in a commentary accompanying the two studies (BMJ 2007 Nov. 2 [Epub doi.10.113/bmj.39337.427500.80]).

In the first study—a review of cohort studies in all languages between 1960 and 2006 covering more than 3 million women—British researchers found an increased risk for vascular disease among women who'd had preeclampsia, compared with those who never had the disorder. The relative risks for women with a history of preeclampsia were 3.7 for hypertension after a mean weighted follow-up of 14 years, 2.2 for ischemic heart disease after 12 years, 1.8 for stroke after 10 years, 1.8 for venous thromboembolism after almost 5 years.

No increase in the risk of any cancer was found, including breast cancer, after 17 years, wrote Leanne Bellamy, a medical student at Imperial College School of Medicine, London, and her associates (BMJ 2007 Nov. 2 [Epub doi:10.1136/bmj.39335.385301.BE]).

The overall risk of mortality was elevated following preeclampsia, with a relative risk of 1.49 after 14.5 years.

"We must recognise that these women are still young, their absolute risk of cardiovascular disease is low over the short term, and their risk will evolve over subsequent decades," wrote Dr. Magee and Dr. von Dadelszen in their commentary. "As such, we have an opportunity for primary prevention, especially as cardiovascular disease is largely preventable."

They added, however, that the findings so far do not help physicians guide their primary prevention strategy. No evidence supports how to screen younger women for risk factors, and while recommending lifestyle change is good for all patients, such a recommendation "is not enough to change their behavior," the authors wrote. "However, women might be more receptive if they have had a complicated pregnancy. Perhaps we could tailor the advice to women with newborns and young children," they wrote.

'We found that cardiovascular risk factors that were present years before pregnancy are associated with a risk of preeclampsia.'

The Norwegian study tracked 3,494 women who gave birth after participating in the Nord-Trøndelag health study to link cardiovascular risk factors and preeclampsia risk. The women were linked to diagnoses for preeclampsia through the Norway birth registry (BMJ 2007 Nov. 2 [Epub doi:10.1136/bmj.39366.416817.BE]).

After adjustment, the odds ratio for preeclampsia in women with a baseline systolic blood pressure greater than 130 mm Hg (highest fifth) was 7.3, compared with those with a systolic blood pressure less than 111 mm Hg (lowest fifth). Similarly, the odds ratio for women with a diastolic blood pressure greater than 78 mm Hg was 6.3, compared with those whose diastolic pressure was less than 64 mm Hg.

Women who were overweight or obese had a higher risk of preeclampsia than did women of normal weight, and the risk for preeclampsia rose with increasing waist circumference.

In addition, there was a weak association between pregnancy lipid levels in the clinically normal range and preeclampsia, and a stronger association with lipid levels above the normal range.

"We found that cardiovascular risk factors that were present years before pregnancy are associated with a risk of preeclampsia," wrote Elisabeth Balstad Magnussen, a research fellow at the Norwegian University of Science and Technology, Trondheim, and associates. "This finding suggests that unfavourable cardiovascular and metabolic profiles may represent primary causes of preeclampsia and that these factors predispose both to preeclampsia and to subsequent cardiovascular disease. This does not, however, rule out the possibility that the pre-eclamptic process in itself may also contribute to cardiovascular risk." ■

Outcomes 'Reassuring' After Repeated Prenatal Steroids

BY MARY ANN MOON
Contributing Writer

Repeated courses of prenatal corticosteroids in pregnant women at high risk of preterm delivery do not appear to have adverse effects on neurocognitive or physical development of the child at 2 years of age, compared with a single course, investigators in two large randomized clinical trials reported.

Both research groups termed these findings "reassuring," given that repeated doses have already become commonplace in the United States, the United Kingdom, and Australia.

U.S. clinicians have widely adopted weekly intramuscular injections of corticosteroids in high-risk pregnancies, even though there is insufficient data to support this practice. Moreover, animal and observational human studies have suggested that repeated steroid injections may inhibit the offspring's growth, impair brain development, predispose to neurosensory disability, increase aggression and hyperactivity, and raise blood pressure, investigators noted.

Survival rates free of major disability were similar in children whose mothers received repeated steroid injections and those whose mothers received placebo.

Current guidelines recommend repeated corticosteroid courses only in subjects participating in large randomized, controlled clinical trials to assess both short-term and long-term safety and efficacy of the treatment. Two such clinical trials are the Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) and a National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network trial.

Investigators in both studies previously reported their findings in neonates who were exposed to either a single dose or weekly repeated doses of steroids. Both studies showed better neonatal outcomes after repeated doses, with less need for mechanical respiratory support and surfactant use, less respiratory distress syndrome, and less serious neonatal morbidity.

Both studies also raised concerns about lower birth weight and smaller head circumference after repeated doses, however, and suggested that short-term benefits in lung maturation might be offset by possible long-term deficits in neurologic development and physical growth. Both research groups now report normal physical and neurocognitive outcomes in the same subjects at age 2-3 years.

In the ACTORDS study, Dr. Caroline A. Crowther of the University of Adelaide (South Australia) and her associates assessed 1,047 children who had been delivered at 23 medical centers.

Women who received an initial course of steroids at least 7 days earlier were randomly assigned to receive an injection of 11.4 mg betamethasone or saline placebo. The dose was repeated weekly if the mother remained at risk of preterm delivery and gestation was less than 32 weeks.

The rates of survival free of major disability were similar in children whose mothers had received repeated steroid injections and those whose mothers had received placebo injections (84% vs. 81%).

There also were no significant differences between the two groups in weight, height, or head circumference; blood pressure; the use of health care resources; mortality; neurosensory impairments such as cerebral palsy, blindness, or developmental delay; or behavioral factors such as emotional reactivity, anxiety, depression, aggression, or sleep problems.

There were more attention problems and more aggression among children exposed to repeated injections, but those associations may have been due to chance, Dr. Crowther and associates said.

Further follow-up is crucial, because other important cognitive outcomes, such as executive function, cannot be determined until the children reach school age.

Still, the investigators noted that "clinicians may wish to consider the use of a single injection of Celestone Chronodose, or equivalent, repeated weekly, if the woman remains at risk for very preterm delivery" 7 days after receiving an initial course (N. Engl. J. Med. 2007;357:1179-89).

In the MFMU study, Dr. Ronald J. Wapner of Columbia University, New York, and his associates assessed 248 children aged approximately 30 months who had been exposed to repeated corticosteroid courses in utero (12 mg given intramuscularly and repeated at 24 hours) and 238 who had been exposed to a single steroid course initially and repeated placebo courses later.

As in the ACTORDS trial, the MFMU researchers found no significant differences between the two groups in anthropomorphic measures; scores on mental and psychomotor tests; blood pressure; or other health outcomes such as seizures, pneumonia, and the need for hospitalization during infancy.

They did find an increased frequency of cerebral palsy in children who had been exposed to repeated courses of corticosteroids, compared with a single course (2.9% vs. 0.5%). Although this difference was not statistically significant, it is still cause for concern, Dr. Wapner and his associates said (N. Engl. J. Med. 2007;357:1190-8).

Like the ACTORDS investigators, the MFMU researchers emphasized that further follow-up of these subjects through later childhood is critical.

And although they characterized these findings as "reassuring," Dr. Wapner and his associates concluded that their results argue against giving repeated prenatal corticosteroids until more data are collected.

This approach may improve the condition of the neonate, but it does not convey long-term benefit and may cause possible harm in later life, they said. ■