

## Podocyturia in Pregnancy Gets New Look

By Tracy Hampton

Hypertension or preeclampsia during pregnancy, while often asymptomatic, can threaten the health of women and their babies. Two Mayo Clinic studies presented at the ASN's Kidney Week 2011 provide new information related to these conditions.

Vesna Garovic, MD, and her team examined the potential of a test done mid-pregnancy to predict which women will later develop preeclampsia, a late-pregnancy disorder that is characterized by hypertension and proteinuria that affects 3 percent to 5 percent of pregnancies. Left untreated or without careful monitoring, preeclampsia can lead to serious—even fatal—complications for a pregnant woman and her baby.

The researchers previously showed that podocyturia, the shedding of live kidney cells called podocytes, is present at delivery in patients with preeclampsia. In this study, they tested whether podocyturia is predictive of later development of preeclampsia, and whether it can differentiate among normotensive pregnancies, gestational hypertension, and preeclampsia. For the analysis, urine sediments are cultured for 24 hours to select for viable cells, and podocytes are then identified on the basis of podocin staining.

Among a group of 315 patients in the study, 15 developed preeclampsia and 15 developed gestational hypertension (but not preeclampsia) during pregnancy. All of the patients who developed preeclampsia tested positive for podocyturia in mid-pregnancy (prior to 210 days gestation). None of the study participants with only hypertension tested positive, and none of 44 women with normal pregnancies tested positive.

The test is highly accurate for predicting preeclampsia, which could alert clinicians to take steps to safeguard against the condition in their patients. The test could also differentiate between later development of gestational hypertension and preeclampsia. The high accuracy of this test further supports the role of podocyte loss in the mechanism of proteinuria in preeclampsia.

"Preeclampsia is well recognized as an endothelial cell disease; however, the precise mechanism of proteinuria has remained somewhat elusive," said Michelle Hladunewich, MD, who was not involved with the research and is a clinical investigator in the divisions of nephrology, critical care, and obstetric medicine at Sunnybrook Health Sciences Center in Toronto. "Although widespread feasibility of the measurement of podocytes in the urine as a predictive marker for preeclampsia is likely limited, these novel insights into the pathophysiology of preeclampsia particularly as it relates to the cross talk between the endothelial cell and the podocyte are most interesting."

Garovic also led another study that looked at the long-term health effects of hypertensive disorders during pregnancy. Her team identified all female residents of Rochester, Minn., and the surrounding townships in Olmsted County who delivered between 1976 and 1982. The women were categorized into two groups: those with hypertensive disorders during pregnancy and those without. The investigators followed the women after they reached 40 years of age to monitor their heart and kidney health.

A total of 6051 mothers delivered between 1976 and 1982, and 607 women had hypertensive pregnancy disorders at the time while 5444 did not. Follow-up after age 40 years was available for 465 (77 percent) cases and 3898 (72 percent) controls. After the women reached age 40, women who had hypertensive disorders during pregnancy were much more likely to experience hypertension, kidney dysfunction (proteinuria, chronic kidney disease, or end stage renal disease), and strokes than women who did not have hypertensive disorders during pregnancy (51 percent vs. 31 percent, 14 percent vs. 10 percent, and 8 percent vs. 4 percent, respectively).

"Studies of the associations of hypertensive pregnancy disorders with maternal risks for future cardiovascular disease could lead to new guidelines for screening and treatment of women at risk, with the ultimate goal of improving cardiovascular health in women," Garovic said. ●

## Fish Oil Cuts Loss of Graft Patency and Cardiovascular Events in Dialysis Patients

For patients with a hemodialysis graft, daily fish oil substantially reduces the frequency of developing stenosis, thrombosis, and cardiovascular complications. That's the message from a large, randomized, placebo-controlled study presented at Kidney Week in November.

The results, according to lead investigator Charmaine Lok, MD, should prompt a fresh look at grafts and the potential of fish oil to improve patient outcomes in hemodialysis. Lok is associate professor of medicine at the University of Toronto and medical director of the Hemodialysis Vascular Access Program at Toronto General Hospital.

Each type of hemodialysis access has its problems, Lok noted, with stenosis and thrombosis being the major problems with grafts. These problems have led to an increasing use of fistulas, but over the past decade, she said, it has become apparent that fistulas often fail, with estimates of failure rates ranging up to 60 percent.

The reasons for stenosis are not entirely clear, although multiple factors are likely involved, including trauma during surgery or during treatment. "It has been known for a long time that fish oil has benefits in cardiovascular disease," Lok said, dating back to studies on Eskimo populations in Greenland, who have very low levels of cardiovascular disease. Fish oil reduces endothelial dysfunction through several mechanisms, including reduction of inflammatory cytokines and inhibition of endothelin-1, which constricts blood vessels.

That led Lok to wonder if fish oil might also have a beneficial effect on blood vessels elsewhere in the body, including the vessels supplying the graft. A small study in 2002 suggested that might be the case, with treatment increasing graft patency fivefold versus placebo over 12 months.

For her study, Lok recruited patients with patent grafts a week after their surgery. Patients were randomized to receive placebo or fish oil at 4 grams per day for 12 months, during which they underwent biweekly follow-up visits to assess patency, and every 3 months to monitor lipid profiles, blood pressure, and cardiovascular events. The study was conducted at 12 sites in Canada and 3 sites in the United States.

The primary outcome was the proportion of patients with loss of patency within 12 months, as evidenced by having either a thrombosis or need for an intervention to maintain graft patency. "Either you have an event or you don't—that's the most conservative endpoint," she said. Prespecified secondary outcomes included the individual rates of thrombosis or need for intervention to restore patency, the time to thrombosis, and changes in

blood pressure, lipid profile, and cardiovascular medications.

The study was designed to enroll 232 patients, but, Lok said, "We had a very hard time recruiting patients, because of the push for fistulas" within the last several years. In the end, she enrolled 201 patients, of whom 101 received fish oil. Patients had a mean age of 62 years, and were well matched except for a higher proportion of congestive heart failure in the fish oil group. That imbalance increased the challenge for active treatment to show benefit, she said, but also meant that a positive result might be more meaningful.

On the primary outcome measure, 48 percent of patients in the fish oil group, and 62 percent in the placebo group, had loss of patency. The difference was just shy of statistical significance, with a p value of 0.06.

Fish oil was superior on almost all the secondary outcome measures. The rate of thrombosis or need for intervention per 1000 days was 3.43 for fish oil, versus 5.95 for placebo ( $p < 0.001$ ). The median time to thrombosis was twice as long for patients on fish oil, and the rate of thrombosis was half, with 1.7 events per 1000 days for patients on fish oil, versus 3.4 for placebo ( $p < 0.001$ ). The rate of any cardiovascular event in patients on fish oil was less than half that of patients on placebo. Blood pressure was reduced, as were medications. Lipid profiles were not different between the groups, perhaps, Lok said, because baseline levels were relatively low, making it difficult for treatment to have much effect.

The failure of treatment to significantly affect the primary endpoint, while providing clear superiority on many clinically important secondary ones, suggests to Lok that, in hindsight, an alternative primary endpoint may have been better. Patients who have an event may continue to use their graft, she noted, and so at that point, the more important clinical question is, "For the duration of the access, how many of these events are you going to have? From a patient and healthcare payer perspective, that is probably the more important endpoint. An intervention is extremely expensive, and inconvenient and painful for the patient."

"Is there a role for grafts in hemodialysis? There absolutely is," Lok said. "After a decade of promoting fistulas, we are finding out there is a high failure rate. For patients who are not eligible for fistulas, grafts are a good alternative."

We were very excited about the cardiovascular outcomes," Lok said, and her group is currently pursuing a larger study in dialysis patients to formally study the effect of fish oil on these events. ●