

A Mouthful of Evidence

What's the link between periodontal disease and low-weight babies?

Pre-term and low-weight babies enter a different world from normal newborns. “Preemies” begin their lives in a world populated with incubators to keep them warm, ventilators to help them breathe. Often, the infants are subjected to phototherapy, a special light that bathes their body to metabolize a reddish-yellow pigment that can cause jaundice.

The vessels of preemies are so fragile that brain-bleeding is possible, and infection is a constant risk. These are only some of the dangers. And working to avert them has a price tag: when a premature baby is admitted to a neonatal intensive care unit, it costs an average of \$30,000 more than if the baby were healthy.

Nationally, an average of 12 percent of births are pre-term, and 8 percent of infants born have a low birth weight. In Kentucky, more than 4,000 infants are premature each year. Prematurity—which has increased by 27 percent in the United States since 1981—is the leading cause of death in this country within the first month of life.

Why some women cannot carry to full-term is not always clear.





Trying to Connect Cause and Effect

Doctors will tell you that the cause of low-weight births may be biological, chemical, genetic, or a combination of factors. At the University of Kentucky, researcher Jeffrey Ebersole, associate dean for research in the College of Dentistry, believes there may be another cause: periodontal disease.

In previous studies, researchers found that expectant mothers with periodontal disease may have a three- to seven-times greater risk of giving birth to premature and low-weight babies, and these findings made Ebersole want to investigate this possible link.

While important, findings from these studies are only “associational,” he says, and do not prove cause and effect. “There are little data distinguishing whether the two problems are linked by causation or due to the same underlying risk factors,” says Ebersole, who

also serves as director of UK’s Center for Oral Health Research. Now, backed by a five-year, \$3.3 million grant from the National Institutes of Health, he is working to find a link between periodontal disease and low-weight babies. “Our goal is simple: we want to help make it possible for mothers to give birth to healthy, normal babies.”

In trying to establish this cause/effect connection, Ebersole first needs to understand the cause of periodontal disease, an inflammatory condition of the gums and bone supporting the teeth that can ultimately lead to an erosion of the gums and the loss of teeth. So he’s starting with bacteria that live in the mouth.

As far as bacteria are concerned, the mouth, home for more than 400 types of bacteria, is the perfect host. Some of these bacterial guests are good guys that live in the mouth symbiotically

and play a part in defending the body against infection by harmful bacteria. Other bacteria could kill us and—if they found their way via the bloodstream superhighway to other parts of the body, such as the brain, liver and heart—they would.

Under certain circumstances, the harmful bacteria may cause periodontal disease. But precisely which factors trigger bacteria to cause this disease is still a scientific mystery, Ebersole says.

“For decades, there appeared to be an easy answer: If you didn’t brush your teeth, you’d get periodontal disease. But we now know that this answer is generally wrong,” he says.

“There’s no doubt that if you brush your teeth and floss, you will improve the health of your gums. But there is clearly a portion of the population that has very poor oral hygiene and yet does not get periodontal disease. There is also evidence that some people can take very good care of their teeth—brushing and flossing—and still get this disease. So it’s not just a matter of the amount of bacteria in the mouth.”

In trying to solve the mystery of periodontal disease, scientists become detectives. First, they identify potential suspects—individual bacteria—and examine them to determine their possible relationship with the disease. In this work researchers aren’t starting from scratch. By now, the usual suspects in periodontal disease have been implicated in an array of medical problems.

Secondly, scientists are looking at known accomplices such as inflammation and genetics. The researchers hope these investigations will help them

discover what causes periodontal disease, an important step to prove the further cause and effect between the disease and the incidence of pre-term and low-birthweight infants.

A Little Help from Baboons

In collaboration with the University of Texas Health Sciences Center at San Antonio and The Forsyth Institute in Boston, Ebersole is attacking the problem from another direction, too. He is studying samples from pregnant baboons.

“Baboons were chosen for several reasons,” Ebersole says. “They develop periodontal disease similar to humans, they are a tough animal, the mother/child bond is stronger than with many other primates, and there is an available colony of about 3,500 baboons at the National Primate Research Center in San Antonio.”

Ebersole and his collaborator, Lakshmyya Kesavalu, a veterinary researcher at UK’s Center for Oral Health Research, are studying the effects of periodontal disease on pre-term birth in the animals.

Research began in July 2002, with samples from a group of 37 baboons. Ebersole will be making three or four trips to San Antonio each year during this project to collect clinical, microbiological and blood samples. The blood samples will then be brought to UK for study. Ebersole expects the study to be completed in 2007.



Mothers-to-Be Take a Research Role

Ebersole’s UK colleague John Novak, professor and associate director of the Center for Oral Health Research, is the principal investigator at UK for a \$7 million study, a human-subjects counterpart to the work Ebersole is doing with baboons. In this first-ever national, multi-center study, Novak and his team will examine pregnant women who already have periodontal disease in a project being funded by the National Institute of Dental and Craniofacial Research.

Jeffrey Ebersole (left) and John Novak in the College of Dentistry are investigating the link between periodontal disease in expectant mothers and low birthweight of their babies. In previous studies, other researchers found that expectant mothers with periodontal disease may have a three- to seven-times greater risk of giving birth to premature and low-weight babies.

“Our goal is simple: we want to help make it possible for mothers to give birth to healthy, normal babies.”

—Jeffrey Ebersole

Delta Dental Ensuring Further Clinical Research

The Delta Dental Plan of Kentucky Clinical Research Center was created in October 2002 with a \$750,000 endowment from Delta Dental, an amount matched by the Kentucky Research Challenge Trust Fund. The center will combine the expertise of medical and dental researchers with research groups around the country, and will serve as a focal point for interdisciplinary research.

The University of Louisville received a similar gift, boosting Delta Dental's investment in oral health research in Kentucky to \$1.5 million. At UK, the center will be the clinical arm of the Center for Oral Health Research, which Jeffrey Ebersole directs.

“The establishment of these centers immediately gives us a greater opportunity to develop and implement collaborative clinical and translational research with investigators in Kentucky, across the country and around the world,” Ebersole says.

The University of Minnesota is leading this study, with research partners at UK, the University of Mississippi and Columbia University. Each university is recruiting 200 patients into the study. Half of the mothers will be treated for periodontal disease during their second trimester and the other half treated after giving birth.

At UK, the research is being done in collaboration with the Department of Obstetrics and Gynecology's High-Risk Maternal Fetal Medicine Clinic. James Ferguson, department chair of obstetrics and gynecology, is a co-investigator on the study. It is the first large, federally funded study to be done as part of the new Delta Dental Plan of Kentucky Clinical Research Center located in the College of Dentistry.

“This is primarily an intervention study,” says Novak. “We will be treating periodontal disease as an infection, then seeing what effect that has on the delivery of the child relative to the adverse outcomes that are associated with pre-term delivery.” He says the primary question is, “Does the mother deliver prematurely?” The secondary question is, “What impact does it have on the baby?”

The researchers began recruiting patients in March 2003 for the study, which will take two to three years to complete. “What we really don't understand is what types of oral infection are associated with pre-term birth,” says Novak. “Is every woman who has an infection in her mouth, who has plaque in her mouth, liable to deliver her baby pre-term? Well, we know this isn't true. Most women deliver normally. So we are also very interested in the types of

infections that make up their dental plaque and the types of bacteria that are colonizing their mouth.”

Novak is targeting seven or eight bacteria, the same ones implicated in many other problems. Interestingly, one of the oral bacterial species may be associated with early fetal loss in horses, a condition called Mare Reproductive Loss Syndrome. Novak and Ebersole are also planning collaborative studies with the College of Agriculture's Department of Veterinary Science to look at the potential contribution of oral infections to fetal deaths in horses.

“Veterinarians have identified a specific organism in the horse that is very closely related to an oral organism in humans,” Novak says. “They don't know how this organism gets from the horse's mouth to the fetus and may create this problem, but they have already isolated the organism from the fetal membranes.”

Novak says this organism, a member of the bacterial family *Actinobacillus*, is closely related to an organism in humans that causes severe periodontal disease in young people. “It appears that similar biologic processes may be occurring in some pregnant mares,” he says.

Ebersole reiterates that the overall goal in his study and Novak's is to identify if there is a link between periodontal disease and pre-term, low-birthweight infants and, if so, how strong this link is. The next step, he says, is to intervene in that process to lower the risk of pre-term birth. “Eventually we hope to have this treated as a public health measure so that every expectant mother receives dental care as part of her prenatal care,” he says. ■

Oral Health and Aging

Infection, disease and aging are inextricably linked in the human health chain, according to John Novak, associate director of the Center for Oral Health Research at UK. He says infection and disease can affect the aging process, and the reverse is also true. “If you get a lot of infections, your body is constantly being stressed, and that may have an impact on aging. Conversely, the aging process itself may affect your susceptibility to disease,” he says.

Backed by a \$1.5 million grant from the National Institute on Aging (NIA), and in collaboration with researchers at the University of Maryland and the NIA, Novak is examining the role of infection and oral health in the aging process. In this work he and his colleagues are using Rhesus monkeys located at the NIA facility in Maryland.

“We’re using the oral cavity as a model to allow us to study infection, inflammation and disease by looking at aging primates on a lifetime calorie-restricted diet. Calorie restriction has been clearly demonstrated to decrease the aging process in rodents, and now these studies are being extended to non-human primates before progressing to human studies,” says Novak.

The first thing he is looking for is whether these animals have fewer infections and less disease than animals that don’t have such calorie restrictions. Then the researchers are going to analyze how these



animals respond to infection that leads to inflammation in the mouth and consequent periodontal disease. “Will those calorie-restricted animals, who are not aging as rapidly, respond better than those aging at a normal pace, and how does aging affect the inflammatory response and the disease process?”

Jeffrey Ebersole, director of UK’s Center for Oral Health Research, and Karen Novak, John’s wife and an associate professor of periodontics, are collaborating on this study.

“People continue to look for aging mechanisms and try to find a magic bullet to prolong life,” John Novak says, “but very few people have looked at chronic infection and inflammation as a package contributing to the aging process. We know that as people age, they are susceptible to more infections and certainly the infections and inflammation can put a stress on your body that may lead to premature aging.

“We are excited because we think we will have some major findings to contribute. With collaborative research, you broaden the impact by bringing together a wider range of expertise, and fresh ideas and perspectives.”