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WHAT EVERY WOMAN NEEDS TO KNOW

Growing evidence suggests that poor oral hygiene during pregnancy can adversely affect the health of newborns

BY STEVEN OFFENBACHER

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In 1981 Judith F. was referred to me

for periodontal care. She was very upset, having just discovered why her front teeth were shifting: she had been diagnosed with severe gum disease. Her dentist had explained to her that periodontal disease is sometimes a “silent” infection that may be painless and without symptoms until very late in the disease process. She had also recently miscarried after having a very difficult time conceiving. She recounted how her gums had flared up after she became pregnant, which prompted her to go to the dentist. As crazy as it might have sounded at the time, she was convinced that the simmering infection in her gums was somehow related to her pregnancy complications.

I suspected that her intuition may have been correct—but told her that we really did not know scientifically whether periodontal disease could cause pregnancy problems. However, I did tell her that both her obstetrician and I were in agreement that any infection during pregnancy is a potential cause for concern.

Just before Judith came to me, my laboratory had begun what would become a 25-year scientific inquiry exploring the potential role of periodontal disease in pregnancy complications. This research has included a multitude of laboratory experiments, animal studies, and randomized human clinical trials.

Today, growing evidence supports the concept that gum infection may indeed play a role in pregnancy complications, possibly inducing miscarriage and premature birth as well as inhibiting the growth and development of the unborn child. Clearly, there are many causes for problems that can arise during pregnancy; but it now appears that with additional research, oral infection might be added to the list of possible risk factors. From a public health perspective, what is most important is that periodontal disease is both preventable and treatable. As a clinician who is trying to help patients, I know that it is critical to identify new causes of disease—and to find ways to prevent them.

In one of our earliest experiments at Emory University in 1981, we gave hamsters intravenous doses of the toxins gen-

erated by oral bacteria. The result: at low doses, about 15 percent miscarried and 30 percent of the surviving offspring were abnormally small. When given high doses, 100 percent of the mothers miscarried. We later induced gum disease in pregnant hamsters. Overall, the resulting babies weighed 18 percent less than normal. We also found elevated levels of prostaglandin-E₂ (PGE₂) in the hamsters’ placentas—similar to the human physiological response to preterm delivery and low-weight births. This chemical is produced as a response to infection; it mediates inflammation in both the placenta and the fetus—and also can induce labor. Around that time, obstetrics research had linked PGE₂ to premature and low-weight SGA (small for gestational age) births.

In a landmark paper published in 2002, Nestor Lopez in Chile reported the results of his study of 400 pregnant women with periodontal disease: half had scaling and root planing periodontal treatment during pregnancy; the other half were treated after their babies were born. Just 1.8 percent of the treated women gave birth early, compared with 10.1 percent in the delayed treatment group.

Marjorie Jeffcoat at the University of Alabama also saw similar benefits in a study of 123 mothers with periodontal disease. After treatment, their rate of preterm delivery (earlier than 37 weeks) was 4.1 percent, compared with 13.7 percent in another group of 733

mothers with untreated periodontal disease who were also being tracked.

These findings provided the rationale for the National Institute of Dental and Craniofacial Research to support two multicentered, randomized clinical trials. One of these, the Obstetrics and Periodontal Therapy (OPT) Study at the University of Minnesota, led by Bryan Michalowicz, tracked the pregnancies of more than 800 pregnant women following gum disease treatment. The second trial, run by our group at the University of North Carolina at Chapel Hill, is entitled MOTOR (Maternal Oral Therapy to Reduce Obstetric Risk) and will ultimately follow 1,800 women. The findings from these large, randomized and controlled trials should ultimately prove whether or not gum disease can cause pregnancy complications. Earlier estimates from pilot studies suggest that up to 18 percent of all preterm births may be attributable to gum disease.

Unfortunately, pregnancy complications are far too common, with about one in 10 babies being born too early in the U.S.—nearly double the rate of other industrialized countries. Improvements in prenatal care and neonatal intensive care medicine have improved the survival rates of these babies, but the rate of premature delivery has steadily climbed since the 1950s. The failure to prevent preterm deliveries is due in part to the fact that we do not understand all of the risk factors, which include race, smoking, alcohol and drug

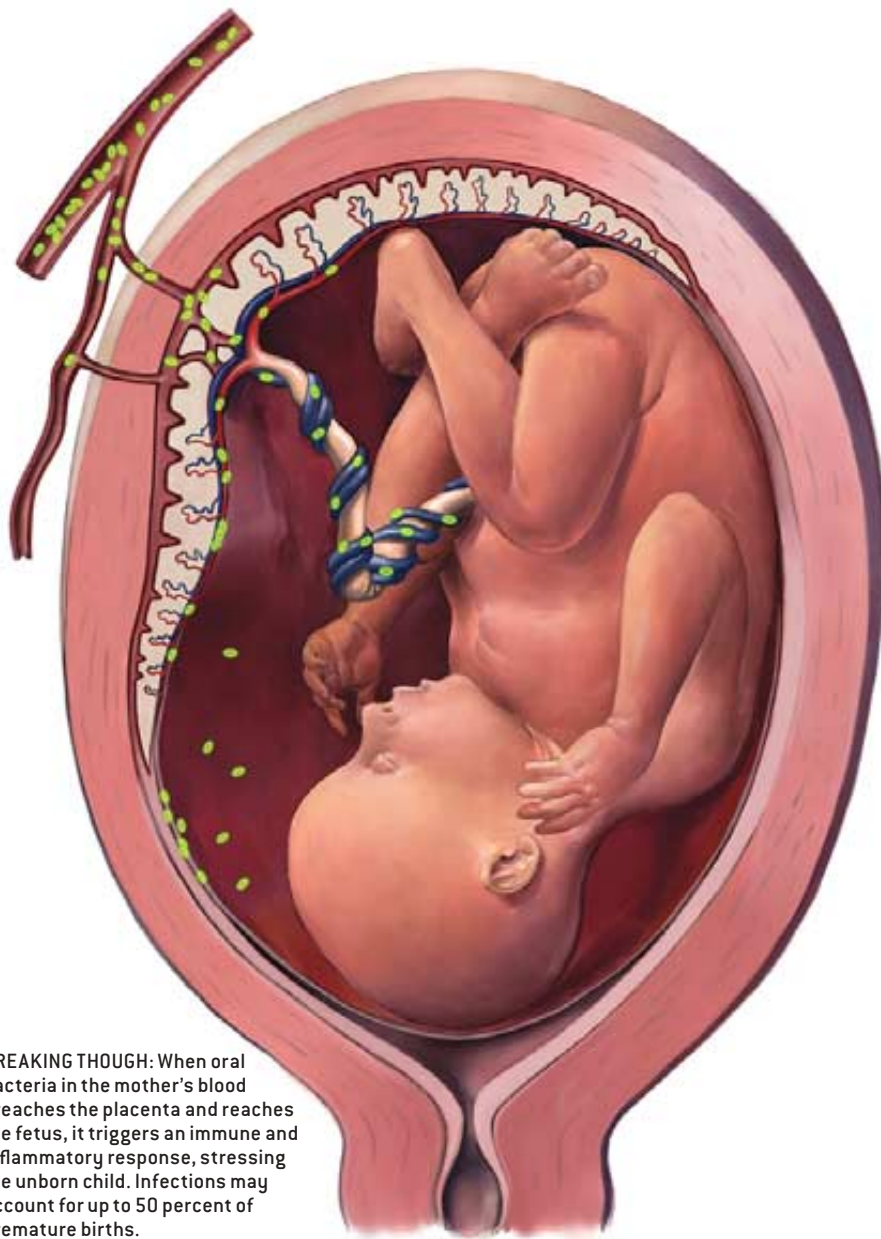
use, low income, and poor education, among others. More than one quarter of all complicated pregnancies occur for no known reason.

Periodontal disease may contribute to the common problems of pregnancy by presenting an infectious, inflammatory challenge to the fetus: when bacteria or their products slip through the placenta and reach the baby, they trigger an immune and inflammatory response—which stresses the fetus. Since pregnancy is such a critical time for human development, this could potentially have debilitating effects on an infant’s health, creating problems that could last a lifetime.

Infections are thought to account for between 30 and 50 percent of all premature deliveries. Maternal infections during pregnancy, especially when they spark a fever, have long been known to cause miscarriage, premature birth and babies that are born abnormally small for their gestational age. This is attributed to the fact that bacteria or viruses in the bloodstream trigger the production of infection-fighting chemicals that threaten the “mother-child unit” and impair fetal growth and development. The chemicals and hormones that mediate the inflammatory response can also dilate the cervix and trigger uterine contractions, leading to preterm labor.

But it’s not just infection and bacterial products that pose a threat—inflammation does, too. Inside the placenta, membranes normally remain intact, holding the fetus suspended in amniotic fluid until just hours before delivery when the water “breaks” to start labor. However, inflammation can make these membranes more fragile; their early rupture often initiates preterm labor.

When the placenta becomes inflamed, structural changes occur that can endanger the fetus and shorten gestation. Studies in mice have shown that placental inflammation causes edema and kills off tissue. It also can cause changes to the intertwined fetal/maternal blood vessels that resemble athero-



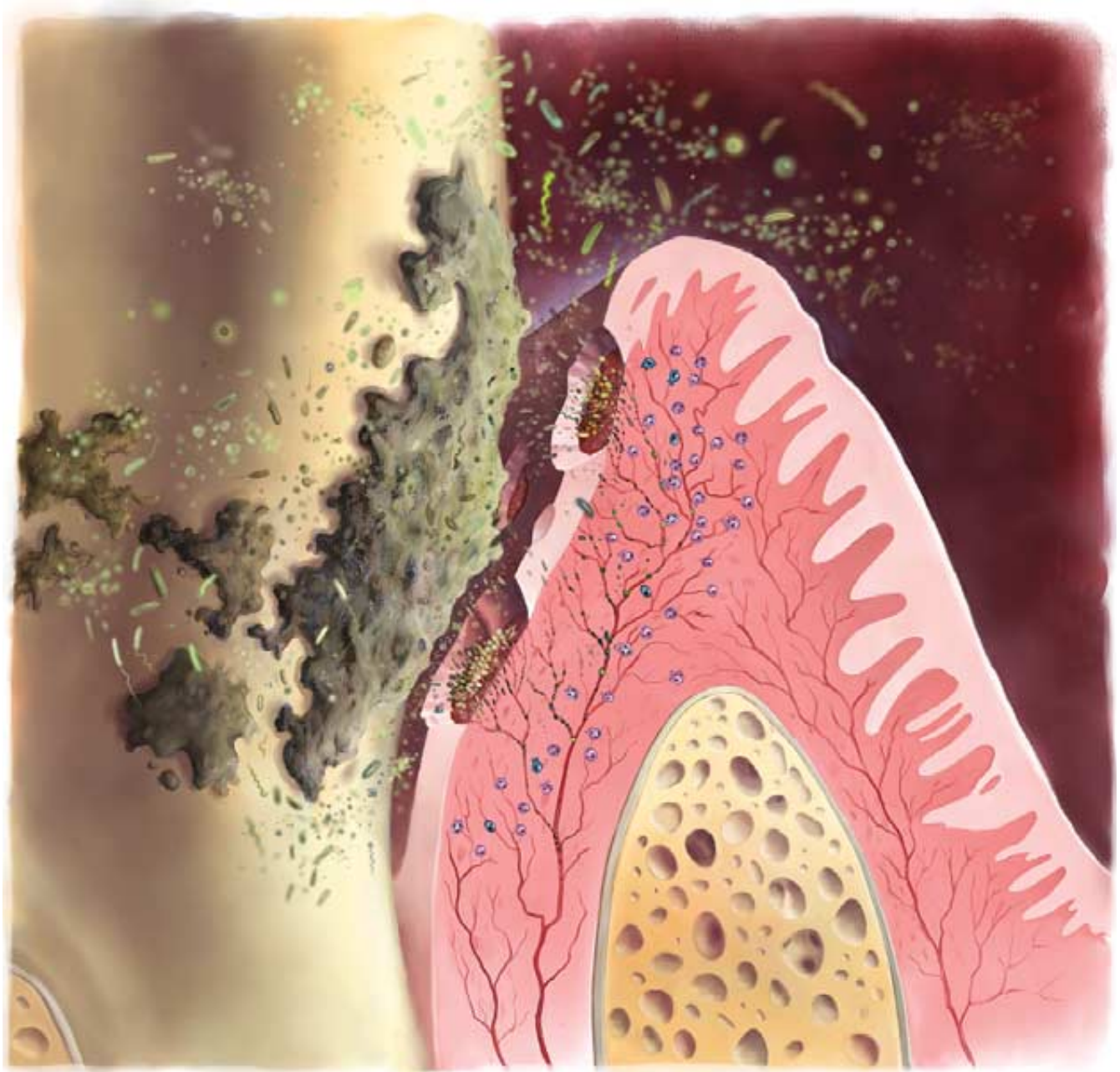
BREAKING THOUGH: When oral bacteria in the mother’s blood breaches the placenta and reaches the fetus, it triggers an immune and inflammatory response, stressing the unborn child. Infections may account for up to 50 percent of premature births.

sclerotic damage to heart arteries: the vessels shrink and do not function properly, compromising the flow of blood and nutrients to the fetus, and impairing growth. Abnormal blood flow in the placenta can also result in an imbalance in the mother’s blood pressure, causing preeclampsia, a mild kidney malfunction that can lead to life-threatening convulsions. This condition can only be cured by delivering the baby.

It now seems that oral infection may be one of a number of factors that can produce these pregnancy complications. Any oral disease, from mild gingivitis to severe periodontitis, causes infection and

inflammation in the mother. At first, the thought of a linkage between a distant oral infection and pregnancy complications was considered “preposterous,” but accumulating scientific evidence is unveiling its biological plausibility.

The increase in hormonal activity during pregnancy can cause gums to bleed more easily and may promote bacterial overgrowth. This bleeding is not normal and signals ulceration between the tooth and gum. In full-blown periodontal disease, the infected area around all 32 teeth becomes a huge ulcerated area—about the size of the palm of your hand. These infected areas no longer



HAVE INFECTION, WILL TRAVEL: Bacteria from dental plaque can enter the bloodstream through small ulcers in the gum and can then travel throughout the body. The increase in hormonal activity during pregnancy can cause gums to bleed more easily and promote bacterial overgrowth.

have the natural skin barrier between the bacteria in dental plaque and the mother's bloodstream. Bacteria enter the blood and travel to the placenta, which normally blocks penetration to the fetus.

For many years, doctors believed that the environment inside the uterus was relatively isolated and protected, with few organisms passing to the placenta or the fetus. But this infection barrier can be breached by a few organisms, including the rubella virus. A rubella (German measles) outbreak in 1964-65

caused at least 10,000 miscarriages and stillbirths, and more than 20,000 babies were born with birth defects. Rubella was first identified as a cause of birth defects several decades ago when researchers discovered the virus floating in amniotic fluid and that fetuses carried antibodies to it—proving that the virus had indeed entered the placenta to infect the growing baby inside.

We conducted studies at U.N.C., Chapel Hill to learn whether unborn babies would show antibody responses

to the organisms that normally live in our mouths with the first human findings being reported in 2001. Studies on mice reported in 2002 and later studies in rabbits proved that oral bacteria could cross the placenta and reach the fetus. Some recent work by Dr. **Yiping W. Han** at Case Western Reserve University demonstrated in 2006 that maternal oral bacteria have been found in human amniotic fluid providing proof of transmission. This strongly suggested fetal infection in

this study—but proving transmission to the fetus of a large population of oral bacteria will be difficult, as babies are not born in a sterile environment.

About eight years ago, we found that in utero exposure to the mother's oral bacteria is a fairly common event. Research conducted by Phoebus Madianos in our lab, published in 2001, showed that contact with enough periodontal bacteria to induce a fetal immune response resulted in a two- to three-fold increase in risk for preterm delivery.

It appears that if the magnitude of exposure is low, either because of a mild infection or effective protection from the mother's antibodies, then the fetus is shielded from these bacteria. But if oral bacteria cross the placental barrier early in gestation, the probability that they will cause problems is much higher than if the security breach occurs late-term. For example, about 28 percent of all unborn babies are exposed to the *Campylobacter rectus* (or *C. rectus*) bacteria—but evidence of exposure to the bacteria is found in 52 percent of infants born before 32 weeks gestation (eight weeks early).

When an unborn child's immune system kicks in to fight off those bacteria, the risk for preterm delivery increases between four- and seven-fold, after adjusting for traditional obstetric risk factors. Elevated levels of the chemicals and hormones that regulate the immune-inflammatory system create a toxic in utero environment that stresses the fetus. It was once thought that the mother's body determined when labor kicked in, but we now know that the baby also contributes to the timing of delivery. Stress may cause the fetus's adrenal glands to produce the hormones that help precipitate its own delivery.

At birth, these babies' umbilical cord blood carries higher-than-normal levels of C-reactive protein, a marker of inflammation which reflects liver activity in both mother and child. Other chemicals, like PGE2 and TNF α (tumor necrosis factor alpha), mediate the body's inflammatory response and act in con-

cert to trigger labor contractions, rupture the amniotic sac, and impair blood flow in the placenta. So the onset of labor is actually a naturally occurring inflammatory response—the mother's body uses inflammation to “reject” the baby—but labor can be triggered early by the abnormal presence of these inflammatory chemicals.

This mechanism—a silent infection leading to fetal inflammation—may also provide a possible explanation for the Barker hypothesis, developed in the early 1900s by David Barker and his colleagues in Southampton, England. They followed the health of low birth weight babies and discovered that prematurity harms health later in life. It seems that deficits in a baby's fetal and infant growth “programs in” risk factors for adult diseases and a lifetime of various disabilities and impairments, including diabetes, high blood pressure and cardiovascular disease. Preterm babies are particularly prone to long-term disability, because their respiratory and neurological systems are especially impacted by premature birth—and the earlier the delivery, the greater the risk of long-term conditions such lung disease, asthma, mental retardation, cerebral palsy and impaired cognitive function. Preterm babies are also at high risk for neonatal death.

Studies in our laboratory demonstrated in 2004 that when pregnant mice were exposed to the *C. rectus* oral bacteria, brain damage in their offspring was similar to that seen in conditions such as cerebral palsy and mental retardation, which can be caused by in utero infections. But clearly, more research is needed, as animal models do not always reflect what happens in humans.

Certainly, there are many reasons for pregnancy complications that do

not involve infection. In fact, there may be underlying conditions, exposures or genetic traits that predispose mothers to abnormal pregnancy outcomes. Some of these risk factors may also predispose mothers to periodontal disease, such as susceptibility to severe inflammation. Nevertheless, the progression of periodontal disease during pregnancy can result in fetal exposure—and trigger a fetal inflammatory response—which may increase the risk for pregnancy complications. The potential importance of these linkages on health care costs and family well-being have not been lost on health insurance companies; some now provide coverage for periodontal care during pregnancy.

Although we do not yet have enough evidence to say unequivocally that periodontal infections can cause adverse pregnancy outcomes, the data supporting this idea are mounting quickly. According to our research, when oral bacteria breaches the “armed guard” of the placenta and reaches the fetus, that baby's risk of being born early rises to 2.8 times that of an unexposed baby. Perhaps in the future a vaccine will be developed to combat these organisms. But in the meantime, the good news is that we know how to prevent and manage periodontal disease—and treatment can be provided safely during pregnancy to improve a mother's oral health, reducing infection and inflammation that may harm her unborn child. An increased dialogue among expectant mothers, their obstetricians and their dental professionals to diagnose, prevent and manage maternal oral infections appears to be a promising strategy for optimizing maternal health during pregnancy. ●

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