Listeria infection causes early pregnancy loss in primates

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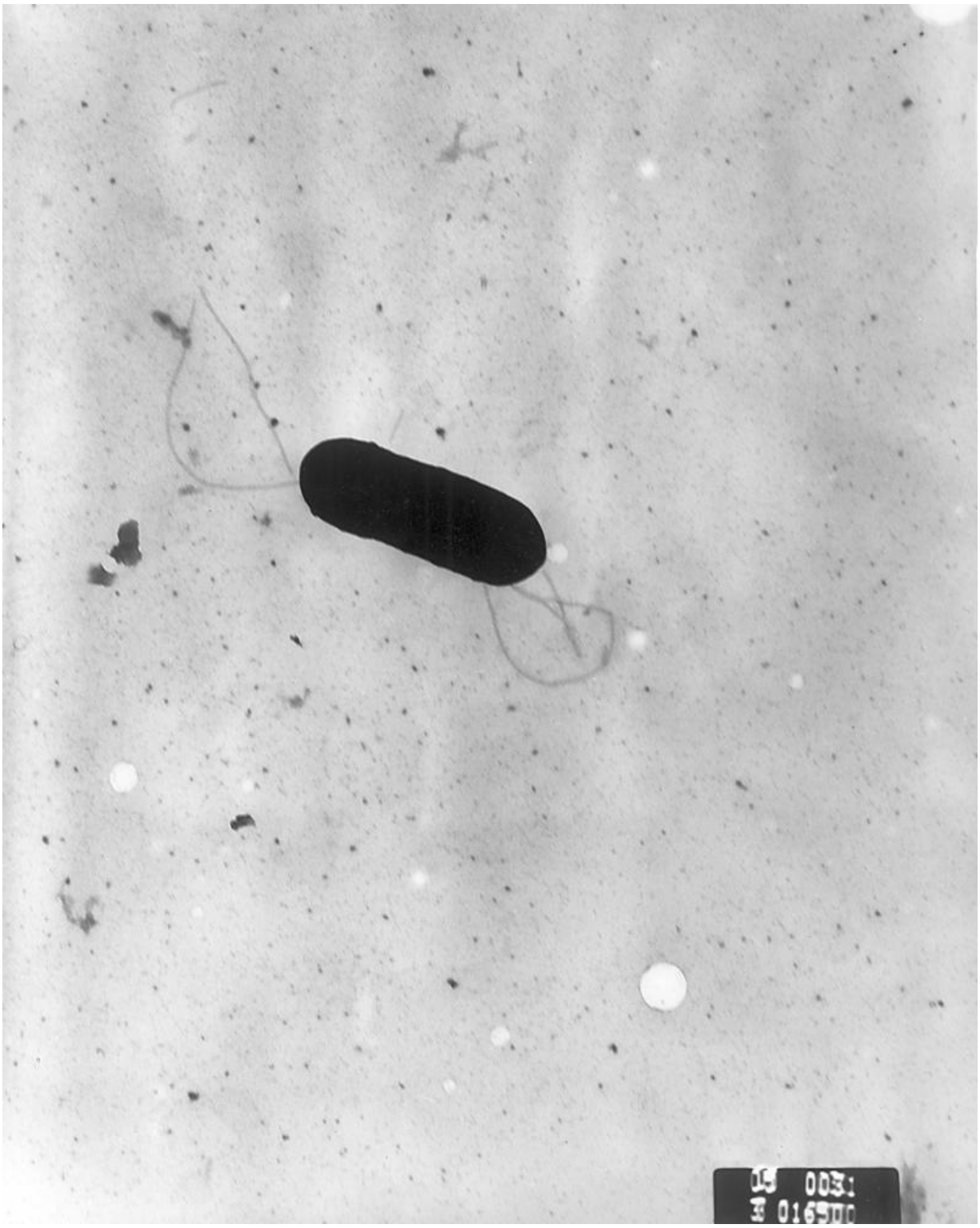

Electron micrograph of a flagellated Listeria monocytogenes bacterium, Magnified 41,250X. Credit: CDC/public domain

Researchers in Wisconsin have discovered how *Listeria monocytogenes*, a common foodborne pathogen, travels through the mother's body to fatally attack the placenta and fetus during early pregnancy in a macaque monkey.

The study, published this week in *mBio*, an open-access journal of the American Society for Microbiology, clarifies why *Listeria* infection is devastating for many infected pregnant women and their fetuses. The work raises questions about our current understanding of the risk for listeriosis in early pregnancy, and reveals clues that may lead to better screening and interventions during pregnancy.

"There was a profound reproductive tract colonization and rapid fetal demise with a first trimester exposure to *Listeria*," says Ted Golos, professor of reproductive sciences at the School of Veterinary Medicine at the University of Wisconsin—Madison and senior author on the study. "At any time during pregnancy, we wish that we could carefully monitor what's happening in the mom and the fetus following exposure to an infectious agent." (image: scanning electron micrograph of *Listeria monocytogenes*, Wikimedia Commons)

Of course, that is nearly impossible to do in human patients, so Golos and his colleagues at the Wisconsin National Primate Research Center have developed a nonhuman primate model of pregnancy using the cynomolgus macaque—a monkey whose pregnancy, placental and fetal development closely matches that of humans.

Listeriosis has been thought to pose the greatest danger to a woman in her third trimester, when it can lead to preterm labor, fetal infection or fetal death. It is the reason pregnant women are cautioned against eating deli meats and milk or soft cheeses that are unpasteurized.

"What makes *Listeria* particularly dangerous is that it can multiply at refrigeration temperatures," says Chuck Czuprynski, director of the Food Research Institute at UW-Madison and project collaborator. Most healthy people can easily clear the bacteria from their systems.

Until now, not much was known about *Listeria*'s impact on early pregnancy. The new research raises the possibility that some first trimester miscarriages might be due to an undetected *Listeria* infection, which often causes no or mild symptoms, like low fever or nausea, in pregnant women.

"Obstetricians will tell you that a number of early pregnancy miscarriages are thought to be due to chromosomal problems," says Golos. "But how many may be due to other causes like infections?"

His team exposed four pregnant macaques to a moderate dose of *Listeria* bacteria by tube-feeding them a dollop of tainted whipped cream on days 36-46 of gestation—corresponding to about week 6 or 7 of a human pregnancy. They expected to see some adverse pregnancy outcomes, but they were surprised by how rapidly infection spread to the fetus: by days 7-13 after exposure, all four fetuses had died in the womb.

Graduate student Bryce Wolfe tracked the infections in the mothers through blood and fecal sampling and in the fetuses via ultrasound. All of the mothers showed signs of bacterial infection in their bloodstream, but displayed few to no symptoms.

When Wolfe examined maternal and fetal tissues for signs of infection, she found that the mothers' immune systems apparently cleared the infections, with very few bacteria showing up in their spleens, livers, and gastrointestinal (GI) lymph nodes. In contrast, Wolfe found high loads of bacteria present in the fetal tissues, amniotic fluid, umbilical cord, placenta, and the decidua, the specialized lining of the pregnant uterus.

"We didn't expect to see the bacteria colonize the fetus so quickly, so consistently," says Wolfe, a PhD candidate at UW-Madison and the lead author on the study. "The decidua and the placenta, which make up the maternal-fetal interface, were loaded with bacteria."

It appears that the monkey's immune system can protect mom, but not the fetus and that the bacteria target the vulnerable reproductive tissues. In the macaques, Wolfe saw cellular damage to the placenta and the fetal membranes that is often seen in *Listeria* infections during human pregnancy. Golos hypothesizes that damage to the decidua and placenta could be disrupting the placental barrier meant to keep pathogens out of the womb.

Czuprynski says the study raises significant questions about whether *Listeria* and perhaps other pathogens cause mild infections in mothers that negatively impact pregnancy. The study is the first to track the progress of a pathogen from the GI tract through a pregnant primate's body to the fetus, he notes. "We have reason to believe it mirrors what happens in women."

Next, the team will investigate what is happening with the immune cells that survey and protect the maternal-fetal interface. Improving our understanding of what those cells are doing during an infection might lead to better ways to detect and treat the infection to protect the fetus.

Again, this takes advantage of the animal model, says Golos. "You can follow the time course of the infection, understand the initiating events, and hopefully devise ways to prevent the damage that leads to a bad pregnancy outcome."

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