Inflammation may cause preterm labor and fetal deaths

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Inflammation from bacterial infections is linked to preterm births and deaths, according to researchers from Case Western Reserve University's School of Dental Medicine and the Case School of Medicine. They found if receptors responding to the presence of dead or living bacteria in the placentas of mice can be blocked, the number of preterm deaths will decline by nearly half.

Yiping Han along with Hongqi Lui from the Case Western Reserve dental school and Raymond Redline from the Case medical school report results from their investigation, "TLR4 promotes F. nucleatum-induced fetal death in mice," in the *Journal of Immunology*.

New findings from the mouse study holds potential to develop ways to curb the emotional and economic toll on families that lose babies to preterm labor and fetal death, said Han, a member of from the department of periodontics.

Currently antibiotic treatments are not very effective at preventing preterm births that are triggered by a bacterial infection. Mice, as well as humans, have several toll-like receptors (TLR) that sense the surface components of living or dead bacteria. TLR2 and 4 are key receptors in recognizing bacterial surfaces. The investigators concentrated their study on these two receptors as a possible link in producing the inflammatory response that is believed to have brought about the fetal death in mice.

In a prior mouse study at Case Western Reserve, the investigators noted that inflammation closely paralleled localization of bacteria. In the present study, the researchers found that mice deficient in TLR4 lacked the necro-inflammatory response to bacteria and produced healthy pups. This discovery led Han and her colleagues to attempt to block the inflammatory process by using synthetic TLR4 antagonist that prevented the receptor from sensing the bacteria.

Fusobacterium nucleatum, a common oral pathogen also found in the amniotic fluid of preterm babies, was used as the model organism for the study. Around day 16 of the gestation period for the mice (the equivalent of the third trimester for humans), F. nucleatum was injected into three groups of mice—one that had TLR4 receptors, a group of TLR4-deficient mice and a group that had TLR4 receptors but were given a synthetic compound to block the receptor's inflammatory response. Within eighteen hours, inflammation was present in the TLR4 mice.

The researchers wrote, "F. nucleatum colonization in the mouse placenta was accompanied by inflammation, similar to intrauterine infection in humans, suggesting placental inflammatory response as an important factor in the pathogenesis of bacterial-inducted preterm birth."

The researchers found that the TLR4-deficient mice gave birth to healthy pups. The TLR4 group that was not given the synthetic compound to block TLR4 from reacting to bacteria had a 50% increase in fetal death over the mice that had TLR4 but were given the compound to block the inflammatory response. In the TLR4-deficient mice, there were very few fetal deaths.

Han said the synthetic TLR4 antagonist appears to be safe for mice mothers and their pups.

The researchers said they hope to find ways to prevent preterm labor that complicates 12% of all live deliveries and results in 70% of neonatal deaths. Preterm births affect nearly half a million babies in the U.S. each year and cost billions of dollars in health costs annually. Han added that the 30% increase in preterm births in recent decades makes it especially important to investigate novel ways of reversing this trend.

Source: Case Western Reserve University