

# Scientists prevent preterm birth caused by gene-environment interactions

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New research in the *Journal of Clinical Investigation* provides evidence that gene-environment interactions are a major contributor to preterm birth and that using a combinatory treatment strategy can prevent preterm delivery in a mouse model.

In findings posted online Aug. 27, scientists from Cincinnati Children's Hospital Medical Center say their study provides important new insights into a major global health problem – one that remains stubbornly persistent in the United States. Preterm birth causes more than 1 million deaths a year and can leave [premature infants](#) who survive with lifelong medical challenges ranging from [respiratory distress](#) to developmental problems.

The study was led by Sudhansu K. Dey, PhD, director of Reproductive Sciences at Cincinnati Children's, first author Jeeyeon Cha, an MD/PhD graduate student in the Dey lab, and Yasushi Hirota, MD/PhD, a former postdoctoral fellow in the Dey lab and faculty member at the Department of Obstetrics & Gynecology in the Graduate School of Medicine at the University of Tokyo.

The combined impact of genetic predisposition and environmental stress on preterm birth has received increased attention by researchers to determine its causes and potential preventive strategies. Scientists in the current study tested gene-environment interactions in a robust mouse model of prematurity and identified a similar molecular signature in human tissue samples from women who experienced premature birth.

"Although gene-environment interactions are assumed to be major contributors to preterm birth, this concept had not been experimentally interrogated," said Dey. "Our studies in mice provide evidence that when a genetic predisposition is combined with mild inflammation, the rate of preterm birth is profoundly increased, provoking preterm birth in 100 percent of the females."

"The results are also clinically relevant because aspects of the molecular signatures observed in the mouse studies are consistent with those observed in tissue samples of women who had undergone preterm birth," he added.

A recent report from the World Health Organization states that while more than 60 percent of preterm births occur in developing countries, the U.S. is among ten countries with the highest numbers of preterm birth. Dey and his colleagues said this suggests that factors behind preterm birth in developing and developed countries may be different. Infection/inflammation may affect developing countries more, while chronic diseases such as diabetes and hypertension and the increased use of assisted reproductive technologies in older women may increase prematurity rates in developed countries.

To conduct their research, the investigators generated a [mouse model](#) of preterm delivery in which the Trp53 gene was conditionally inactivated in the uterus. Trp53 encodes the p53 protein, which is a tumor suppressor and regulates cell growth and replication.

Through a series of studies, the scientists have reported these mice exhibit a preterm birth rate of 50 percent just from the genetic deletion. The scientists have also shown the mice exhibit increased signaling by mammalian target of rapamycin complex 1 (mTORC1) and cyclooxygenase-2 (COX2), which generates fatty acids called prostaglandins that trigger uterine contractions. These pathways are

associated with premature senescence of uterine decidual cells, provoking spontaneous early birth.

In the current study, Trp53-deficient females were subjected to mild inflammation with LPS (endotoxin), resulting in a preterm birth rate of 100 percent. They also observed that women who had experienced preterm birth showed similar increases in mTORC1 and COX2 signaling.

The scientists then designed an experimental [treatment strategy](#) to prevent preterm birth in Trp53-deficient mice exposed to LPS – a combination of rapamycin (an mTORC1 inhibitor) and progesterone, an ovarian hormone necessary for pregnancy success. They report the treatment was effective at preventing preterm birth with no apparent adverse effects on maternal or fetal health.

Progesterone is currently in clinical use to prevent preterm birth in select populations of at-risk women. Although further in-depth investigation is required, the scientists suggest that a combined therapy with low doses of an mTORC1 inhibitor and progesterone may help reduce the incidence of [preterm birth](#) in high-risk women.

Provided by Cincinnati Children's Hospital Medical Center

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