

# Common diabetes drug may help prevent preterm birth

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Metformin, a medication routinely used by millions of people with type 2 diabetes, may also play an unexpected role in blocking a significant cause of preterm birth, according to research findings published July 25.

The early-stage study, based on results from mice bred to be prone to [premature birth](#), was led by a team of scientists at Cincinnati Children's along with colleagues in France and Japan. Their findings were posted online in *JCI: The Journal of Clinical Investigation*.

The study is important for two reasons. First, it details a little-understood molecular pathway that can lead to premature birth by disrupting the function of the decidua - a thick membrane that lines the uterus and supports the continued growth of developing fetuses. Second, the researchers demonstrate - in mice—two successful methods for restoring the lining's function and achieving healthy, full-term births.

"This proof-of-concept study illuminates a potential mechanism behind preterm birth," says Sudhansu K. Dey, PhD, director of the Division of Reproductive Sciences at Cincinnati Children's and senior author of the new study. "It also demonstrates possible remedies that are already approved for human use."

## New clues in the mystery of preterm birth

The study involved analyzing mice bred to lack the [p53 gene](#) in the

uterus, a condition known to make pregnancies more likely to end in premature birth. The new study adds new detail to why this occurs.

Without the gene, decidual cells show increased activity of a protein complex called mammalian target of rapamycin complex 1 (mTORC1). They also show reduced activity of a signaling protein called AMP-activated protein kinase (AMPK).

Combined, these two changes can lead to premature cellular aging in the decidua, which in turn, can trick the mother's body into going into labor. The sooner this occurs, the higher the risk of a miscarriage or premature birth.

Digging deeper, the research team learned that another protein, called sestrin 2, plays a critical role in coordinating the relationship between AMPK and mTORC1 signaling. Levels of sestrin 2 also decline in mice missing the p53 gene.

## **Discovery leads to intriguing potential solution**

The researchers found that treating the mice with metformin reversed the early aging cycle, causing sestrin 2 levels and AMPK activity to increase and mTORC1 signaling to decrease. The mice treated with metformin went on to have full-term births.

The team also reported similar - but less effective - results when treating mice with resveratrol, an anti-oxidant and anti-aging dietary supplement made from grape seed extract.

The latest findings continue a line of research that Dey has pursued for several years. In previous studies, Dey and colleagues discovered that rapamycin, an immune suppressing agent, showed promise in mice at preventing preterm birth. However, that medication may be risky for use

in pregnant women.

Metformin appears to be a potentially safer alternative that works along the same molecular pathway, Dey says.

## Next steps

Preterm birth can be caused by many factors. It remains unclear how many preterm births are triggered by early decidual aging, but Dey says it could be a significant number.

Advancing these mice-based findings into a treatment available for would-be mothers at risk for preterm birth will require extensive work. The process of preparing and conducting human clinical trials to further test the medications could take several years.

Currently, other investigators are studying metformin and resveratrol for their potential to act as anti-aging drugs. However, Dey says his team has not found any human clinical trials investigating the medications for use in preventing [preterm birth](#).

Experts working to reduce stubbornly high premature birth rates in Cincinnati and other cities say the new findings merit further investigation - especially to establish the safety of [metformin](#) use during pregnancy.

"I think the study has interesting implications. It forms the first step in a potential new intervention that would have to be carefully evaluated in human [clinical trials](#). Metformin has been widely used, but only to a limited extent in pregnancy. Future studies will be needed," says Louis Muglia, MD, PhD, director of the Center for Prevention of Preterm Birth at Cincinnati Children's.

## **A collaborative achievement**

The research team at Cincinnati Children's included Wenbo Deng, PhD, Jeeyeon Cha, MD, PhD, Jia Yuan, PhD, and other colleagues led by Dey in the Division of Reproductive Sciences. Collaborators also included Yasushi Hirota, University of Tokyo, Benoit Viollet at INSERM in France, and Heather Bradshaw from Indiana University Bloomington.

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Provided by Cincinnati Children's Hospital Medical Center

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