Study reveals process to explain how maternal stress triggers idiopathic preterm birth

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The preclinical study providing molecular insights into maternal stress and preterm birth of unknown cause was co-led by Charles J. Lockwood, MD, senior vice president of USF Health, dean of the USF Health Morsani College of Medicine, and a professor of obstetrics and gynecology specializing in maternal-fetal medicine. Credit: USF Health/University of South Florida

Preterm birth is a leading cause of infant deaths and illness in the U.S.—yet its underlying molecular causes remain largely unclear. About 40 to 50% of preterm births, defined as births before 37 weeks of pregnancy, are estimated to be "idiopathic," meaning they arise from unexplained or spontaneous labor. And, maternal stress linked to depression and post-traumatic stress disorders as well as fetal stress have been strongly implicated in preterm births with no known cause.

Now, for the first time, a University of South Florida Health (USF Health) preclinical study has uncovered a mechanism to help explain how psychological and/or physiological stress in pregnant women triggers idiopathic preterm birth. A research team at the USF Health Morsani College of Medicine Department of Obstetrics and Gynecology shows how cortisol—the "fight-or-flight" hormone critical for regulating the body's response to stress—acts through stress-responsive protein FKBP51 binding to progesterone receptors to inhibit progesterone receptor function in the uterus. This reduced progesterone receptor activity stimulates labor.

The findings were reported online first March 8 in *Proceedings of the National Academy of Sciences (PNAS).*

"This new study fills in some longstanding mechanistic gaps in our understanding of how normal labor begins and how stress causes preterm birth," said the paper's senior author Charles J. Lockwood, MD, senior vice president of USF Health, dean of the USF Health Morsani College of Medicine, and a professor of obstetrics and gynecology specializing in maternal-fetal medicine.

Dr. Lockwood was a co-principal investigator for the study along with the paper's lead author Ozlem Guzeloglu-Kayisli, Ph.D., a USF Health associate professor of obstetrics and gynecology. Nihan Semerci, MSc, a senior biological scientist, shares the lead authorship with Dr. Guzeloglu-

Kayisli.

Progesterone reduces contractions of the uterus and sustained levels are essential to prevent a baby from being born too early. Reduced uterine progesterone receptor expression and signaling stimulates labor. In the brain, elevated FKBP51 expression has been strongly associated with increased risk for stress-related disorders.

Previous work by the USF Health team showed that normal human labor starting at term (between 37 and 42 weeks of pregnancy) was associated with reduced expression of progesterone receptors and increased expression of FKBP51, specifically in maternal decidual cells (specialized cells lining the uterus).

Ozlem Guzeloglu-Kayisli, PhD, an associate professor of obstetrics and gynecology at USF Health, co-led the preclinical study showing that FKBP51-progesterone receptor binding plays a critical role in maternal stress-induced preterm birth. Credit: USF Health/University of South Florida

For the current study focused on maternal stress-induced idiopathic preterm birth, the researchers combined experiments in human maternal decidual cells and a mouse model in which FKBP5, the gene that makes FKBP51, had been removed, or "knocked out." Altogether, their results revealed a novel functional progesterone withdrawal mechanism, mediated by maternal stress-induced uterine FKBP51 overexpression and enhanced FKPB51-progesterone receptor binding, that decreased progestational effects and triggered preterm birth. The researchers found that Fkbp5 knockout mice (with depletion of the gene encoding for FKBP51) exhibit prolonged gestation and are completely resistant to maternal stress-induced preterm birth.

Among the USF Health team's key findings:

- FKPB51 levels were greater and FKPB51 binding to progesterone receptors was significantly increased in the decidual cells of women with idiopathic preterm birth, compared to decidual cells of gestational age-matched controls.
- The study reports for the first time that Fkbp5-deficient (knockout) mice are completely resistant to maternal stress-induced preterm birth and exhibit prolonged pregnancies accompanied by slower decline in systemic progesterone levels. This indicates that FKBP51 plays a crucial role in the length of pregnancy and initiation of labor and delivery.
- In contrast, mice with the FKPB5 gene intact and normal levels of FKPB51 protein (wild type mice) delivered earlier when

exposed to maternal stress than either non-stressed wild type mice or FKPB5 knockout mice under nonstressed or stressed conditions.

"Collectively, these results suggest that FKBP51 plays a pivotal role both in term labor and stress-associated preterm parturition (birth) and that inhibition of FKBP51 may prove to be a novel therapy to prevent idiopathic preterm birth," the study authors conclude.

Currently, injectable progesterone is the only drug approved to help prevent preterm birth in high-risk women who have had a previous preterm birth. However, its effectiveness was not confirmed by a recent large clinical trial, sparking debate in the health care community. The authors finding that progesterone receptor activity was reduced in idiopathic preterm birth may explain the apparent lack of effectiveness of supplemental progesterone.

Babies born before 37 weeks, particularly those born before 34 weeks, have more health problems and may face long-term health complications, including childhood lung or heart disease and neurodevelopmental delays, Dr. Guzeloglu-Kayisli said. The likelihood of poor outcomes decreases as gestational age (length of the pregnancy) increases.

"Prevention of idiopathic preterm birth by extending gestation even two or three weeks can benefit the newborn, because it provides critical time needed for the fetus's lungs and brain to mature," Dr. Guzeloglu-Kayisli said. "Our research indicates the importance of investigating the potential use of FKBP51 inhibitors as a targeted therapy to reduce the risk of stress-related preterm birth."

More information: Ozlem Guzeloglu-Kayisli et al, Decidual cell FKBP51–progesterone receptor binding mediates maternal

stress–induced preterm birth, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2010282118