Preterm birth, prolonged labor influenced by progesterone balance

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New research by the National Institutes of Health found that unbalanced progesterone signals may cause some pregnant women to experience preterm labor or prolonged labor. The study in mice—published online in the *Proceedings of the National Academy of Sciences*—provides novel insights for developing treatments.

During pregnancy, the hormone progesterone helps to prevent the uterus from contracting and going into labor prematurely. This occurs through molecular signaling involving progesterone receptor types A and B, referred to as PGR-A and PGR-B. In this first-of-its-kind study, the scientists showed how unbalanced PGR-A and PGR-B signaling can affect pregnancy duration.

"We used genetically engineered mouse models to alter the ratio of PGR-A and PGR-B in the muscle compartment of the uterus, called the myometrium," said senior author Francesco DeMayo, Ph.D., head of the National Institute of Environmental Health Sciences Reproductive and Developmental Biology Laboratory. "Our team found that PGR-A promotes muscle contraction and PGR-B prevents such contraction, and we identified the biological pathways influenced by both forms."

Previous research showed that PGR-A regulates processes involved in initiating childbirth and that PGR-B affects molecular pathways related to maintaining the normal course of pregnancy. This study builds on those findings, revealing that the relative abundance of PGR-A and PGR-B may be critical in promoting healthy pregnancy. The public health implications are significant.

Preterm birth affects 10% of all pregnancies and is the primary cause of neonatal morbidity and mortality worldwide, while prolonged labor increases the risks of infection, uterine rupture, and neonatal distress, according to the researchers.

The scientists pointed out that care for preterm deliveries can result in high social and economic costs, with infants born preterm at greater risk for experiencing disorders ranging from blindness to cerebral palsy. Prolonged labor can harm both mother and infant and lead to cesarean delivery.

Progesterone treatment aimed at preventing premature labor can help a subset of patients, but for other individuals, confounding factors may reduce effectiveness, noted Steve Wu, Ph.D., first author on the study and a staff scientist in DeMayo's lab. Wu said that the research team found novel molecules that control uterine muscle contraction, and they could serve as future therapeutic targets. He added that the current study also may help to advance treatment for labor dystocia—the clinical name for abnormally slow or protracted labor.

"Although labor stimulation by oxytocin infusion is an approved measure to mitigate labor dystocia, serious side effects have been associated with this treatment," said Wu. "Novel proteins that we identified as being part of progesterone signaling could serve as a key molecular switch of uterine

contraction, through drug-dependent regulation of their activities," he explained.

"Hormone signaling in pregnancy is complicated and involves both the hormone levels and the types of receptors in the uterus that sense the hormones," said co-first author Mary Peavey, M.D., from the department of obstetrics and gynecology at the University of North Carolina at Chapel Hill. "This publication sheds light on how hormones influence labor and can thus be used to help women when the uterus goes into labor too soon or for a prolonged period."

More information: Mary C. Peavey et al, Progesterone receptor isoform B regulates the Oxtr-Plcl2-Trpc3 pathway to suppress uterine contractility, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2011643118

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