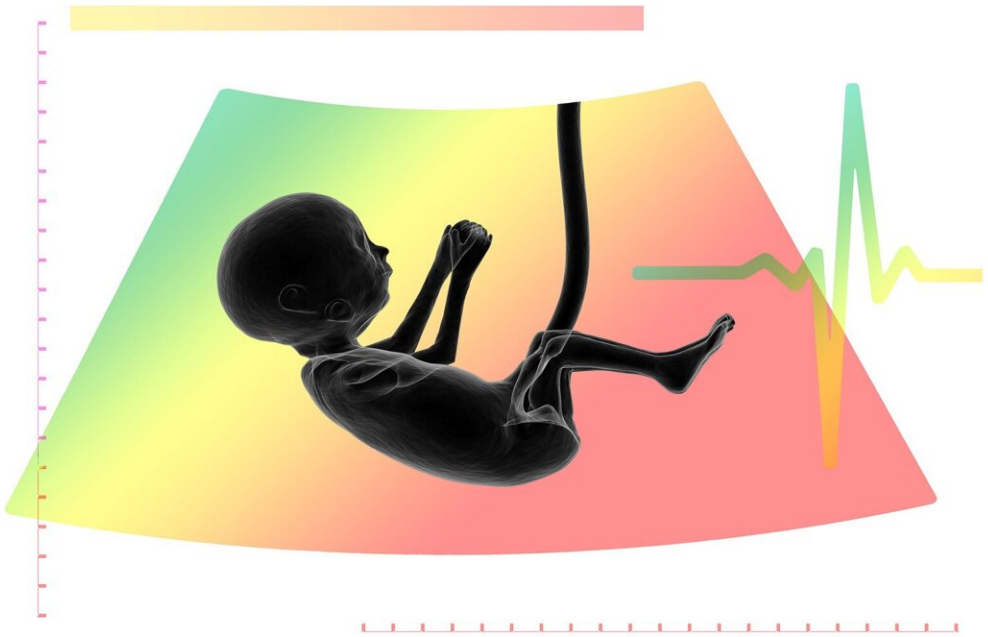
Study provides new explanation for why placenta may not properly separate at birth, putting mother and newborn at risk

January 30 2024



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A new study led by researchers at UCLA may change the way clinicians and scientists understand, diagnose and treat placenta accreta spectrum

disorder, a serious condition in which the placenta fails to separate from the uterus at birth, jeopardizing the life and health of both mother and baby.

Researchers previously believed that certain overly invasive placental cells, called trophoblasts, were responsible for keeping the connection intact. But this new research, which identifies genetic and cellular changes within single cells where the placenta and uterus join, shifts the focus to how the structural support of tissues, and the blood vessels of the uterus, can cause a "loss of normal boundary limits" between the placenta and the uterus.

"We utilized two new techniques in single-cell analysis to create an atlas of cells involved in placenta accreta to better understand this increasingly prevalent disorder that can have devastating implications for maternal and neonatal health," said Dr. Yalda Afshar, a maternal-fetal medicine specialist and researcher at the David Geffen School of Medicine at UCLA, and the first and corresponding author of an article describing the findings in the *American Journal of Obstetrics & Gynecology*.

"This work revealed a subset of genes differentially expressed in placenta accreta spectrum disorder, which provides the basis for the 'permissive environment' for the placenta to attach to the uterine lining," said Dr. Deborah Krakow, a maternal-fetal medicine specialist and researcher, chair of the Department of Obstetrics and Gynecology at the David Geffen School of Medicine at UCLA, and the paper's senior author.

The research showed that the decidua, the layer of the uterine lining that forms during pregnancy, and blood vessels, are sending different signals to the placenta when a pregnant person has placenta accreta. Normally, the placenta—the temporary organ that provides support for a fetus—is shed after birth. In placenta accreta, it is stuck on too tight, which

becomes the reason for many of the maternal complications of placenta accreta.

"Our goal was to characterize the intimate relationship between the maternal and fetal tissue at the site of accreta or malfunction," Afshar said. "The genes and signaling pathways we identified go beyond providing a better understanding of the mechanism of the disease; they may be used as targets to help us refine diagnostic tests, track disease progression over time, and discover new, more effective therapies."

The incidence of placenta accreta spectrum (PAS) disorders has increased dramatically in recent decades, the cause of which is not certain, though cesarean deliveries, is one of several risk factors. Today, incidence is estimated at one in 272 births in the U.S., up from one in about 30,000 pregnancies in the 1960s, researchers say.

For this study, the research team performed multiple placental biopsies on 12 placentas—six with PAS disorder and six controls—conducting single-cell RNA analysis on 31,406 individual cells. The researchers also applied spatial transcriptomics to 36 regions of interest—12 in PAS-adherent, 12 in PAS-nonadherent, and 12 in controls. Spatial transcriptomics allow researchers to precisely measure and map the gene activity within a single tissue sample.

"At the end of the day, understanding the biology of pregnancy and pregnancy-related diseases, like accreta, is inspired by only one thing—finding ways to improve the care we can provide to pregnant people and their families," said Afshar, a physician-scientist who manages the care of many patients with placenta accreta spectrum disorders at UCLA Health.

In addition to Dr. Krakow and Dr. Afshar, UCLA co-authors include Ophelia Yin, MD; Anhyo Jeong; Guadalupe Martinez; Feiyang Ma,

Ph.D.; Christine Jang, PharmD; Sarah Tabatabaei; Hsian-Rong Tseng, Ph.D.; and Yazhen Zhu, MD, Ph.D. Dr. Yin is also with the University of California, San Francisco. From Cedars-Sinai Medical Center: Jina Kim, Ph.D.; and Sungyong You, Ph.D.

More information: Yalda Afshar et al, Placenta accreta spectrum disorder at single-cell resolution: a loss of boundary limits in the decidua and endothelium, *American Journal of Obstetrics and Gynecology* (2024). DOI: 10.1016/j.ajog.2023.10.001