Pregnancy complications in assisted reproduction linked to a specific process

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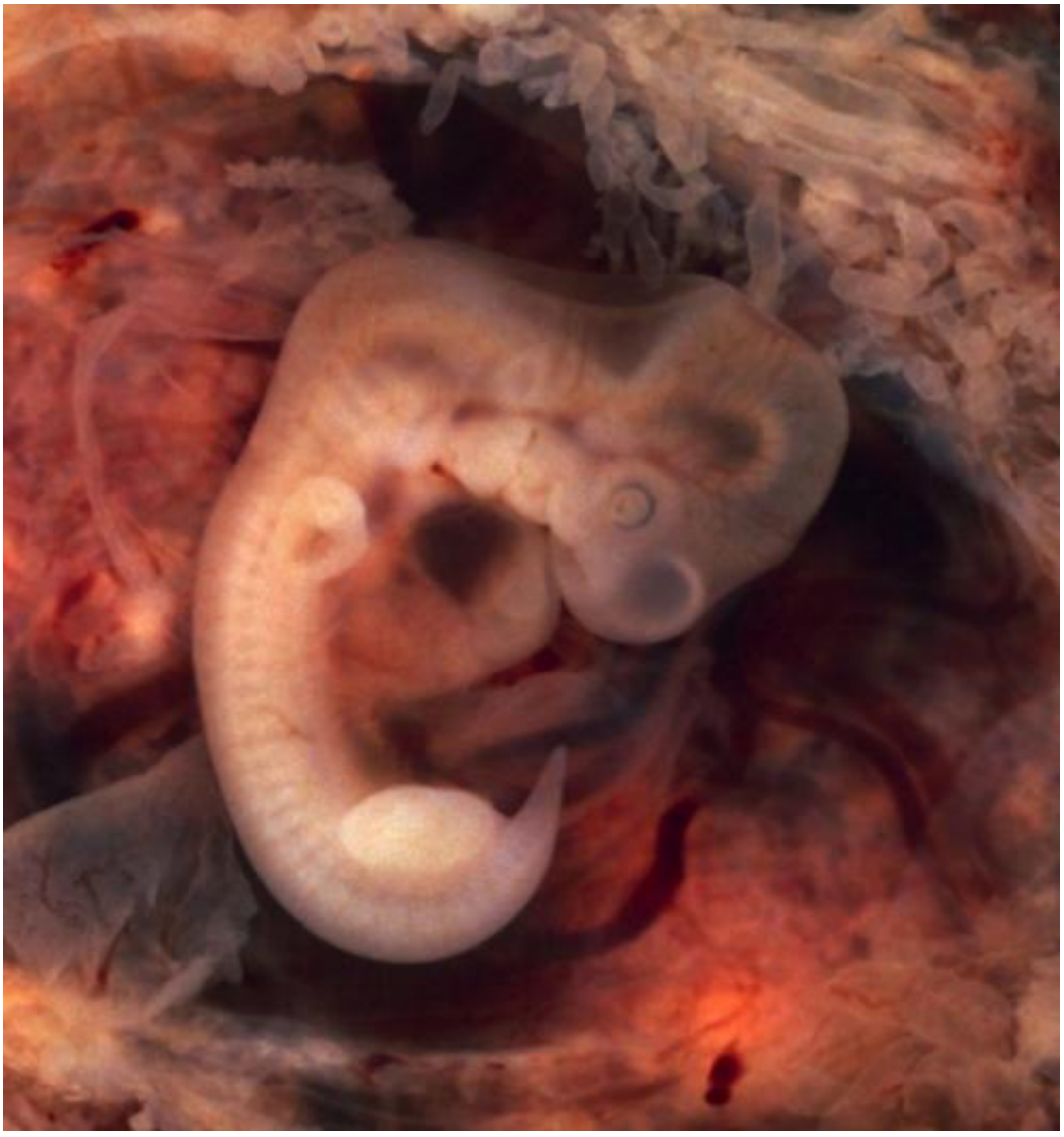

Human Embryo. Credit: Ed Uthman, MD/Wikipedia

An experimental study from researchers in the Perelman School of Medicine at the University of Pennsylvania links a specific procedure—embryo culture—that is part of the assisted reproduction process (ART) to placental abnormalities, risk for preeclampsia, and abnormal fetal growth. The team, led by Marisa Bartolemei, Ph.D., a professor of Cell and Developmental Biology, published their findings today in *Development*.

Millions of births across the world have occurred with the aid of ART, and while its use continues to rise globally, this revolution in human reproduction does come with some problems, the underlying cause of these issues remain unclear.

"The question has always been, is increased risk a function of infertility or is it due to these procedures, because you're doing all these manipulations outside the normal environment," Bartolomei said.

Bartolomei and colleagues used a mouse model to study the effects of four individual ART procedures—hormone stimulation, in vitro fertilization (IVF), embryo culture and embryo transfer—on placental development and fetal growth. All four procedures led to reduced fetal weight at mid-gestation, and at late gestation groups utilizing embryo culture still had reduced fetal weight, larger placentas, and altered placental cell composition. The full IVF procedure led to an increased risk of preeclampsia, and the embryo culture procedure, a necessary component of IVF, was associated with defective methylation of placental DNA, which has the potential to result in abnormalities in the placenta and possible adverse effects on the fetus.

"With the ART process, there's hormone stimulation to produce eggs, the actual IVF, the embryo culture, and the embryo transfer procedure—there's a lot going on," said Lisa Vrooman, Ph.D., a postdoctoral fellow of Cell and Developmental Biology and first author

on the paper. "In the mouse model, we were able to pull apart those four different procedures and look at how they individually contribute to placental development. We also looked at different time points—one close to placental formation, a mid-point, and then at term—to try to understand how placental development may be altered at these different time points."

ART procedures in mice cause placental abnormalities unrelated to underlying infertility. Researchers found that the embryo culture procedure—where the fertilization of the egg with the sperm takes place in a medium meant to replicate the essential nutrients found in the oviduct and is placed in an incubator meant to mimic the womb—had the strongest effects on abnormalities and adverse outcomes.

"ART is more art than science," Bartolomei said. "We don't really know exactly what's going on in the human body. Reproductive endocrinologists are looking at whether or not the embryo in the embryo culture developed in what we think is the right amount of time, with the right number of cells for the stage it's in, and so on. The embryo sits in culture for a week, as opposed to oviducts in the mother's body and the embryo culture is an attempt to simulate that environment."

The authors conclude that efforts should be focused on optimizing embryo culture to ensure healthy outcomes for mothers and offspring.

This study is part of a larger effort to investigate infertility and reproduction at Penn through the National Centers for Translational Research in Fertility and Reproduction. Bartolomei's research team partners with Christos Coutifaris, MD, Ph.D., Professor of Obstetrics and Gynecology, Monica Mainigi, MD, Assistant Professor of Obstetrics and Gynecology, and Jeremy Wang, MD, Ph.D., Professor of Developmental Biology at the School of Veterinary Medicine.

"This collaboration between clinical and basic researchers is designed to look at causes of infertility and when you have infertility using assisted reproduction, what are features that can be optimized for healthier outcomes—that's the goal of this work," said Bartolomei.

More information: Lisa A. Vrooman et al, Assisted reproductive technologies induce temporally specific placental defects and the preeclampsia risk marker sFLT1 in mouse, *Development* (2020). DOI: 10.1242/dev.186551

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