Progesterone from an unexpected source may affect miscarriage risk

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About twenty percent of confirmed pregnancies end in miscarriage, most often in the first trimester, for reasons ranging from infection to chromosomal abnormality. But some women have recurrent miscarriages, a painful process that points to underlying issues. Clinical studies have been uneven, but some evidence shows that for women with a history of recurrent miscarriage, taking progesterone early in a pregnancy might moderately improve these women's chances of carrying a pregnancy to term.

A recent study in the *Journal of Lipid Research* sheds some light on a new facet of progesterone signaling between maternal and embryonic tissue, and hints at a preliminary link between disruptions to this signaling and recurrent miscarriage.

Progesterone plays an important role in embedding the placenta into the endometrium, the lining of the uterus. The hormone is key for thickening the endometrium, reorganizing blood flow to supply the uterus with oxygen and nutrients, and suppressing the maternal immune system.

Progesterone is made in the ovary as a normal part of the menstrual cycle, and at first, this continues after fertilization. About six weeks into pregnancy, the placenta takes over making progesterone, a critical handoff. (The placenta also makes other hormones, including human chorionic gonadotropin, which is detected in a pregnancy test.) Placental progesterone comes mostly from surface tissue organized into fingerlike projections that integrate into the endometrium and absorb nutrients. Some cells leave those projections and migrate into the endometrium, where they help to direct the reorganization of arteries.

Using cells from terminated pregnancies, Austrian researchers led by Sigrid Vondra and supervised by Jürgen Pollheimer and Clemens Röhrl compared the cells that stay on the placenta's surface with those that migrate into the endometrium. They discovered that the enzymes responsible for progesterone production differ between the two cell types early in pregnancy.

As a steroid hormone, progesterone is derived from cholesterol. Although the overall production of progesterone appears to be about the same in migratory and surface cells, migratory cells accumulate more cholesterol and express more of a key enzyme for converting cholesterol to progesterone. Among women who have had recurrent miscarriages, that enzyme is lower in migratory cells from the placenta compared to women with healthy pregnancies. In contrast, levels of the enzyme don't differ between healthy and miscarried pregnancies in cells from the surface of the placenta.

The team's findings suggest that production of progesterone by the migratory cells may have a specific and necessary role in early pregnancy and that disruption to that process could be linked to miscarriage.

More information: Sigrid Vondra et al,

Metabolism of cholesterol and progesterone is differentially regulated in primary trophoblastic subtypes and might be disturbed in recurrent miscarriages, *Journal of Lipid Research* (2019). DOI: 10.1194/jlr.P093427