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Ob/Gyn

Molecular determinant of implantation success uncovered

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MedWire News: A signaling sequence initiated by the embryo and hinging on the epithelial Na^+ channel (ENaC) leads to successful implantation, researchers report in *Nature Medicine*.

The team's results come mainly from experiments in cultured cells. But Hsiao Chang Chan (The Chinese University of Hong Kong) and colleagues found that pharmacologic inhibition of ENaC caused a dose-dependent reduction in implantation rates in mice after mating, and they also found supporting evidence in women undergoing IVF.

ENaC levels in endometrial samples obtained prior to embryo transfer were significantly lower in 16 women with successful pregnancies than in 16 with failed pregnancies. Age, ovarian hormonal profiles, endometrial thickness, and oocyte quality were similar between the groups.

"As ENaC expression is subject to regulation by ovarian hormones, its normal expression pattern may be altered during IVF with ovarian overstimulation, which may contribute to the low pregnancy rate achieved through IVF," says the team.

"Thus, defects in ENaC, either in its expression or its function, may be one of the underlying mechanisms for spontaneous miscarriage and implantation failure during IVF."

Further analysis of separate groups of 16 women with successful and 17 with failed pregnancies showed that the latter group had significantly reduced expression of the ENaCα and ENaCaγ subunits, but not the ENaβ subunit.

The ENaCγ subunit contains a protease activation site. The researchers' laboratory experiments show that the chain of events leading to stromal decidualization (a prerequisite for embryo transplantation) begins with the release of a serine protease, trypsin, from the embryo.

Trypsin release caused ENaC activation and Na^+ influx in endometrial epithelial cells, leading to membrane depolarization. Depolarization triggered Ca^{2+} mobilization, upregulation of cyclooxygenase-2, and release of prostaglandin E_2 (PGE_2), which is essential for embryo implantation.

"The ability of ENaC to regulate PGE_2 production and release, as we showed here, may have far-reaching implications beyond embryo implantation or reproduction, as ENaC is widely distributed throughout the body and PGE_2 is a versatile regulator of many physiological functions and pathological processes," say the researchers.

PGE_2 release from the epithelial cells culminated in the decidualization of stromal cells, which underwent marked morphologic changes from elongated into polygonal and multinuclear cells.

The researchers comment: "Given that ENaC is mechanosensitive, the presently demonstrated involvement of ENaC in decidualization also provides an explanation for the long-observed induction of decidualization by mechanical stimuli in animal models and improved implantation rate in women undergoing IVF after endometrial scratch."

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