

Researchers discover faulty molecular switch that cause infertility, miscarriage

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Scientists have discovered an enzyme that acts as a 'fertility switch', in a study published in *Nature Medicine* today. High levels of the protein are associated with infertility, while low levels make a woman more likely to have a miscarriage, the research has shown.

The findings have implications for the treatment of infertility and recurrent miscarriage and could also lead to new [contraceptives](#). Around one in six women have difficulty getting pregnant and one in 100 women trying to conceive have recurrent miscarriages, defined as the loss of three or more consecutive pregnancies.

Researchers from Imperial College London looked at tissue samples from the [womb](#) lining, donated by 106 women who were being treated at Imperial College Healthcare NHS Trust either for unexplained infertility or for recurrent pregnancy loss.

The women with unexplained infertility had been trying to get pregnant for two years or more and the most common reasons for infertility had been ruled out. The researchers discovered that the womb lining in these women had high levels of the enzyme SGK1. Conversely, the women suffering from recurrent pregnancy loss had low levels of SGK1.

The team found further evidence of SGK1's importance in experiments using mouse models. Levels of SGK1 in the womb lining decline during the fertile window in mice. When the researchers implanted extra copies of the SGK1 gene into the womb lining, the mice were unable to get

pregnant, suggesting that a fall in SGK1 levels is essential for making the uterus receptive to embryos.

The research at the Institute of Reproductive and [Developmental Biology](#) (IRDB) at Imperial College London was led by Professor Jan Brosens, who is now based at the University of Warwick. "Our experiments on mice suggest that a temporary loss of SGK1 during the fertile window is essential for pregnancy, but human tissue samples show that they remain high in some women who have trouble getting pregnant," he said. "I can envisage that in the future, we might treat the womb lining by flushing it with drugs that block SGK1 before women undergo IVF. Another potential application is that increasing SGK1 levels might be used as a new method of contraception."

Any [infertility](#) treatment that blocks SGK1 would have to have a short-lived effect, as low levels of the protein after conception seem to be linked to miscarriage. When the researchers blocked the gene that codes for SGK1 in mice, the mice had no problem getting pregnant. However, they had smaller litters and showed signs of bleeding in the uterus, suggesting that lack of SGK1 made miscarriage more likely.

After an embryo is implanted, the lining of the uterus develops into a specialised structure called the decidua, and this process can be made to occur when cells from the [uterus](#) are cultured in the lab. Cultured cells from women who had had three or more consecutive miscarriages had significantly lower levels of SGK1 compared to cells from controls.

Blocking the SGK1 gene, both in pregnant mice and in human cell cultures, impaired the cells' ability to protect themselves against oxidative stress, a condition in which there is an excess of reactive chemicals inside cells.

"We found that low levels of SGK1 make the womb lining vulnerable to

cellular stress, which might explain why low SGK1 was more common in [women](#) who have had recurrent miscarriage," said Madhuri Salker, the study's first author, Institute of Reproductive and Developmental Biology (IRDB) at Imperial College London. "In the future, we might take biopsies of the womb lining to identify abnormalities that might give them a higher risk of pregnancy complications, so that we can start treating them before they get pregnant."

More information: Salker MS, Christian M, Steel JH, Nautiyal J, Lavery S, Trew G, Webster Z, Al-Sabbagh M, Puchchakayala G, Föller M, Landles C, Sharkey AM, Quenby S, Aplin JD, Regan L, Lang F and Brosens JJ, "Deregulation of the serum- and glucocorticoid-inducible kinase SGK1 in the endometrium causes reproductive failure," Advance Online Publication (AOP) in *Nature Medicine*, October 16, 2011. [DOI:10.1038/nm.2498](https://doi.org/10.1038/nm.2498)

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