# An iTSC-derived placental model of SARS-CoV-2 infection reveals ACE2-dependent susceptibility and differentiation impairment in syncytiotrophoblasts

**Authors:**
Neil JA[1], Chen J[2], Tan JP[2], Rudraraju R[1], Mohenska M[2], Drew D[3], Pymm P[3], Tham WH[3], Polo JM[2,4], Subbarao K[1,5]

[1]Department of Microbiology and Immunology, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia, [2]Department of Anatomy and Developmental Biology, Monash Biomedicine Discovery Institute and Australian Regenerative Medicine Institute, Monash University, Clayton, Victoria, Australia, [3]Infectious Diseases and Immune Defences Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia, [4]Adelaide Centre for Epigenetics and South Australian Immunogenomics Cancer Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia, [5]WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Victoria, Australia.

**Background:** Several clinical reports have linked COVID-19 with negative birth outcomes, early miscarriages and placentitis. This is often associated with the detection of SARS-CoV-2 antigen or genomes in the placenta. However, the pathophysiological mechanisms underpinning SARS-CoV-2 infection during placentation and early pregnancy are not clear.

**Methods:** To shed light on the potential of SARS-CoV-2 to infect early placental cells and the possible molecular and cellular consequences, we utilised induced trophoblast stem cells (iTSCs) to generate an *in vitro* model of SARS-CoV-2 infection of early placenta. Using this model we evaluated virus growth, cellular function and analysed the effects of monoclonal antibodies and antivirals.

**Results:** We identified the expression of ACE2, critical for SARS-CoV-2 virus entry, in placenta-specific cell types including extravillous trophoblasts (EVTs) and syncytiotrophoblasts (STs). Interestingly, despite the expression of ACE2 in both placental cell types, only STs were productively infected by several SARS-CoV-2 variants. We observed that infected ST cultures had reduced expression of key cellular structure and differentiation genes, which led to impairment of cellular processes and morphology vital for their function. This included a significant reduction in their survival, differentiation and production of human chorionic gonadotropin (bHCG), which is a key hormone for the maintenance of pregnancy. Finally, we showed that anti-ACE2 antibody and antiviral drugs could prevent SARS-CoV-2 infection and restored normal ST differentiation and function.

**Conclusion:** In summary, we have uncovered the mechanism underpinning the recent clinical reports associating SARS-CoV-2 and placental pathology using a scalable and tractable platform to study early placental cell types. We also highlight the use of this platform to identify approaches to protect the placenta from SARS-CoV-2 during early pregnancy and development.

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