Role Of Complement Activation And Tissue Factor In The Immunological Attack Of The Placenta And Embryo

Professor Guillermina Girardi
Chair in Women’s Health
Division of Women’s Health
King’s College London

Abstract
An estimated 340 000 maternal deaths, 2.7 million stillbirths and 1.3 million neonatal deaths occur worldwide each year. The majority of these deaths can be attributed to placental dysfunction. A fully active complement system deriving from the maternal circulation as well as from local production is present in the placenta and is crucial for successful pregnancies. As fetal tissues are semi-allogeneic and alloantibodies commonly develop in the mother, the placenta is potentially subject to complement-mediated immune attack at the fetomaternatal interface with the potential risk of adverse pregnancy outcomes. Using animal models that closely resemble the clinical cases we identified the complement components and inflammatory cells involved in the immune attack of the embryo and tested therapies to prevent it. We found a pivotal role for complement activation in recurrent miscarriages, preeclampsia, preterm birth and also in the abnormal neurodevelopment observed in these pregnancies. In vivo in utero non invasive MRI-based method were used to detect complement activation/inflammation as well as metabolism in placenta and fetal brain and predict pregnancy outcomes. Tissue factor plays an important role in the cross-talk between coagulation and inflammation leading to pregnancy complications such as fetal loss and preeclampsia. Targeting different components of the coagulation cascade and their interaction with protease activated receptors (PARs) a key role for tissue factor/factorVIIa/PAR2 signaling in neutrophil activation and placentaland fetal injury was identified. Statins showed to down regulate TF and PAR-2 synthesis and thus, by decreasing neutrophil activity, prevented fetal death. Statins also prevent adverse pregnancy outcomes in different mouse models of preeclampsia. Recently we translated our observations in mice to women successfully. Pravastatin prevented pregnancy complications in women with antiphospholipid antibodies leading to live births.

Selected Publications for Reference