The role of human cytomegalovirus in stillbirth

Research Institution: Virology Division, SEALS Microbiology, Prince of Wales Hospital and the University of New South Wales

Chief Investigator: Professor William Rawlinson

Other Investigators: Stuart Hamilton, Dr Gillian Scott

Amount granted: $90,000
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Research funded by the Stillbirth Foundation Australia investigating viral causes of stillbirth has revealed findings that shed new light on how infections during pregnancy may result in stillbirth. This research was primarily carried out by Stuart Hamilton, who received the inaugural Stillbirth Foundation Australia PhD Scholarship in 2010, and led by Professor William Rawlinson at the Virology Division, SEALS Microbiology, Prince of Wales Hospital and the University of New South Wales.

Almost half of all stillbirths are of unknown cause, even after autopsy examination. We know some viral and bacterial infections during pregnancy cause stillbirth. However, in many cases the exact mechanisms by which infection leads to stillbirth remain unclear. One such infection is a common virus known as human cytomegalovirus (CMV). CMV can cause a number of serious birth defects to the developing baby including mental disability, hearing and vision loss and in the most severe cases result in fetal death. Fetal injury is usually caused directly by the virus infecting the baby in utero; however, recent evidence suggests CMV may indirectly cause fetal injury via infection of the placenta.

This research investigated the immune environment within placental tissue from stillborn babies infected with the CMV virus and then used a novel in vitro model of placental infection to confirm these findings (Hamilton et al, 2012, PLOS ONE). The research found the placenta from stillborn babies naturally infected with CMV had a shift from a balanced immune environment towards a more pro-inflammatory state. A similar immune shift was observed in artificially-infected placental tissues cultured in the laboratory that were donated from women undergoing elective Caesarean sections. Furthermore, infection of cell cultures in vitro showed this pro-inflammatory shift was most likely a direct cellular response to CMV replication within infected cells of the placenta (Hamilton et al, 2013, Journal of General Virology).
A pro-inflammatory shift within the placenta has been associated with a number of adverse pregnancy outcomes, and can negatively affect many aspects of placental development and function. Placental dysfunction would in turn lead to the developing baby not receiving enough nutrients and oxygen and could lead to fetal injury and death in utero. This research suggests that monitoring the immune environment of pregnant women at high risk of certain infections may be used as an indicator of at risk pregnancies of stillbirth and could give rise to new therapeutic treatments.

A systematic review of the scientific literature showed there are limited therapeutic options available to prevent or treat CMV infection during pregnancy (Hamilton et al. 2014, Reviews in Medical Virology). This is mainly due to significant drug toxicity and limited clinical evidence for drug efficacy. Therefore, this research also worked on the development of novel antiviral therapeutics for safe use during pregnancy, one of which utilises small interfering RNA (siRNA) molecules (Hamilton et al, 2014, PLOS ONE). These siRNA molecules bind to the viruses’ genomic material and prevents generation of essential proteins needed for the virus to replicate, thus inhibiting viral growth and spread.

Current investigations are now focused on using the novel placental explant model developed in this study to test the efficacy and safety profiles of various established and novel anti-CMV therapeutics for use during pregnancy. These studies will better inform decision making on future clinical trials and help lead the way in the prevention of infectious causes of stillbirth and other virus-associated adverse pregnancy outcomes.
PUBLICATIONS AND PRESENTATIONS

Throughout the course of this candidature, the following manuscripts were published:


Presentations arising from this candidature were as follows:


