Exogenous Fibrin Induces Inflammatory Injury in the Rhesus Macaque Placenta

Introduction

In human pregnancy, both healthy and unhealthy placentas commonly exhibit pathology, such as fibrin deposition (FBD), calcification (CAL), and traits of acute and/or chronic inflammation (INF). These features are thought to contribute to adverse pregnancy outcomes such as fetal growth restriction (FGR), though the quantity and location of said pathologies that result in disease manifestation remains unclear. Furthermore, the role a given pathology plays with respect to another's manifestation has yet to be elucidated.

Inducing these histological features in the placenta could lead to a model of FGR, and uncover insights to its pathogenesis. Tissel is a biological tissue sealant used in surgical applications, in which thrombin cleaves fibrinogen to form fibrin. By introducing fibrin into the placenta with Tissel, we may be able to mimic pathological and biometric attributes of FGR.

Hypothesis

We hypothesized that an injection of Tissel into the intervillous space of pregnant rhesus macaques would result in placental pathology and fetal biometrics observed in FGR.

Methods

On gestational day (GD) 90, 0.5 mL of saline (n = 3) or Tissel (n = 3) was injected into the placental villi of theses macaques above. On GD 155 a c-section was performed, and maternal and fetal tissues were collected for biometric, histological, and cytokine analysis.

Tissue center cuts were obtained from each placential cotyledon, stained with H&E, and scanned at 4x magnification. Pixels containing chorionic plate (pale green), placental villi (blue), trophoblastic shell (red) and decidual (yellow) were first outlined. Next, pixels containing pathological features (bright green) or red blood cells (pink) were outlined (detailed below). Fibrin deposition, inflammatory injury, calcification, and red blood cell pixels were quantified in relation to their specific tissue (chorion, villi, etc.). Final counts from each cotyledon were then transformed by natural log (ln) pixels) and plotted with respect to treatment (Results, Figure 8).

Conclusions

A 0.5 mL Tissel injection into the placenta did not result in FGR, but did result in an increase in the fetal brain/body ratio, a hallmark of asymmetric FGR. The Tissel treatment was sufficient to induce significant increase fibrin deposition and inflammatory injury, as evidenced by pathology. Additionally, 6 of the top 7 samples expressing inflammatory cytokines were from Tissel treatment group. Together, these findings implicate fibrin deposition as a potential inducer of sterile inflammation at the placenta.