

## **[O-W-004] MATERNAL PLATELETS AND THE THROMBIN RECEPTOR, PAR4, DISRUPT PLACENTAL MORPHOGENESIS AND CAUSE FETAL LOSS IN FACTOR V LEIDEN MICE**

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**Introduction:** Maternal factor V Leiden status is associated with fetal loss. Due to the uncertain etiology of the disorder and the lack of established criteria for more precise risk stratification, prophylactic anticoagulation during pregnancy is a subject of intense debate. We have recently developed a mouse model of pregnancy disorder in factor V Leiden mothers, establishing a cause-effect relation for the epidemiologic association. We exploit this model to identify risk modifiers of fetal loss in factor V Leiden mothers and to characterize disease pathogenesis.

**Methods:** Genetic and histological approaches were used to clarify disease pathogenesis. Placental perfusion was assessed by intravenous FITC-dextran injections. Platelet depleting antibodies were used to examine the role of maternal platelets in fetal loss.

**Results:** We show that: (1) Fetal defects in thrombomodulin and endothelial protein C receptor genes precipitate pregnancy loss in factor V Leiden mothers; the same mutations in the factor V Leiden animal are compatible with normal functioning of other vascular compartments. (2) Heterozygous deficiency of tissue factor pathway inhibitor is inconsequential with respect to fetal loss. (3) Fetal loss is caused by disruption of placental morphogenesis at the stage of labyrinth layer formation, and occurs in the absence of overt thrombosis or perfusion defects. (4) Platelet depletion or genetic elimination of the thrombin receptor Par4 from the mother allows normal placentation and prevents fetal loss.

**Conclusions:** Our results identify fetal gene defects in the thrombomodulin-protein C pathway as risk modifiers of fetal loss in factor V Leiden mothers; show the existence of vascular bed-specific pathogenic mechanisms in the placenta; and identify platelets and the thrombin receptor Par4 as critical mediators of fetal loss, likely involving a pathogenic mechanism independent of occlusive thrombosis. This model provides an opportunity to test the efficacy of anti-thrombotic and anti-platelet treatments.

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