

Alternative complement pathway dysregulation in women with pre-eclampsia.

Dr Hannah Blakey¹, Prof Claire Harris², Dr Ruyue Sun², Dr Long Xie², Ms Rebecca Russell², Dr Edwin Wong³, Prof Neil Sheerin³, Dr Kate Bramham⁴, Dr Ellen Knox⁵, Prof Mark Drayson⁶, Dr Graham Lipkin¹
¹Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom, ²Institute of Cellular Medicine, Newcastle University, United Kingdom, ³National Renal Complement Therapeutics Centre, Newcastle, United Kingdom, ⁴King's College Hospital, London, United Kingdom, ⁵Birmingham Women's Hospital, Birmingham, United Kingdom, ⁶University of Birmingham, Birmingham, United Kingdom

Background and Aims

Pre-eclampsia (PE) is a leading cause of maternal and fetal morbidity and mortality, and women with chronic kidney disease are at particularly high risk. There remains no definitive therapy other than prompt delivery which is often required preterm. Research suggests evidence of complement dysregulation in patients with PE (1-4), although the evidence base requires strengthening to develop a better mechanistic understanding of the role of complement and the pathways involved to guide potential complement-modifying therapies. Our aim was to compare patterns of complement in the circulation (maternal blood), and at the maternal-fetal interface (umbilical cord blood) in healthy pregnant women, and those with PE.

Methods

Women without pre-existing medical conditions with PE and healthy controls were recruited from a tertiary obstetric centre. PE was defined as new onset hypertension (blood pressure $\geq 140/90$ mmHg on 2 or more occasions), and proteinuria (protein to creatinine ratio ≥ 30 mg/mmol), after 20 weeks' gestation. Maternal blood samples were collected within one week prior to delivery, and umbilical cord samples collected immediately following birth. Samples were centrifuged and frozen at -80°C within 4 hours of collection. Maternal and cord plasma were tested for markers of complement activity (iC3b, C3, properdin, C5b-9 and Ba) using electrochemiluminescent multiplex immunoassays (MesoScale Discovery). Clinical outcome data were collated.

Results

68 subjects were recruited (35 women with PE, 33 healthy pregnant controls). There were no significant differences in age, BMI, ethnicity, parity, or mode of delivery between groups, although samples were taken at an earlier mean gestational age in women with PE (35 weeks + 5 days versus 39+6, $p < 0.001$).

When compared to healthy controls, women with PE demonstrated significantly reduced maternal plasma concentrations of properdin (4828.47 ng/ml versus 6876.85 ng/ml, $p < 0.001$), iC3b (488.81 ng/ml versus 605.74 ng/ml, $p = 0.003$), and C3 (1.90 g/l versus 2.36 g/l, $p < 0.001$), and elevated maternal plasma concentrations of Ba (149.53 ng/ml versus 112.75 ng/ml, $p = 0.012$). However, there were no significant differences in iC3b:C3 ratio or C5b-9 between study groups. See Table 1.

Cord blood analysis also identified significantly higher Ba concentrations in women with PE compared to controls (380.73 ng/ml vs 210.47 ng/ml, $p = 0.015$). There were no other significant differences in complement components tested in cord blood between groups.

Discussion

This study, for the first time, highlights abnormalities in circulating properdin and Ba concentrations in the plasma of women with PE, and elevated concentrations of Ba in umbilical cord blood, suggesting activation

of the alternative complement pathway. Properdin acts as a positive regulator of the alternative complement pathway. Reduced plasma properdin concentrations seen in PE cases may suggest properdin consumption. Similarly, raised concentrations of circulating Ba, (an activation fragment of Factor B and also specific to the alternative pathway) are suggestive of heightened alternative pathway activity in maternal and cord blood in women with PE.

These findings contribute to evidence of raised complement activity in women with PE, thus complement inhibition therapy may be a potential therapeutic option as an alternative to expedited delivery in the treatment of PE.