A potential new biomarker for Preeclampsia

Preeclampsia (PE) is a devastating disorder which effects more than 3-5% of pregnancies worldwide and remains to be one of the leading causes of global maternal and perinatal mortality and morbidity. These deaths are even more prevalent in middle to lower income countries. PE is a common disorder of pregnancy presenting clinically with hypertension and proteinuria. The placenta plays a significant role in determining the clinical presentation of the disease due to a number of factors secreted into maternal circulation by the placenta as a result of syncytiotrophoblast stress. Insufficient or incorrect placentation may be the primary cause of such disorders as this occurs in the initial stages of pregnancy.

During early pregnancy, the maternal immune system has to undergo several adaptations in order to develop immune tolerance for the semi-allogenic fetus and failure at such significant development may be the *first trigger in the pathogenetic cascade leading to poor placentation and PE*. In a previous study, Tersigni, et al., *observed aberrant expression of human leukocyte antigen (HLA)-DR molecules in the syncytiotrophoblast of placentas obtained from women with PE* ([doi: 10.1016/j.jri.2018.06.024),](doi: 10.1016/j.jri.2018.06.024) which could be a potential biomarker for the pathophysiology of the disease. A class II molecule constitutively expressed on mature antigen presenting cells, HLA-DR, presents exogenous antigens to T cells to elicit an antigen specific immune response. Successful

pregnancy is dependent on the regulation of HLA class I and class II expression in villous (VT) and extra-villous trophoblast (EVT). *The lack of HLA class II (-DP, -DQ and -DR) molecule expression on trophoblasts prevents maternal T cell allo-immune responses against paternal-derived antigens.*

Abnormal expression of HLA-DR antigen in trophoblast cells has been shown to be found in about 40% of syncytiotrophoblast-derived extracellular vesicles (STBEVs), obtained from women suffering from PE. The syncytiotrophoblast, where HLA-DR was found to be expressed, is the cell type responsible for the release of STBEVs in maternal circulation *in vivo*. In addition, this cell type defines the later stages of pregnancy and repsresents the majority at the maternal-fetal interface.

To extend on their previous findings and in an effort to further establish a unique biomarker for PE, Tersigni, et al., investigated whether HLA-DR aberrant expression might be confirmed in STBEVs collected from the peripheral blood of women with clinical diagnosis of PE.

Using flow cytometry and analysing only a small volume of plasma (3 ml of blood), the researchers observed, within this study, that HLA-DR molecules can be detected in STBEVs from 64% of PE women analysed. However, due to the small sample size, no definitive conclusions could be made and further work is needed.

As listed within the study, there were interesting findings that hold great potential for diagnostic developments for PE. These include:

- HLA-DR specific expression in PE i.e. in women with normal pregnancy, this protein was not detected in the Syncytiotrophoblast.
- Up to 60% positivity of this protein in the PE cases analysed.
- A minimally invasive liquid biopsy was the effective

technique used to detect the marker.

- The potential for early detection of HLA-DR positive STBEVs in the first trimester is significant for the treatment of the disorder.

In conclusion, this was a pilot study whereby the researchers interrogated plasma for STBEVs *using the plasma as a "liquid biopsy" of the syncytiotrophoblast in women with clinical diagnosis of PE, to search for HLA-DR aberrant expression in circulating placental STBEVs (corroborated by placental alkaline phosphatase (PLAP) positivity).*

In their own words:

"HLA-DR is a possible candidate marker worthy to be investigated for its potential application in the prediction and early diagnosis of PE."

Following such a fascinating study, a larger longitudinal study is needed, interrogating a larger and more diverse population. This would make such findings more accurate and add to the potential predictive power of HLA-DR as a biomarker for PE. In addition, a larger longitudinal study would help confirm if circulatory STBEVs positive for HLA-DR found in pregnant women could predict whether they are at risk of developing PE.

Journal Article: Tersigni, et al., 2021. [Circulating Placental Vesicles Carry HLA-DR in Pre-Eclampsia: A New Potential Marker of the Syndrome](). Frontiers in Immunology.

Summary by Stefan Botha