Cardiovascular Research Supplements (2014) **103**, S9–S46

POSTER SESSION 1

Session held on 4 July 2014

doi:10.1093/cvr/cvu082

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Elevated free fetal haemoglobin threatens vasculoprotection in the fetal circulation of preeclamptic pregnancy

P. Brownbill[1]; EEC. Yoong[1]; A. Brook[1]; L. Erlandsson[2]; M. Gram[3]; I. Lang[4]; G. Desoye; H. Schneider; S. Hansson[2]; IP. Crocker[1]

[1]University of Manchester, Maternal & Fetal Health Research Group, Manchester, United Kingdom; [2]Lund University, Department of Obstetrics and Gynecology, Lund, Sweden; [3]Medical University of Graz, Institute of Histology and Embryology, Graz, Austria; [4]University of Bern, Department of Obstetrics and Gynecology, Bern, Switzerland

Placental up-regulation of free fetal haemoglobin (fHbF) occurs in preeclamptic (PE) pregnancy. Heme oxygenase-1 (HO-1) is an important vasculoprotective enzyme in the catabolism of the associated heme porphyrin structure. We have previously shown that fHbF negatively influences the vasculoprotective capacity of the fetal circulation. Here we study fHbF levels in the fetal cord blood of pregnancies complicated by PE; a pathology associated with dysregulated fetoplacental vascular tone. We have previously shown that fHbF binds nitric oxide (NO) to elicit elevated vascular resistance in the fetoplacental circulation, using ex vivo human dual placental perfusion and in vitro placental endothelial cell shear stress studies. Furthermore, fHbF causes morphological changes to the fetoplacental endothelium. Here we hypothesise that elevated levels of fHbF in fetal plasma associated with placental pathology contribute to fetoplacental hypertension. Purpose: To evaluate and derive a robust cord blood collection and processing protocol for the accurate measurement of fetal plasma fHbF levels in normal and PE pregnancies.

Methods: Fetal venous cord blood was collected by syringe and needle, or Vacutainer method into either EDTA or citrate tubes, within 10 minutes of partum. Plasma recovery occurred immediately, or after 30 minutes, prior to centrifugation at 2000g x 10 min at room temperature. Following evaluation to reduce mechanical haemolysis, newly collected normal & PE plasma (n=13 & 6, respectively) was subjected to ELISAs for HbF and HO-1. Results: Venipuncture collection of cord venous blood taken from the cord-placenta insertion point by Vacutainer system with a 21G needle, into citrate collection tubes with immediate centrifugation prevented mechanical haemolysis. There was no difference in plasma HO-1 between groups (medians = 5.9 & 5.3 ng/mL; normal & PE, respectively; Mann-Whitney). Whilst there was no difference in fHbF between groups (Mann-Whitney), variability was high in the PE group and there were some very high values for fHbF compared to the normal range, whilst fHbF values in the control group were within a tighter lower range (medians & ranges = 45.9 & 0-206 and 118.8 & 29-640 μg/mL).

Conclusion: Fetal plasma HO-1 levels appear stable in preeclamptic fetal plasma, permitting fHbF to remain unchecked in some cases. High pathophysiological levels of fHbF in some cases of PE pregnancies are capable of evoking elevated vascular resistance within the fetoplacental circulation, caused by nitric oxide sequestration and disruption to the endothelium. Further evaluation is required.