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### Maternal tissue blood flow and oxygen saturation in pre-eclampsia and intrauterine growth restriction

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#### ABSTRACT

*Objective:* To investigate the hypothesis that impaired maternal tissue perfusion occurs in pre-eclampsia and intrauterine growth restriction (IUGR) and this correlates with maternal tissue oxygenation. *Study design:* Strain gauge plethysmography was used to compare maternal calf blood flow during the third trimester in 16 women with pre-eclampsia, 6 women with IUGR and 16 normal pregnant controls. A Mediaid iPOX pulse oximeter was used to measure maternal tissue oxygenation in the three groups and these were compared with tissue blood flow.

*Results:* Maternal tissue blood flow was significantly reduced in pre-eclampsia compared to the two other groups (p = 0.003). Blood flow was significantly reduced in pre-eclampsia compared to IUGR (p = 0.03). However there was no difference in blood flow between normal pregnancy and IUGR groups (p = 0.76). No significant difference was noted in maternal tissue oxygenation between the normal pregnancy, pre-eclampsia and IUGR groups (mean  $\pm$  S.E.M. [97.13  $\pm$  0.4, 96.69  $\pm$  0.33, 97.83  $\pm$  0.47 respectively], p = 0.26). No correlation was noted between blood flow and tissue oxygenation in the three groups of women.

*Conclusion:* We have demonstrated that reduced maternal resting tissue blood flow present in women with pre-eclampsia is not seen in women with IUGR and the reduction in blood flow in pre-eclampsia is not associated with changes in maternal tissue oxygenation.

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### Introduction

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Pre-eclampsia is a multi system disorder of the second half of pregnancy, which is characterized by increased vascular reactivity and peripheral resistance with pathological changes that are consistent with impaired blood flow to the affected vascular beds [1]. In severe pre-eclampsia, there is generalized vasoconstriction with multiple organ dysfunction [2]. There is also considerable evidence that generalized endothelial dysfunction underlies the clinical manifestations of the disease [3].

It has been demonstrated that peripheral nutritive blood flow is impaired in pregnancies complicated by pre-eclampsia and precedes onset of the disorder [4]. Furthermore, the clinical manifestations of the disorder are suggestive of tissue hypoxia [5]. Studies on oxygen delivery and consumption indices in women with severe pre-eclampsia showed that the changes were similar to that observed in distributive shock [6]. However, so far it is not clear

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http://dx.doi.org/10.1016/j.ejogrb.2014.03.042 0301-2115/© 2014 Elsevier Ireland Ltd. All rights reserved. whether the reduced blood flow correlates with maternal tissue 25 oxygenation. IUGR is a recognized complication of pre-eclampsia 26 however IUGR may occur in the absence of pre-eclampsia. De novo 27 IUGR and pre-eclampsia appear to share the same primary 28 pathology with endothelial dysfunction as a central feature [7,8]. 29 However, it is unclear whether the generalized endothelial 30 dysfunction seen in IUGR is associated with reduced maternal 31 tissue perfusion and/or impaired tissue oxygenation. In this study 32 we hypothesized that the reduced blood flow seen in women with 33 pre-eclampsia is also present in pregnancies complicated by IUGR 34 and this is associated with impaired maternal tissue oxygen 35 saturation. To investigate this hypothesis, maternal tissue blood 36 flow and oxygen saturation was measured in women with pre-37 eclampsia, IUGR and normal pregnancy. 38

#### Materials and methods

#### Study subjects and demographics

In a cross sectional study during the third trimester, we 41 compared maternal tissue blood flow and oxygen saturation 42

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43 between 16 women with pre-eclampsia, 6 women with pregnancies complicated with IUGR and 16 women with normal 44 pregnancy. All the study participants were recruited from Kingston 45 46 Hospital maternity unit and were matched for maternal age, BMI 47 and gestational age. Gestational age was determined by first 48 trimester ultrasound scan. Informed written consent was obtained 49 from all the participants and the study was approved by the local 50 research and development committee.

51 Pre-eclampsia was defined as new onset hypertension of more 52 than or equal to 140/90 mmHg on two separate occasions at least 53 4 h apart and with significant new onset proteinuria after 20 weeks 54 of gestation and reversal of both by six weeks after delivery [9]. 55 Proteinuria was considered significant if the urinary protein 56 creatinine ratio was more than 30 mg/mmol or a 24 h urine 57 collection showed more than 300 mg protein. IUGR was estab-58 lished by foetal weight and size below the fifth centile, along with 59 asymmetrical pattern of growth measurements on ultrasound 60 [10]. Women with known medical disorders or pregnancy related 61 complications that may result in IUGR such as pre-eclampsia with 62 IUGR or with a history of TORCH (toxoplasmosis, congenital 63 syphilis and other viral infections, including rubella, cytomegalo-64 virus and herpes simplex) and substance misuse (recreational drug 65 use) were not included in the study. None of the babies born 66 showed any signs of chromosomal abnormalities. All women 67 recruited for the study had early first trimester scan which was 68 used for calculating the gestational age.

#### 69 Study protocol

70 The study was performed in a quiet room with a temperature 71 range of 23-24 °C. Blood flow was measured using Filtrass strain-72 gauge plethysmograph (Filtrass; DOMED, Munich, Germany). 73 The device is mercury-free, with an integrated automatic 74 calibration system [11]. Briefly, the congestion pressure cuff was 75 placed around the right thigh with the women on left lateral 76 position and enclosed in a rigid corset. The venous congestion 77 pressure was raised rapidly by 40 mmHg and the pressure was 78 held for 20 s. Since this pressure occludes venous return, but not 79 arterial blood inflow, the initial swelling rate will equal arterial 80 blood flow. The change in circumference of the calf was estimated 81 from the slope of the first 3 s of the volume response to 82 the pressure step. This procedure was repeated three times, with 83 the congestion pressure kept at zero for 5 min between each of the measurements. The system analysis programme calculates the 84 change in circumference and uses it to estimate the f blood flow in 85 ml/min/100 ml<sup>-1</sup>. A Mediaid iPOX Pulse Oximeter (960 series, 86 87 Mediaid Inc.) with a universal hinged oximetry sensor which is 88 routinely used in many clinical situations was used to compare the 89 oxygen saturation in the three groups of women [12]. Arterial 90 blood pressure was measured non-invasively in the ipsi-lateral calf 91 and arm, using a Dinamap Vital Sign Monitor (Type 1800; Critikon, 92 Tampa, FL, USA).

#### Statistical analysis

All the data were normally distributed and the results are 94 presented as means  $\pm$  S.E.M. Statistical differences between the 95 groups were compared using one way ANOVA with Bonferroni 96 correction for multiple comparisons. Pearson correlation coefficients 97 were calculated and a forward multiple regression analysis 98 performed to detect any associations between blood flow and tissue oxygen saturation. This was also used to determine any correlations with clinical and biochemical variables. Statistical significance was assumed at p < 0.05. GraphPad Prism version 6 was used for the analysis.

#### Results

Table 1 shows the clinical and demographic characteristics of 105 the three groups of women. The pre-eclamptic group had 106 significantly higher systolic and diastolic blood pressures com-107 pared to the IUGR and normal pregnant groups (p = 0.001). None of 108 the women with pre-eclampsia or IUGR required antihypertensive 109 medication. As expected IUGR babies were significantly smaller 110 compared to babies born to mothers with pre-eclampsia without 111 IUGR and normal pregnant controls (p = 0.0001). There were no 112 significant differences in maternal age and haemoglobin levels 113 between the groups. However, women with pre-eclampsia were 114 delivered at significantly earlier gestational age (p = 0.0004), had 115 lower haematocrit (p = 0.014) and platelet counts (p = 0.043) 116 compared to the other groups. 117

Comparison of maternal tissue blood flow in normal, pre-eclampsia and IUGR pregnancies

Calf blood flow was significantly reduced in the pre-eclampsia 120 group compared to the other groups (1.050 ml/min/ 121  $100 \pm 0.101$  ml/min/100 ml:  $2.104 \text{ ml/min}/100 \pm 0.228 \text{ ml/min}/$ 122 100 ml and 1.95 ml/min/100  $\pm$  0.594 ml/min/100 ml for pre-eclamp-123 sia), normal pregnancy and IUGR respectively (ANOVA, p = 0.003) 124 (Fig. 1). Calf blood flow was significantly reduced in pre-eclampsia 125 compared to the normal pregnant controls (p = 0.002) and IUGR 126 group (p = 0.03). There was no difference in blood flow between the 127 normal pregnant controls and the IUGR women (p = 0.76). 128

In the normal pregnancy group, there was no correlation 129 between blood flow and any of the clinical and demographic 130 parameters such as maternal age (r = 0.061, p = 0.823), gestational 131 age (r = 0.039. p = 0.825), systolic blood pressure (r = 0.09, 132 p = 0.740), diastolic blood pressure (r = 0.180, p = 0.505), haemo-133 globin levels (r = 0.09, p = 0.740) or haematocrit (r = 0.034, 134 p = 0.901). However, there was a significant positive correlation 135 between the blood flow and platelet levels (r = 0.525, p = 0.037). 136 Nonetheless, there was no correlation between blood flow and 137 any of the clinical, demographic or laboratory parameters. In the 138 IUGR group, there was a significant positive correlation between 139

#### Table 1

Clinical and demographic characteristics of the normal, IUGR and pre-eclamptic subjects. Values are expressed as mean  $\pm$  S.E.M.

Variable	Normal	Pre-eclampsia	IUGR	p value
Mean maternal age (years)	$33.62\pm0.87$	$\textbf{33.62}\pm\textbf{0.83}$	$\textbf{34.66} \pm \textbf{1.02}$	0.73
Gestational age (weeks)	$39.37\pm0.27$	$37.06 \pm 0.50$	$\textbf{36.5} \pm \textbf{0.56}$	0.0004
Nulliparity	10	10	3	
Normal delivery	8	7	2	
Caesarean section	8	9	4	
Haematocrit	$0.352\pm0.003$	$\textbf{0.348} \pm \textbf{0.006}$	$\textbf{0.390} \pm \textbf{0.014}$	0.014
Platelets (10 <sup>9</sup> l <sup>-1</sup> )	$256.18 \pm 11.39$	$185\pm23.56$	$216.33 \pm 9.97$	0.043
Haemoglobin (gm/dl)	$11.88\pm0.17$	$11.76\pm0.27$	$12.8\pm0.503$	0.205
Systolic blood pressure (mmHg)	$118.93 \pm 1.60$	$154.37\pm2.4$	$120.33\pm2.98$	0.0001
Diastolic pressure (mmHg)	$\textbf{75.25} \pm \textbf{1.86}$	$99\pm2.06$	$\textbf{79.66} \pm \textbf{1.89}$	0.0001
Mean birth weight (g)	$3406.37 \pm 70.28$	$2854.06 \pm 149.6$	$2190\pm 66.08$	0.0001

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