Tissue pathway factor inhibitor (TFPI) activity is elevated in pregnant patients at 20 weeks gestation who subsequently develop preeclampsia

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Dear Sir,

Tissue factor (TF) acts as the trigger in the activation of the extrinsic mediated coagulation pathway and plays a key role in the regulation of haemostasis. Tissue factor pathway inhibitor (TFPI) is the principle inhibitor of TF. Only 15% of TFPI is circulating, the rest is bound to the vascular endothelial cell surface; only 20% of the circulating pool is free, the remainder is bound to lipoproteins (1). It has been shown that the inhibitory function of plasma TFPI is enhanced in the presence of protein S (2).

A role for TFPI has been proposed in several diseases that are characterized by activation of coagulation and thrombus formation, such as ischaemic heart disease, sepsis and stroke (3). In cases of hyper-coagulation, its elevated levels suggest an inhibitory response to counteract the disease process. TFPI has actually proved to be a good therapeutic agent of sepsis, inflammatory shock, and disseminated intravascular coagulation (DIC) (4).

Pre-eclamptic toxemia (PET), or pre-eclampsia, is a multisystem disorder occurring in pregnancy which is characterized by reduced organ perfusion related to vasospasm and activation of the coagulation system. It can cause placental insufficiency, with secondary damage in the form of fibrin deposition and thrombosis (5). A maternal systemic response follows as endothelial damage induces a rise in blood pressure associated with disturbed renal, hepatic, and coagulation functions (6). A number of haemostatic disturbances have been described in pre-eclampsia, including thrombocytopenia, consumption of coagulation factors and inhibitors with evidence of thrombin generation and inhibited fibrinolysis (7, 8).

Of interest are recent studies suggesting that free TFPI is elevated in PET and non-proteinuric hypertension. TFPI is synthesized primarily by the vascular endothelium and controls the activity of TF. In regards to PET, studies have shown the physiologically active free form of TFPI to be elevated in established

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BMI, body mass index; BP, blood pressure; PET, pre-eclamptic toxemia.
disease (9). Given this elevation in established PET at term, we investigated whether an elevation in TFPI activity occurred prior to the onset of the disease since this might allow identification of patients who are likely to go on to develop pre-eclampsia.

Women were recruited at 20 weeks gestation at University Hospital Coventry and Warwickshire (500 women in total). The patients were followed up and of the 500 recruited 20 developed PET. These cases were matched to 20 controls for age, ethnicity and body mass index (BMI).

PET was defined according to Davey & McGillivray, i.e. systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg on two occasions at least 6 hours (h) apart and proteinuria 300 mg/24 h or ≥2+ on urine dipstick (10). Ethical approval was granted (COREC 05/Q2802/122). TFPI activity was measured using the Actichrome TFPI Activity assay (American Diagnostica Inc., Stamford, CT, USA). This assay measures the ability of TFPI to inhibit the catalytic activity of the TF/FVIIa complex to activate factor X to factor Xa. Total TFPI was measured using the Imubind Total TFPI ELISA kit (American Diagnostica Inc.). In addition, protein S was measured using the Imuclone Protein S ELISA (American Diagnostica Inc, Stamford, CT, USA). The clinical characteristics of the patients are shown in Table 1.

At 20 weeks gestation no differences were found in any clinical parameters. Conversely at delivery those patients who subsequently developed PET had a significant elevation in their blood pressure and proteinuria. TFPI activity, total TFPI and protein S levels in both cases and matched controls were found to follow a normal distribution (Kolmogorov-Smirnov test for normal distribution was used). TFPI activity (mean ± standard error of the mean, SEM) was measured as; healthy controls (0.82 ± 0.15), and PET cases (1.33 ± 0.12). TFPI activity was significantly raised in women that developed PET when a paired t-test was performed (p=0.017) (Fig. 1A).

Protein S levels showed healthy controls (38.7 ± 3.29) and PET cases (32.2 ± 3.39) whilst total TFPI showed healthy controls (50.3 ± 2.34) and PET cases (52.2 ± 3.13). No significant difference was noted between cases and controls when paired t-tests were performed for either protein S or total TFPI (Fig. 1B and C).

This study finds that at 20 weeks gestation TFPI activity levels were significantly higher in those patients that developed pre-eclampsia when compared with matched controls. This is the first study that has shown an elevation in TFPI activity at such an early gestation.

As previously recognised, pre-eclampsia is a relatively common complication of pregnancy with potentially devastating consequences. Much research has been undertaken in the hope of finding a marker that may predate the onset of clinical symptoms and signs. Angiogenic factors involved in the vasculogenesis of placental invasion: PIGF and sFlt-1 have been highlighted as potential candidates. However neither has been found to vary significantly until later in the disease process (11–13).

The aetiology of pre-eclampsia is not fully understood, but women with pre-eclampsia tend to be more hypercoagulable than women in normal pregnancy. Multiple microthrombi can be found, particularly in the placental tissue of these women. It would therefore seem likely that TFPI would be elevated in these women, as...
has been found in other hypercoagulable disease processes. Studies have shown that while total TFPI levels in women with pre-eclampsia do not significantly differ from normal pregnancy (9, 14) free TFPI is elevated in pre-eclamptic women at term (8). In conclusion this elevation raises interesting questions regarding the disease prior to the onset of clinical signs. TFPI activity could behave as a coagulation inhibitory mechanism attenuating hypercoagulability in pre-eclampsia very early in the disease process, and warrants further investigation. This study is the first to show that TFPI activity is raised well before clinical signs of pre-eclampsia. It also raises the possibility of utilising measurement of TFPI activity as a clinical predictor of preeclampsia.

References