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Pre-eclampsia — a disease of oxidative stress resulting from the catabolism of DNA (primarily fetal) to uric acid by xanthine oxidase in the maternal liver: A hypothesis

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Abstract Pre-eclamptic toxaemia or toxaemia has become outdated terminology for the disease of pregnancy called pre-eclampsia (PE) but, according to this hypothesis, these may be more relevant. This hypothesis is that PE is a toxaemia or poisoning of the blood that results in multi-organ dysfunction and injury, putting at risk the lives of both the infant and the mother. Yet these dysfunctions and injuries are reversible with the cessation of the pregnancy and the disease can be reduced with vitamins (antioxidants) and aspirin.

This hypothesis is that the PE cascade starts with excessive shedding/embolisation of trophoblast from the placenta into the maternal venous circulation. This trophoblast embolisation ('deportation') is secondary either to an excessively large amount of trophoblast tissue ('hyperplacentosis') or to vascular trophoblast injury from a faulty uteroplacental circulation. The deported nuclear rich trophoblast is largely filtered out of the circulation in the lungs, and breaks down releasing fetal DNA. Accordingly, the level of fetal DNA in the maternal circulation rises. This DNA is then broken down in the maternal liver with the hepatocytes being presented with excessive amounts of purines for catabolism. In the hepatocytes of patients who subsequently develop PE, there is activation of xanthine oxidase (XO), the more toxic isoenzyme of xanthine oxidoreductase (XOR), with the generation of superoxide anion (O_2^-) as a by-product. Excessive superoxide production overwhelms the normal antioxidant ability of the tissues to produce oxidative stress.

In the hepatocytes, the excessive superoxide causes the peroxidation of polyunsaturated lipids to form microvesicular fat deposition. Excessive superoxide also causes hepatocellular damage with leakage of enzymes, lipids, DNA and superoxide into the circulation. In the circulation, oxidative injury of the blood corpuscles occurs releasing more DNA and accelerating purine catabolism and oxidative stress.

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The toxins, superoxide and the other reactive oxygen species (ROS), then travel in the arterial blood to the peripheral circulation where the microvasculature, the arterioles, capillaries, endothelial cells and venules, is injured. The damaged microvasculature leaks intravascular fluid into the extravascular compartment causing an intravascular dehydration and tissue oedema. In the kidneys, protein leaks through the damaged glomerular capillaries causing proteinuria. ROS causes arteriolar vasospasm and impairs vasorelaxation, mechanisms of hypertension. Micro-haemorrhages can occur and in the brain these, in combination with hypertension and oedema, can result in seizures or eclampsia.

Introduction

Why is it that only humans get toxaemia? Is it due to the fact that we lack the enzyme urate oxidase? Humans lack that enzyme because we have a defect in the gene that transcribes it [1] and so our UA is higher in comparison to other mammals. In humans, the final two reactions of the purine catabolic pathway are catalysed by the enzyme xanthine oxidoreductase (XOR) with the conversion of hypoxanthine to xanthine and then to UA. This reaction occurs mainly in the liver.

Hypertension, proteinuria and oedema define pre-eclampsia (PE) [2] but ''their causes are largely unknown'' [3]. For some, proteinuria is not essential to the definition [4]. Redman et al. [5] found that in terms of fetal outcome in PE, uric acid (UA) was a more important feature than hypertension. Roberts et al. [6] found that UA was ''at least as important as proteinuria in identifying pregnancies with gestational hypertension with at-risk infants.'' Many others have confirmed the importance of hyperuricaemia in PE with Yassaee [7] finding that all major measures of perinatal and maternal outcome were significantly worse in patients with higher UA. Roberts et al. [6] went on to recommend that hyperuricaemia be included in the definition of PE, at least for research purposes, as we have previously done [8,9].

As hyperuricaemia is quantitatively related to the outcome of the pregnancy for both the infant and the mother, Fay [10] proposed that UA production was an important factor in the PE disease process. He suggested that hyperuricaemia is mainly a metabolic outcome of placental injury via purine catabolism and concluded that ''the rise in UA in PE, which seems to mirror the disease process so closely, would be more logically related to some relevant process, such as placental damage, rather than some ill defined alteration in renal tubular function with, as yet, no known direct relationship to the PE disease process.''

Background

Trophoblast embolisation

Attwood and Park [11] analysed the findings from the post-mortem examination of the lungs of 220 women who died in association with pregnancy. They found embolised syncytiotrophoblast (STB) in the pulmonary capillaries of 84% of women who died of PE/eclampsia whereas they found STB present in only 27% of those dying from all other causes. They quantitated the amount of trophoblast present with a 'trophoblastic index'. Of those women who had detectable STB in their pulmonary capillaries, those dying of PE/eclampsia had more than twice the amount of STB than those dying of other causes. With PE/eclampsia the amount of STB was proportional to the severity of the disease. Blood collected from the uterine veins at the time of caesarean delivery in patients with PE had significantly more STB (microvilli) than in controls [12].

Uteroplacental circulation

In patients who develop PE, there is a failure in the development of the normal uteroplacental circulation, with a failure of the spiral arteries (the maternal vessels that supply the intervillous space of the placenta) to dilate and accommodate the ever increasing blood requirements of the pregnancy. The normal process by which this dilatation of the spiral arteries occurs is termed '*physiological change*' and this is the final stage of placentation is completed by 22—24 weeks gestation [13]. The spiral arteries that fail to develop normal *physiological change* may subsequently undergo a disease process of atheromatous change with a further narrowing and sometimes frank obstruction of these vessels and this process is termed '*acute atherosis*'.

The failure to develop a normal uteroplacental circulation results in placental injury with increased shedding of STB particles into the maternal circulation. The STB particles are made up of conglomerations of STB nuclei, the largest of which are filtered out in the maternal lungs. The STB particles and broken down releasing fetal DNA into the maternal circulation.

Fetal DNA

Cell-free fetal DNA (cffDNA) can be detected in the maternal blood in the form of the *SRY* gene from the Y chromosome from male fetal DNA. cffDNA has been found to be elevated in patients with PE with a male infant, with the elevation in cffDNA being proportional to the severity of the disease [14].

Levine et al. [15] in a large series of 120 cases and 120 controls demonstrated that in the 3 weeks before delivery the cffDNA levels in the maternal serum of PE patients rose to more than twice the levels in the controls. They also demonstrated a two-stage elevation of cffDNA in the maternal serum before the onset of PE. The first significant elevation of cffDNA occurred at the end of the second