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Review Article

Free Oxygen Radicals: The Toxins of Preeclamptic and Eclamptic Toxaemia of Pregnancy

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Abstract

This is a review of the roles of an abnormal uteroplacental circulation (UPC) and oxidative stress pathogenesis of preeclampsia (PE), as well as aspirin prophylaxis.

Two models of the pathogenesis (PE); Redman and Sergeant's (1991) and McMaster-Fay's (2008) are used in this review and are analysed in relation to the results of recent publications.

Both models agree on the primary importance of the development of an abnormal UPC or the failure to develop normal UPC. They also both agree on the importance of oxidative stress in the disease process but Redman and Sargent believe its importance is only in the clinical phase of the disease as McMaster-Fay believes it is important throughout the PE pregnancy. Recently published data would tend to confirm the later hypothesis.

Aspirin is known to ameliorate PE, with recent studies showing a delay the onset of the disease. The mechanisms by which this occurs are probably due to both aspirins antiplatelet and antioxidant activities. Controversy exists around when the therapy should start.

INTRODUCTION

Preeclampsia (PE) is the development of hypertension in pregnancy usually associated with proteinuria and hyperuricaemia. Most body systems are affected in the disease process and threaten both the lives of mother and infant. The disease processes of a reduced uteroplacental circulation and oxidative stress are here regarded as central to the pathogenesis of the disease and not a secondary result of it.

Redman and Sargent proposed a two stage model of PE [1]. The first stage is reduced placental perfusion (vascular) and the second stage, the maternal syndrome is due to inflammation / oxidative stress.

McMaster-Fay's model [2] on oxidative stress linked to the enzyme xanthine oxidase in the maternal liver. The first model relegates oxidative stress to the clinical stage of the disease, whereas the second emphasises the importance of oxidative stress throughout PE pregnancy.

Both models agree on the primary importance of the inadequate development of a normal uteroplacental circulation (UPC) in the first two trimesters of pregnancy in the predisposition to preeclampsia (PE). Despite this the majority of women with an inadequately developed UPC do not go on to develop PE. Uteroplacental Doppler flow studies and the measurement of circulating cell free fetal DNA (cffDNA) are reliable markers of an abnormal UPC.

Recently published data allows for further analysis if the two models and better understanding of the disease process.

Aspirin is known to provide prophylaxis against PE, but there is controversy as to the mechanism or mechanisms of action and also when this the therapy should start.

PATHOGENESIS OF PE

Redman and Sargent proposed a two stage model of preeclampsia (PE) [1]. The first stage is reduced placental perfusion (vascular) and the second stage, the maternal syndrome is due to inflammation / oxidative stress. In the first stage the spiral arteries of the placental bed fail to undergo normal *'physiological change'* where "the spiral arteries after being breeched by the non-villous trophoblast, undergo extensive adaptations and structural alterations in order to provide the intervillous space of the growing placenta with an adequate amount of maternal blood" [3]. This process they termed 'physiological change'. Then "from 15 or 16 weeks' gestation, there seems to be a wave of intra-arterial trophoblast migration beyond the deciduo-myometrial junction into the true

myometrial segments of the spiral arteries" [4].

We described the Doppler changes in the uteroplacental circulation in the mid-trimester of normal nulliparous pregnancy, observing the development of a low resistance circulation [5]. All the indices of flow showed a fall in resistance from 14 to 18 weeks and there was a further in resistance from 18 to 24 weeks. We are further investigating the abnormal features of the mid-trimester uterine artery flow velocity waveforms [6].

Not all pregnancies where the spiral arteries fail to undergo normal physiological change develop PE. In fact only a third [7] to a quarter [8] of pregnant women with reduced placental perfusion go on to develop PE. There are other abnormal pregnancy outcomes in patients with reduced placental perfusion than PE: IUGR; preterm delivery; placental abruption [9].

Subsequently, first trimester uterine artery Doppler studies along with biophysical and biochemical markers were shown to predict PE with a modest degree of accuracy [10]. Mid-trimester uterine artery Doppler studies on their own, are more accurate.

Histologically, in the second phase of the UPC disease process the spiral arteries undergo an atherotic disease process (termed *'acute atherosis'*) [11], which results in restriction of blood flow and even complete vascular occlusion. We proposed that this process is probably related to the release of reactive oxygen species (ROS) into the maternal circulation or systemic oxidative stress [2,12].

CELL-FREE FETAL DNA (cffDNA)

It has been found to be elevated in patients with PE, with the elevation in cffDNA being proportional to the severity of the disease [13]. The cffDNA levels rise in the maternal blood, primarily fetal from the syncitotrophoblast due to the uteroplacental vascular injury.

Levine et al. [14], in a prospective 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 trimester and the second elevation occurred in the last few weeks prior to the development of PE (above). These two peaks in cffDNA are synchronistic with the maldevelopment of the uteroplacental circulation of patients who develop PE, i.e. the failure of physiological change and the development of *acute atherosis*. We have recently communications as to the role of cffDNA in the pathogenesis of PE [15].

OXIDATIVE STRESS

In 2008, McMaster-Fay proposed that PE is 'a disease of oxidative stress resulting from the catabolism of DNA (primarily fetal) to uric acid by xanthine oxidase in the maternal liver' [2].

The purine component of the fetal DNA is catabolised in the maternal liver to uric acid by Xanthine oxidoreductase (XOR). XOR has two isoenzymes: xanthine dehydrogenase (XDH) and XO. The dehydrogenase is the most commonly active form of the enzyme although this can be converted to the oxidase. XO is the more toxic of these isoenzymes as it produces reactive oxygen species (ROS). ROS are toxic when their production increases beyond the natural antioxidant capacity of the tissues a state of 'oxidative stress' arises. The excess of ROS causes lipid peroxidation which disrupts membrane architecture as well as effecting a lysosomal enzyme release, all of which result in tissue injury.

Moretti et al. [16], studied multiple the chemicals in the exhaled breath of women with PE. These exhaled chemicals are representative of the chemical nature of the pulmonary arterial blood. They found significantly higher levels of the most of the multiple markers of oxidative stress in PE.

Recently, Ferguson et al. [17], reported on urinary metabolites as indicators of oxidative stress. They found 8-Isoprostane; a marker of lipid peroxidation; to be elevated throughout all trimesters of preeclamptic pregnancy. They also found that "the start of the second trimester appears to be a particularly important time point for the measurement of [this] biomarker". This data indicates that oxidative stress is occurring in Redman and Sergeant's [1] first (reduced placental perfusion) stage. Although their data is at odds with Redman and Sergeant's model, would fit with McMaster-Fay's model [2], where the substrate of XO is the cffDNA from the trophoblast in the 'placental perfusion' phase. In this later model, the primary oxidative stress in PE occurs from the catabolism of cffDNA in the maternal liver. This stress is coped with the naturally occurring antioxidants in the maternal hepatocytes. The balance is tipped once the hepatocytes become injured and the ROS leaks into the maternal circulation injuring white blood cells and vascular endothelium.

Both Ferguson et al.'s1 8-Isoprostane data and my model would be in agreement with the proposal of Roberts and Hubel [18], that oxidative stress could be the link in the two stage model of PE. According to McMaster-Fay's model of PE, purines are catabolised to produce uric acid via XO, whereas those who do not develop PE use the XDH isoenzyme [19].

It was recently demonstrated that the oxidative stress injury to the DNA of the placenta in PE is localized to the maternal and not the fetal side of the placenta' [20], indicating that the oxidative stress in PE is maternal in origin rather than from the feto-placental unit.

Using proton magnetic resonance spectroscopy (H-MRS) [1], we propose to study the oxidative stress within the hepatocyte in PE pregnancy.

ASPIRIN PROPHYLAXIS

Aspirin has been long known to be prophylactic against PE. Rolnik et al. [21], recently demonstrated that aspirin ameliorates PE by delaying the onset of the disease. They were able to demonstrate a significant reduction in preterm (<37 weeks) PE and dramatically, but not significantly, reduce the incidence of PE <34 weeks.

Tong et al. [22], state that possible biological mechanism of action of aspirin in the prevention of preeclampsia are that it: (1) "facilitates early placental embedding, a process that is in fact poorly understood but is likely to be complete by 16 weeks' gestation"; and/or (2) also increases prostacyclin (vasodilator); and/or (3) may decrease endothelial (blood vessel) dysfunction.

But they did not mention the effect of aspirin on platelets. By the inhibition of prostaglandin synthetase, aspirin blocks the production of thromboxane, the mediator of platelet activity. Thus aspirin renders the platelets non-functional and hence maintains circulation in small diseased blood vessels [23]. Tong et al. [21], also did not mention the antioxidant of activity of aspirin. Aspirin is known as an antioxidant [24] although this fact has escaped discussion in most of the obstetrics literature. Non-aspirin antioxidants offer prophylaxis against PE [8].

Our uterine artery Doppler observations of patients at high risk of preeclampsia at 12 weeks' gestation [25], were that both patients treated with aspirin and those not treated showed a reduction in uteroplacental resistance toward the expected median at 24 weeks' gestation. Also there was no significant difference between the observational and aspirin- treated cohorts. These observations would tend to indicate that aspirin does not have an effect on the failure of the normal physiological change of the spiral arterioles. Hence the effect of aspirin the UPC would appear to be the prevention of acute atherosis.

Aspirin probably treats the disease process in the preclinical phase by its antioxidant effect in the hepatocytes. Aspirin seems not to improve the maldevelopment of the spiral arteries of the UPC. Aspirins antiplatelet activity seems to prevent the secondary / clinical aspects of the disease.

There is controversy as to when aspirin prophylaxis should be started before 16 weeks or later with two meta-analyses publish in the same journal [26,27]. One meta-analysis published in 2001 [28] of randomised controlled studies that looked only at studies that started aspirin after 17 weeks gestation and included our randomised controlled study [29], This analysis showed a significant reduction in PE When aspirin is started in the second trimester. So much for meta-analyses as we previously questioned [30].

SUMMARY

The central pathogenic process of PE, are failure to develop a normal UPC and oxidative stress.

With the UPC in PE, the failure of normal 'physiological change' is followed by the development of 'acute atherosis' with narrowing and obstruction to the spiral arteries / arterioles.

Most of the pregnancies with failure to develop a normal UPC do not develop PE. It is proposed that those who develop PE do so because they produce ROS from purine catabolism because they use the isoenzyme XO. The ROS cause oxidative stress. The majority an abnormal UPC use the non-toxic isoenzyme XDH.

In the preclinical phase of PE, most of the oxidative stress is contained within the hepatocytes. But leakage occurs and the oxidative stress becomes systemic, leading to the clinical disease.

Aspirin probably treats the disease process in the preclinical phase by its antioxidant effect in the hepatocytes. Aspirins antiplatelet activity seems to prevent the secondary /clinical aspects of the disease.

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