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Review Article

A Role of Oxidative Markers in Pregnancy Induced Hypertension (PIH)

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ABSTRACT

Pregnancy induced hypertension (PIH) is a pregnancy related disorder characterized by hypertension and proteinuria noticeable after 20 wk of gestation. It is a leading cause of maternal and foetal mortality and morbidity worldwide. The aetiology of the disease is unknown, but recent studies have revealed that this disorder appears to originate in placenta and is characterized by widespread maternal endothelial dysfunction. Till date, delivery of placenta is the only cure for the disease. So, there is a need for the identification of highly specific and sensitive biochemical markers that would allow early identification of patients at risk and thus help in providing proper prenatal care. Several promising biomarkers have been proposed, alone or in combination, that may help in predicting women who are likely to develop PIH. This review focuses on the various oxidative biomarkers in prediction of pregnancy induced hypertension (PIH).

Key words: PIH, oxidative markers, hypertension.

INTRODUCTION

Hypertension is the most common medical problem encountered during pregnancy. Pregnancy induced hypertension (PIH) is defined as a direct result of the gravid state. American Congress of Obstetricians and Gynaecologists [ACOG] classified hypertensive disorders during pregnancy as [1]

1) Chronic hypertension preceding pregnancy
2) Gestational hypertension
3) Pregnancy-induced hypertension
a) Preeclampsia
- Mild
- Severe
b) Eclampsia
4) Chronic hypertension with superimposed PIH
- Superimposed preeclampsia
- Superimposed eclampsia

Hypertensive disorders complicate 5 to 10 % of all pregnancies. [2,3] In India, the prevalence is approximately 4-5%. [4,5]

About 5% females with pre-eclampsia develop eclampsia and of these 15% die from PIH itself or its complications. Pre-eclampsia is more common at the extremes of maternal age i.e. less than 18 and more than 35 yrs. Symptoms of PIH includes. [4,5]

Severe maternal complications include eclamptic seizures, intracerebral haemorrhage, pulmonary oedema due to

capillary leak, myocardial dysfunction, Acute Renal Failure due to vasospasm, hepatic damage. Fetal mortality is high due to increased incidence of premature delivery and uteroplacental insufficiency. PIH may be associated with placental abruption and low birth weight. HELLP syndrome is a complication of severe preeclampsia or eclampsia. HELLP syndrome is a group of physical changes including Hemolysis-the breakdown of red blood cells, Elevated Liver enzymes, and Low Platelet count. [6]

The definite cause of PIH is unknown but geographic, ethnic, racial, nutrition, immunologic, familial factors, pre-existing vascular disease may contribute. Pre-eclampsia has been described as a disease of theories because the cause is unknown. Some theories put forth are [7-10]

- Endothelial cell injury
- Compromised placental perfusion
- Imbalance between prostacyclin and thromboxane
- Dietary factors, including vitamin deficiency
- Decreased intravascular volume Genetic factors

The relatively new theory of endothelial injury explains many of the clinical findings in preeclampsia. Primarily, there is placental dysfunction leading to a syndrome of endothelial dysfunction with associated vasospasm. It was hypothesized that intermittent placental perfusion, secondary to deficient trophoblast invasion of the endometrial arteries, leads to an ischemia–reperfusion-type insult and results in the generation of free radicals. Free radicals attack fatty acids in cell membranes and lipid hydroperoxides are formed. Consequently, lipid peroxides may cause endothelial dysfunction and an increase in sensitivity to vasopressors in preeclampsia. Free radical production occurs continuously in all cells during normal aerobic metabolism as part of normal cellular function. However, cells have multiple protective mechanisms against oxidative stress. There is an equilibrium between prooxidant and antioxidant systems in intact cells. Imbalance favours prooxidants, which may lead to cell and tissue damage in preeclampsia. It is envisaged that increased free radical activity arises from increased production of free radicals or deficiency in protective antioxidant system. The vascular endothelium has many important functions, including control of smooth muscle tone through release of vasoconstrictor and vasodilatory substances, and regulation of anticoagulation, antiplatelet and fibrinolysis functions via release of different soluble factors. One potential mechanism for elevation in arterial pressure in response to a chronic reduction in uteroplacental perfusion is reduction in renal nitric oxide ($NO^{\cdot}$) synthesis. [11] Nitric oxide is a molecule with wide spectrum of physiological functions. One of them is maintenance of vascular tone and regulation of blood pressure by vasodilatation. [12,13] Thus, in conditions associated with abnormal blood pressure, there must be abnormality in nitric oxide metabolism. Chemically, Nitric oxide is a free radical. It reacts with many molecules, particularly with superoxide radicals. On exposure to superoxide anion, nitric oxide is converted to highly reactive peroxynitrite which causes lipid and protein oxidation, cell injury and cell death. [14]

Reaction of peroxynitrite with amino acid like tyrosine and cysteine givesnitrotyrosine and nitrothiol respectively. Superoxide is generated during normal aerobic metabolism. This free radical is neutralized by the enzyme Superoxide dismutase [SOD]. [15] However, SOD itself may be rendered functionless by NOÿ. Thus, increased synthesis of $NO^{\cdot}$ may lead to decreased neutralization of O2. Availability of more and more O2. may lead to formation of peroxynitrite.

Thus, this oxidant-antioxidant system may be more important in the pathogenesis of pre-eclampsia.

Pathogenesis: Though the exact mechanism of action continues to be elusive, the following factors may contribute to pregnancy induced-hypertension:

1. Abnormal trophoblast invasion: Normally, trophoblastic tissues invade spiral arteries and convert them into a delta, which is known to improve fetoplacental circulation. But deficient trophoblastic migration and expression of adhesion molecules form trophoblastic cells that may affect curtail the increased blood supply required by the fetoplacental unit in the laterstages of pregnancy. [16,17]

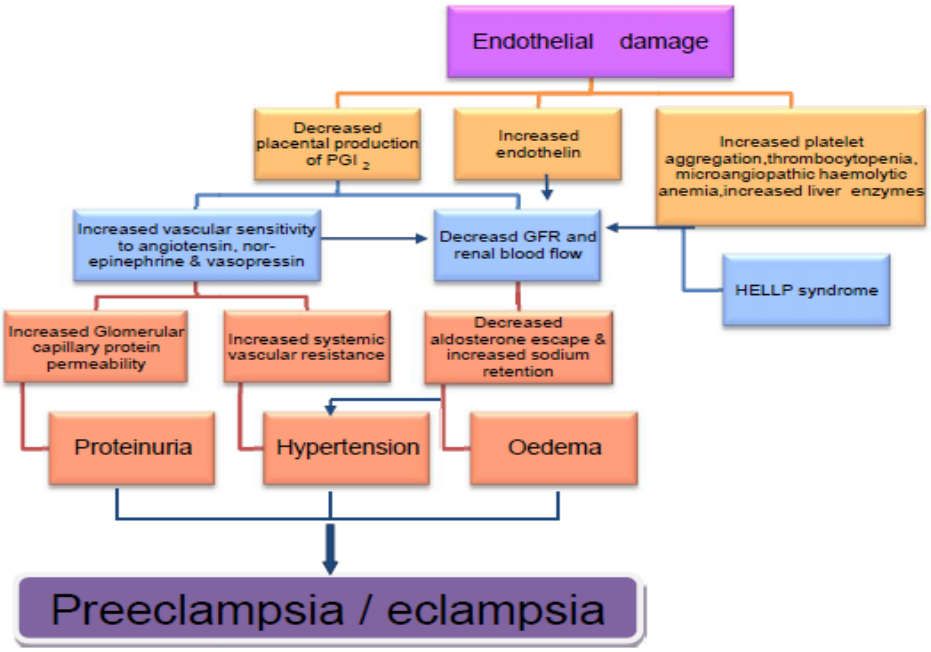
2. Uteroplacental hypoperfusion: The decreased uteroplacental blood flow and the clearance of steroid precursors for the synthesis of estrogens by the placenta, used as an indicator of placental perfusion, supports uteroplacental hypoperfusion. [17- 20]

3. Prostaglandin imbalance: Prostaglandin imbalance is due to defective production of vasoconstricting and vasodilating prostaglandin. Vasoconstriction and vasodilatation may affect the pathophysiology of preeclampsia as well as eclampsia. [21] Vascular constriction causes resistance to blood flow and accounts for the development of arterial hypertension. Goodmanet.al. reported elevated concentration of vasodilating prostaglandins during normal pregnancy. Elevated concentration of thromboxane along with decreased concentration of prostacyclin and PGE2 were observed in preeclamptic women, which resulted in vasoconstriction and platelet aggregation.

4. Endothelial dysfunction: The endothelium is a monolayer of polygonal flat cells, a biological barrier strategically located between the vascular smooth muscle and the blood stream. The endothelium participates in the modulation of vascular tone, control of primary haemostasis. The deficiency in the trophoblast invasion of the placental-bed spiral arteries leads to a poorly perfused fetoplacental unit, causing the secretion of a factor or factors into maternal circulation. These may lead to activation of the vascular endothelium with the clinical syndrome resulting in widespread changes in endothelial cell function resulting in the generation of free radicals.

5. Inappropriate intravascular coagulation: Platelets play a crucial role in the pathophysiology of preeclampsia by promoting vascular damage and obstruction, leading to tissue ischemia. [22,23] Redman concluded that preeclampsia is a trophoblast dependent process that is obviously mediated by platelet dysfunction.

6. Unexplained immunologic injury probably due to exposure to a foreign antigen: Immunologic factors may play an important role in the development of preeclampsia. [24] A marked reduction in C3 and C4 components in preeclampsia have been found, suggesting increased complement use in the acute phase of the disease [C3 and C4 are proteins involved in immune system]. Hofmeyr et.al. reported that C4 concentration decreased only in hypertensive pregnant women with proteinuria, whereas other findings showed the occurrence of neutrophil activation in preeclampsia localized in part of the placental bed. Perhaps the most popular concept in the pathophysiology of preeclampsia is endothelial dysfunction which explains most of the clinical findings in pre-eclampsia.



FACTORS LEADING TO PRE ECLAMPSIA

Prediction and Prevention: Prevention of any disease process requires knowledge of its etiology and pathogenesis, as well as the availability of methods to predict or identify those at high risk for this disorder. Numerous clinical, biophysical, and biochemical tests have been proposed for the prediction or early detection of preeclampsia. Unfortunately, most of these tests suffer from poor sensitivity and poor positive predictive values, and the majority of them are not suitable for routine use in clinical practice. At present, there is no single screening test that is considered reliable and cost-effective for predicting preeclampsia.

Maternal evaluation includes measurements of hematocrit, platelet count, liver function tests, and 24-hour urine protein testing once weekly. The women are usually seen twice a week for evaluation of maternal BP, urine protein by dipstick, and symptoms of impending eclampsia. [25,26] This evaluation is extremely important for early detection of progression to preeclampsia or severe hypertension. Maternal and perinatal outcomes in preeclampsia are usually dependent on one or more of the following: gestational age at onset of preeclampsia as well as at time of delivery, the severity of the disease process, the presence of multifetal gestation, and the presence of preexisting medical conditions such as pregestational diabetes, renal disease, or thrombophilias.

Perinatal mortality and morbidities as well as the rates of abruptio placentae are substantially increased in women with severe preeclampsia. There is a considerable literature devoted to the prevention of preeclampsia. However, there is some controversy over whether or not prevention of preeclampsia per se is a worthy goal, rather than the prevention of the complications of preeclampsia.

Oxidative markers: Table showing different Reactive Oxygen Species and Reactive Nitrogen- Oxygen Species.

ROS & RNOS	Description
$O_2^{\cdot-}$, superoxide anion	One-electron reduction state of O_2, Produced by the electron transport chain. Cannot diffuse far from the site of origin. Generates other ROS. Undergoes dismutation to form H_2O_2 spontaneously.
H_2O_2, hydrogen peroxide	Not a free radical, but can generate free radicals by reaction with a transition metal (e.g., Fe). Can diffuse into and through cell membranes. Two-electron reduction state, formed by dismutation of $O_2^{\cdot-}$ or by direct reduction of O_2.
$OH^{\cdot}$, hydroxyl radical	Three-electron reduction state, formed by Fenton reaction and decomposition of peroxynitrite. Extremely reactive, will attack most cellular components.
ROOH, organic hydroperoxide	Formed by radical reactions with cellular components such as lipids and nucleobases.
RO•, alkoxy and ROO•, peroxy radicals	Oxygen centred organic radicals. Lipid forms participate in lipid peroxidation reactions. Produced in the presence of oxygen by radical addition to double bonds or hydrogen abstraction.
HOCl, hypochlorous acid	Formed from H_2O_2 by myeloperoxidase. Lipid soluble and highly reactive. Will readily oxidize protein constituents, including thiol groups, amino groups and methionine. Attacking species is OCl.
ONOO-, peroxynitrite	RNOS. A strong oxidizing agent that is not a free radical. It can generate NO (nitrogen dioxide), which is a radical. Formed in a rapid reaction between $O_2^{\cdot-}$ and $NO^{\cdot}$. Lipid soluble and similar in reactivity to hypochlorous acid. Protonation forms peroxynitrous acid, which can undergo homolytic cleavage to form hydroxyl radical and nitrogen dioxide.
$O_2^{\uparrow\downarrow}$ Singlet oxygen	Oxygen with antiparallel spins. Produced at high oxygen tensions from absorption of uv light. Decays so fast that it is probably not a significant in vivo source of toxicity.
$NO^{\cdot}$ Nitric oxide	RNOS. A free radical produced endogenously by nitric oxide synthase. Binds to metal ions. Combines with O_2 or other oxygen-containing radicals to produce additional RNOS.

Nitric oxide: Nitric oxide is a double-edged sword as at optimum levels it acts as vasodilator, whereas when generated at high levels it is converted to prooxidant species as peroxynitrite and nitrogen dioxide. Peroxynitrite mediates peroxidation of unsaturated fatty acids. In vitro, peroxynitrite oxidizes diverse classes of lipids forming conjugated diene, malonyldialdehyde, lipid peroxide and lipid hydroxide etc. NO˙ can be protective against oxidative injury, depending on the specific conditions. A nitric oxide radical can both stimulate lipid oxidation and mediate oxidant-protective reactions in membranes. At high rates of NO production, the pro-oxidant versus antioxidant outcome depends critically on the relative concentrations of the individual reactive species. [27]

Performed extensive research on lipid peroxidation and antioxidant status in pre-eclampsia and observed that preeclampsia is associated with increased concentrations of oxidative stress markers including lipid peroxidation products, and a reduction in antioxidant concentrations and thus concluded that estimation of oxidative stress markers may be predictive of development of preeclampsia. [27] The increase in NO˙ production and the reduction of vascular resistance and arterial pressure during normal pregnancy has led investigators to hypothesize that a reduction in NO˙ production could be the cause of the increased vascular resistance and arterial pressure during preeclampsia. In support of this hypothesis, alterations in NO˙ production have been reported in women with preeclampsia.

Granger et.al. (2001) has suggested an increase in oxidative stress secondary to reduced placental perfusion as a possible mediator of the endothelial cell dysfunction associated with preeclampsia. [28]

Mutlu-Turkoglu U et.al.(1999) studied plasma Nitric Oxide metabolites and Lipid Peroxide levels in Preeclamptic pregnant women before and after delivery suggested that oxidative stress may cause endothelial dysfunction and that endothelial dysfunction may lead to hypertension by reduced release of vasodilating agents such as nitric oxide (NO˙). [29]

Choi et.al, (2002) investigated the changes in nitric oxide (NO˙) production during and after normal pregnancy and in pregnancies complicated by preeclampsia and observed that NO˙ production increases with advancing gestation during normal pregnancy and decreases in preeclampsia. [30] Kim and Park, (2006) suggest that decreased placental eNOS expression constitutes a characteristic finding in preeclampsia. Reduced larginine levels and therefore reduced nitric oxide is a cause for preeclampsia. [31]

Sultana Begum and co-workers, (2010) studied the physiological role of nitric oxide (NO˙) in normal pregnancy and preeclampsia and suggested that NO˙ may modulate the cardiovascular changes during pregnancy and impaired production of the molecule may play a significant role in the pathophysiology of preeclampsia. [32]

Nitrothiol: As a general rule, S-nitrosylation reactions cause specific physiological or pathophysiological activities by modifying protein function. Protein activity may be increased (e.g., p21 ras or thioredoxin) or inhibited (e.g., caspases, or methionine adenosyl transferase) by S-nitrosylation of specific systems. Endogenous S-nitrosylation reactions signal a broad spectrum of cellular activities independently of NOÿ radical formation/guanylyl cyclase activation. These include transcriptional and post-transcriptional regulation of protein expression as well as regulation of

membrane, cytosolic, mitochondrial, nuclear, and extracellular protein functions. The cellular synthesis, compartmentalization, and catabolism of low-molecular weight and proteinS-nitrosothiols appear to be specifically regulated; however, the study of each of these topics is in its infancy. [33]

Tyurin et.al., (2001) tested the hypothesis that total S-nitrosothiol and S-nitrosoalbumin concentrations are increased in preeclampsia .The study reported increased concentration of S-nitrosoalbumin in preeclampsia that almost completely accounted for the increased levels of S-nitrosothiols. They concluded that S-nitrosoalbumin and total S-nitrosothiol concentrations are significantly increased in preeclampsia plasma and may reflect insufficient release of $NO^{\cdot}$ groups in this condition. Because ascorbate is essential for the decomposition of S-nitrothiols and the release of $NO^{\cdot}$, we speculated that the ascorbate deficiency typical of preeclampsia plasma might result in decreased rates of decomposition of S-nitrosothiols. [34]

Gandley and Vladimir, (2005) also concluded that increased nitrothiol owing to deficiency in ascorbate and copper has a role in PIH. [35,36] The relaxation responses of nitrothiol in pooled plasma from normal and pre eclamptic pregnancies were examined in isolated mouse arteries. Free copper and ascorbate was added in excess and at lower levels and vasodilatory response of nitrothiol was observed in isolated arteries. The data indicated that nitrothiol alone can act as a potent vasodilator and sufficient ascorbate and copper promotes this action. [37]

Thiol: Thiols (sulfhydryls, mercaptans, [R-SH]) exist in vivo in three forms which include the free thiol (e.g., RSH), and two types of disulfides. [38] The latter include homodisulfides (RSSR) formed between two identical thiols (e.g., glutathione disulfide) and heterodisulfides (RSSR) (mixed disulfides) formed between two different thiols (e.g., protein bound homocysteine). [39] Thiols are powerful reducing agents capable of acting as antioxidants in vivo. For example, glutathione (γ-glutamyl-cysteinyl-glycine-GSH) in the presence of glutathione peroxidase readily reacts with the pro-oxidant, hydrogen peroxide to form water and glutathione disulfide (GSSG). [40,41]

2GSH + H2O2 >>GSSG + 2H2O

The thiol status in the body can be assessed easily by determining the serum levels of thiols. Decreased levels of thiols has been noted in various medical disorders including chronic renal failure and other disorders related to kidney, cardiovascular disorders, stroke and other neurological disorders, diabetes mellitus, alcoholic cirrhosis and various other disorders. [42] Therapy using thiols has been under investigation for certain disorders.

Wronska-Nofer et. al. (2007) investigated whether plasma thiols act as prooxidants or antioxidants. For this they compared plasma oxidative status in patients with coronary heart disease (CHD) and in subjects occupationally exposed to carbon disulfide (CS(2))and the results demonstrated that regardless of their metabolic origin increased thiols are associated with increased oxidative stress in plasma. [43]

Raijmakers and colleagues (2001) measured levels of oxidized and free thiols in whole blood of normotensive pregnant and preeclamptic women and evaluated the role of oxidative stress. The conclusion was significantly lower ratios of free to oxidized cysteine, homocysteine, and cysteinylglycine in preeclampsia which might indicate oxidative stress. [44]

Simmi Kharb (2005) studied alterations in the balance of the thiol in PIH. In preeclampsia both plasma and red blood

cells' thiol levels were significantly lower compared to controls. [45]

Superoxide dismutase (SOD): Superoxide dismutases (SOD, EC 1.15.1.1) are enzymes that catalyse the dismutation of superoxide into oxygen and hydrogen peroxide. Dismutation which is also called as disproportionation is a specific type of redox reaction in which a species is simultaneously reduced and oxidized to form two different products. Thus, they are an important antioxidant defense in nearly all cells exposed to oxygen. Superoxide may be generated nonenzymatically from Coenzyme Q(CoQ), or from metal-containing enzymes. (e.g., cytochrome P450, xanthine oxidase, and NADPH oxidase). [45]

Llurba et.al. (2004) analyzed in depth the potential role of oxidative stress as a mechanism underlying endothelial damage in pre eclampsia and the pregnant woman's susceptibility to the disease. Globally, these data reflect mild oxidative stress in blood of preeclamptic women, as oxidative processes seem to be counteracted by the physiologic activation of antioxidant enzymes. [46]

Anne and colleagues (1999) summarised that there appears to be an increase in ROS generation in the placenta of preeclamptic women. There is evidence for increased nitrotyrosine formation in the preeclampsia placenta suggestive of ONOOÿ production, perhaps arising from local NOÿ production coupled with increased xanthine oxidase generation of O2. and either regionally decreased or inadequate SOD. Whether this could lead to oxidative stress and/or endothelial dysfunction in the systemic circulation is uncertain. Beneficial/compensatory effects of ONOO - are also plausible. For example, ONOO can lessen leukocyte rolling and adhesion to endothelial cells and inhibit platelet aggregation. [47]

Roggensack (1999) suggested the evidence of peroxynitrite formation in the vasculature of women with preeclampsia. In striking parallel to data in the placenta, immunohisto chemical analysis of microvessels from biopsies of subcutaneous fat suggests increased peroxynitrite formation in preeclampsia. The percentage of vascular endothelium staining for nitrotyrosine was greater in preeclampsia (73%) than normal pregnancy (3%). Greater staining was also seen just outside the endothelium, possibly due to diffusion of peroxynitrite from the endothelium. In conjunction, the intensity of endothelial cell immunostaining was significantly lower for SOD. [47,48]

Wilson et.al., (1994) investigated SOD levels in PIH study and confirmed that there was a decreased SOD activity in PIH. [49] The author further investigated whether decreased SOD activity in PIH resulted from gene abnormalities. Genomic DNA and m RNA were isolated from white blood cells and subjected to Southern and Northern blot analysis with 600bp Cu Zn-SOD. probe. SOD activity was also determined in white blood cells and red blood cells. The results showed that SOD activity was significantly reduced in PIH as compared to control group. There was no significant difference in the size of the Cu Zn-SOD gene and its expression between the patients with PIH and the controls. So, the results suggested that decreased SOD levels in PIH are not due to abnormalities in the Cu Zn-SOD gene but an acquired phenomenon which occurs during the development of disease.

Bargale and co-workers (2011), studied SOD levels in pre-eclampsia and found their values to be less pointing its role in pathogenesis of PIH. [50] The author attributed decreased SOD activity to its utilization towards detoxification of hydrogen peroxide and other toxic metabolites produced during gestation in pre eclampsia.

Chamy et.al (2006) elaborated the reason of low enzymatic SOD activity shown in the pre-eclamptic patients. He explained it as lack of induction for production of SOD, since superoxide anion is reacting with nitric oxide to produce high peroxynitrite levels and, at the same time, explains the low nitric oxide levels that are usually found. [51]

CONCLUSION

It is concluded from this study that oxidative stress represents a point of convergence for several contributing factors potentially leading to the clinical manifestations of pregnancy induced hypertension. The antioxidants are used up while scavenging the free radicals. Adaptive mechanisms enhancing the maternal antioxidant defence system that counteract the effects of free radicals through enzymatic induction could prevent the occurrence of oxidative stress.

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