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ISCHEMIA MODIFIED ALBUMIN (IMA) IN SERUM AS A BIOCHEMICAL MARKER IN PRE-ECLAMPSIA

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ABSTRACT

BACKGROUND: Pre-eclampsia (PE) , a pregnancy specific disorder is the most common cause of foetal and maternal death. Yet no specific prevention and treatment is available. Ischemia Modified Albumin (IMA) has emerged as a marker in different diseases where ischemia is the origin or consequence behind disease pathology. Reliable biochemical markers for prediction and diagnosis of PE can have a better impact on maternal health and several of the markers have been suggested till now. MATERIALS & METHODS: 30 patients with PE were selected for the study and compared with 30 pregnant healthy controls. IMA were estimated in these patients. The results were then statistically analysed. RESULTS: IMA levels were found significantly raised in PE patients as compared to normal pregnant controls (p value<0.001). CONCLUSION: IMA which is generated by hypoxia/ischemia driven oxidative stress is also raised in PE and hence can be used as a biomarker in PE. Further studies are needed to establish the relationship between IMA and the disease process and its association with severity of disease.

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INTRODUCTION

Hypertensive disorders of pregnancy are one of the major cause of maternal mortality. It occurs in approximately 6-8% of all pregnancies, 10% of first pregnancies and almost 20% of women with a history of hypertension. Pre-eclampsia is a multisystem disorder of unknown aetiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after the 20th week of gestation in a previously normotensive and non-proteinuric women. It accounts for approximately one fourth of all antenatal admissions. Incidence of pre-eclampsia in India is reported to be 8-10% of all pregnancies.

Impaired endovascular invasion of cytotrophoblast into the spiral arteries is implicated as a causal factor of the condition. Other theories regarding its pathogenesis include increased insulin resistance, oxidative stress, immunological tolerance between maternal and foetal tissue

Pre-eclampsia is one of the most common causes of prematurity accounting for 25% of all very low birth weight infants with birth weight less than 1500 grams. Recurrence risk is of 32% for pre-eclampsia and 46% for pre-eclampsia superimposed on pre-existing chronic hypertension.[1]

Hypertensive disorder of pregnancy was classified by working group of National High Blood Pressure Education Programme (NHBPEP 2000) into five types-

Gestational Hypertension

- Elevation of blood pressure ≥ 140/90 mm Hg noted for the first time during pregnancy after 20 weeks of gestation.
- No proteinuria.

Pre-eclampsia

- Elevation of blood pressure ≥ 140/90 mm of Hg noted for the first time during pregnancy after 20 weeks of gestation.
- Proteinuria of ≥300 mg/24 hours by dipstick method in a random urine sample.

Eclampsia

- Eclampsia is defined as development of seizures that cannot be attributed to other causes in women with pre-eclampsia.

Pre-eclampsia superimposed on chronic hypertension

- New onset of proteinuria ≥300 mg/24 hours in hypertensive women but no proteinuria before 20 weeks of gestation.

Chronic hypertension

- It is defined as presence of BP≥140/90 mm Hg before pregnancy or diagnosed before 20 weeks gestation or hypertension first diagnosed after 20 weeks gestation and persisted after12 weeks postpartum.

Pre-eclampsia is associated with defective endovascular trophoblast invasion and inadequate remodelling of uterine spiral arteries leading to hypoxic intrauterine environment and generation of hypoxic environment and generation of oxidative free radicals. Accumulation of biomarkers of oxidative stress accompanied by depletion of antioxidant reserves is considered as a hallmark of Pre-eclampsia.

As placental hypoxic conditions are found in Pre-eclampsia and oxidative stress is implicated in its pathogenesis, maternal serum Ischemia Modified Albumin (IMA) can be a potent biomarker of pre-eclampsia.

Under normal conditions the amino terminal of Human Serum Albumin (HSA) binds to transition metals.[2] Ischemia reperfusion injury generates reactive oxygen species which modifies the N-terminal region of HSA, which further reduces its capacity to bind to the transition metals. This chemically modified albumin is known as Ischemia Modified Albumin (IMA).[3]

AIM & OBJECTIVES

To determine and compare the values of IMA in pre-eclamptic primigravida and healthy pregnant females.

MATERIALS AND METHODS

This cross sectional clinical study was conducted with pre-eclampsia patients as cases and healthy pregnant females as controls from April 2017 to April 2018.

The cases and controls were selected from tertiary care hospitals in local geographical area.

Written informed consent was taken from each study subject.

Selection of study subjects

- Based on inclusion and exclusion criteria total 60 study subjects (30 cases and 30 controls) were selected for the study. A proforma was used to record relevant information and patient's data.
- CASES = 30 women with hypertensive disorders of pregnancy were selected on the basis of definition given by National High Blood Pressure Education Programme (NHBPEP 2000).
- CONTROLS =30 healthy pregnant females.

INCLUSION CRITERIA

- 30 diagnosed cases of pre-eclampsia in the age group of 20-45 years.
- Pregnant females of ≥ 20 weeks of gestation with blood pressure of ≥140/90 mm of Hg noted first time during pregnancy on ≥2 occasions at least 6 hours apart with proteinuria of ≥ 1+ by dipstick method in a random urine sample was considered to have pre-eclampsia.
- Control = healthy sex matched 30 controls were taken.

EXCLUSION CRITERIA

- History of chronic hypertension that was present before pregnancy.
- History of diabetes mellitus and/or who are on insulin therapy.
- Subjects taking anti-hypertensive drugs.
- Liver disease patients.

Collection of Blood samples

- About 6ml of blood was drawn under aseptic precautions from selected subjects with overnight fasting of 12 hours.
- 3 ml of blood was collected in a plain vial for serum IMA (maternal).
- The blood samples were centrifuged at 3000 rpm for 10 minutes to obtain the serum.

Parameters to be Measured

The parameters which are to be measured in the cases and controls is maternal serum IMA.

Measurement of serum Ischemia Modified Albumin (IMA)

It is done according to Bar Or et al 2000.[4]Unbounded cobalt was measured by the intensity of coloured complex formed after reacting with dithiothreitol by spectrophotometer at 470 nm.[5]

RESULTS

Table 1 – IMA in cases & controls.

Parameter	Case	Control	p-value
Mean Age	26.7 ± 4.20	26.4 ± 4.32	0.5367
IMA	0.475 ± 0.072	0.262± 0.043	<0.0001*

*significant difference.

The IMA variables were noted on cases as well as control. All the variables were continuous in nature. T-test for two independent variables has been applied to analyse the data as the samples are independent. It was observed that IMA levels were found to be higher in cases compared to control.

DISCUSSION

Pre-eclampsia is associated with defective placentation leading to failure of conversion of small diameter high resistance vessels to large diameter low resistance vessels leading to ischemic reperfusion injury leading oxidative stress and generation of free radicals. Eclampsia is the end stage of the disease characterized by other features along with generalized seizures.[6]

Biochemical markers in pre-eclampsia can not only allow early detection of patients at risk but can also help in management according to their severity for timely intervention. Many different biophysical and biochemical markers have been investigated based upon pathophysiology of the disease but their reliability in predicting pre-eclampsia has not been studied extensively.

In the present study a significant rise in serum IMA was observed in patients with pre-eclampsia compared to normal pregnant women.. There occurs haemodilution in pregnancy leading to decrease in plasma albumin concentration so IMA was normalized to albumin by calculating IMA/Albumin ratio. Our findings were in line with the studies by Gaf Sou et al and Yusuf Ustun et al. Serum IMA has also been observed to be significantly higher in clinical states where oxidative stress is the consequence of the disease process Placental hypoxia leads to ischemic reperfusion injury resulting in the generation of free radicals which leads to alteration of NH^2 terminus of albumin resulting in reduced binding of albumin to cobalt compared to normal pregnant control.[7,8]

In a study done by Van Rijn et al IMA was found to be increased in normal pregnant controls compared to the non-pregnant controls (p=0.015) but the IMA levels in pre-eclampsia were similar to those of normal pregnant controls (p=0.65). The discrepancy in these studies could possibly be explained by smaller number of patients and differences in severity of pre-eclampsia.[9]

Increase in serum MDA was also observed in various studies like the observations by Ebru Dikensoy et al, Yoneyama Y et al and Mohd. Sahail et al. These findings on maternal serum MDA provides further emphasizes that excessive lipid peroxidation may play an important role in pathophysiology of pre-eclampsia.[10] There is significant positive correlation between the maternal serum IMA and MDA as well as serum IMA/Albumin and MDA in pre-eclampsia suggesting that IMA levels increase with increase in oxidative stress due to ischemia induced by reperfusion injury or free radicals. This is in line with the work by Debasis Roy et al where it was suggested that increased IMA levels may result from increased oxidative stress whether caused by ischemia reperfusion injury or other mechanisms primarily due to reduction in blood flow.[11]

CONCLUSION

Significant increase of IMA pre-eclampsia suggests that measurement of this oxidative biomarker may be useful in identifying patients at risk of developing pre-eclampsia as well as monitoring the treatment modalities of pregnancies with pre-eclampsia.

IMPLICATIONS

IMA can be useful biomarker in monitoring pregnancies with respect to the development of pre-eclampsia. It shall be very useful in near future to compare and elucidate proper diagnosis of pre-eclampsia followed by its treatment.

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