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Association of Ischemia Modified Albumin with Pregnancy Induced Hypertension

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INTRODUCTION

Pre-eclampsia occurs in 5% to 8% of pregnancies worldwide and is the second leading cause of direct maternal and fetal deaths [1]. Its prevalence in India is 54% and 56.2% in urban and rural communities respectively. Its occurrence in Tamil Nadu is 47.4 % to 48.7%[2].

Pre-eclampsia affects both mother and fetus. It may lead to eclampsia, HELLP syndrome, ischemic stroke, liver dysfunction and acute respiratory distress syndrome (ARDS)[3].

Abnormal placental vascular development is the basis of common obstetric disorders such as preeclampsia and intrauterine growth restriction[4].

Preeclampsia associated with defective endovascular trophoblastic invasion and inadequate remodeling of uterine spiral arteries leads to hypoxic intrauterine environment and generation of reactive oxygen species (ROS) which is implicated in its pathogenesis[5].

Roy et al revealed reactive oxygen species (ROS) produced during ischemia/reperfusion, can generate the highly reactive hydroxyl radical, resulting in site-specific modification to the N-terminus of the albumin moiety thereby producing Ischemia Modified Albumin (IMA).This occurs within minutes of the tissue insult, and its relatively short half-life makes it a marker of ongoing ischemia[6].

Uterine artery Doppler velocimetry has revolutionized the investigation of the developing placental vasculature. Increased resistance to flow within the uterine arteries results in an abnormal waveform pattern or by the persistence of unilateral and bilateral diastolic notch. Doppler Ultrasonography technique, done in second trimester, is used to find the uterine artery notching in pregnancy induced hypertension[7].

But according to Reem Mustafa, among high-risk patients with previous preeclampsia, Doppler ultrasound of the uterine arteries has an excellent negative predictive value[8].Blood flow velocity measured by Doppler ultrasound is currently used to assess fetal health and to aid in decision for intervention of growth restricted fetus. Maternal uterine artery Doppler velocimerty is used to predict placental dysfunction[9].

Uterine artery Doppler velocimetry by itself or in combination with other biochemical markers seems to be an effective second-trimester screening tool for preeclampsia and in particular early-onset preeclampsia[10].

This study attempts to make a correlation between Ischemia Modified Albumin(IMA) and Uterine artery Doppler Utrasonography in diagnosing pregnancy induced hypertension.

REVIEW OF LITERATURE

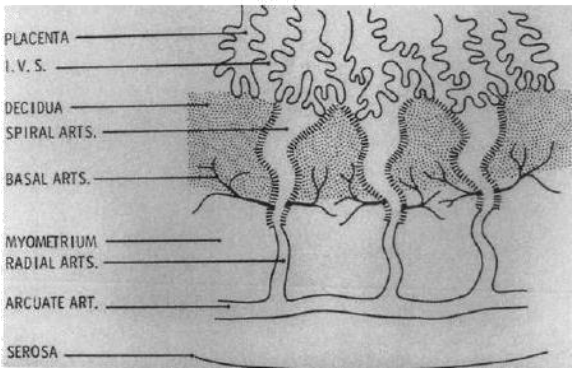
Hypertensive disorders of pregnancy, including preeclampsia, consists of a broad spectrum of conditions which are associated with substantial maternal and fetal morbidity and mortality. Its incidence is estimated to a range between 3%to 10% among all pregnancies [11]. Approximately 12-25% of growth restricted fetuses and small for gestational age infants as well as 15-20% of all preterm births are attributable to preeclampsia[12]. More than 3 million newborn babies die every year and an additional 2.6 million babies are stillborn[13].Prevalence in India is about 54 to 56.2% and Tamil Nadu being 47.4 to 48.7%[2].

Preeclampsia is defined as the new onset of sustained elevated blood pressure i.e, 140mm of Hg systolic and 90mm of Hg of diastole, on at least two occasions 6 hours apart and proteinuria (300mg in a 24 hour urine collection or 1+ in dip stick) first occurring after 20 weeks of gestation[14].

Risk factors of preeclampsia are nulliparity, age, race, obesity, multiple pregnancy, smoking, family history of preeclampsia, diabetes mellitus, molar pregnancy[15].

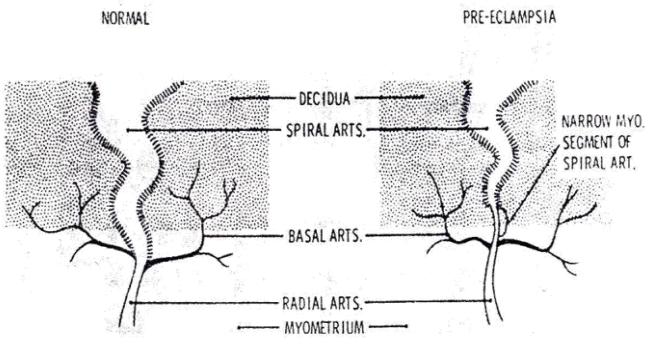
The clinical symptoms of preeclampsia are headache, visual disturbances, altered mental status, dyspnea, edema, epigastric pain, weakness, clonus[16].

In normal placental development the cytotrophoblasts invade the maternal spiral arterioles and transform them from small caliber resistance vessels to high caliber conduit vessels. This initial event begins at the end of first trimester (10-12 week) and ends by 18 to 20 weeks of gestation. During this vascular invasion the cytotrophoblasts differentiate from epithelial phenotype to an endothelial phenotype, a process known as pseudovasculogenesis. During this process, these make a direct contact with maternal blood. This process involves a considerable number of transcription factors, growth factors and cytokines like VE-cadherin and alpha V beta-3integrins[17].



*Fully developed physiological changes in the uteroplacental arteries during normal pregnancy. Hatched portion of the wall of these vessels indicate the extent of the physiological changes. (I.V.S – Intervillous space)[29].

During pre-eclampsia, the invasive cytotrophoblasts fail to transform epithelial phenotype into endothelial phenotype, instead the invasion of the spiral arterioles is shallow and these remain as small caliber resistance vessel which leads to defective uteroplacental circulation and placental perfusion worsens which subsequently leads to release of antiangiogenic factors into the maternal circulation that alter maternal systemic endothelial function and cause hypertension and other manifestations of the disease[16,18].



*Difference between normal and preeclamptic pregnancies regarding the extent of physiological changes in the uteroplacental arteries[29].

Placental hypoperfusion resulting from the incomplete invasion leads by an unclear pathway to the release of systemic vasoactive compounds that cause and exaggerated inflammatory response, vasoconstriction, endothelial damage, capillary leak, hypercoagulability and platelet dysfunction, all of which contribute to organ dysfunction and the various clinical features of the disease[19].

Pathophysiologic processes underlying this disorder are described as occurring in two stages. The first stage is characterized by reduced placental perfusion, possibly related to abnormal placentation, with impaired trophoblast invasion and inadequate remodeling of the uterine spiral arteries. The second stage refers to the maternal systemic manifestations characterized by inflammatory, metabolic and thrombotic responses that converge to alter vascular function, which can result in multiorgan damage[20].

Due to failure of conversion of high resistance vessel to a low resistance vessel, reactive oxygen species (ROS) are formed, generate highly reactive hydroxyl free radicals resulting in site-specific modification of the N-terminus of the albumin moiety, especially of the *N* Asp–Ala–His–Lys sequence, which result in a significant change in the ability of albumin to bind transition metals, notably, cobalt[21].

Droy and colleagues were the first to show that IMA formation is directly linked with the presence of reactive oxygen species (ROS), especially the hydroxyl radical (•OH). IMA is formed when serum albumin passes through ischemic tissues where the oxidative stress induces an increase in oxygen free radicals, which results in IMA formation *in vivo* by oxidative modification of serum albumin[22].

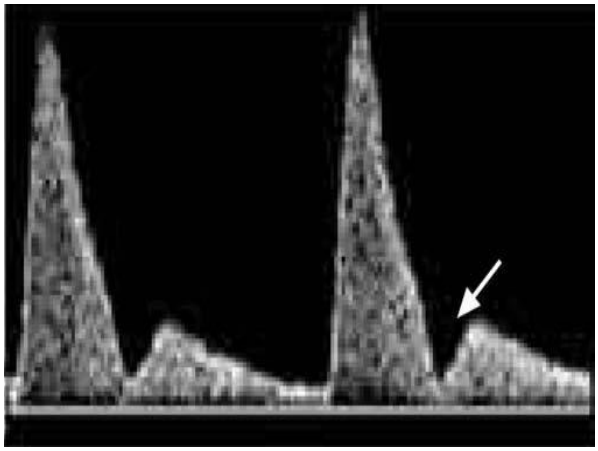
As hypoxia and oxidative stress are considered in etiopathogenesis of preeclampsia, serum IMA levels are also elevated in preeclampsia[23].

Previous studies have mentioned elevated levels of serum IMA in preeclampsia when compared with normal pregnancy. Very few studies have demonstrated the correlation of serum IMA with severity of preeclampsia[24].

Therefore the aim of this study is find an association between ischemia modified albumin and preeclampsia.

Pre-eclampsia and intrauterine growth restrictions are characterized by abnormal placenta formation, which results in inadequate uteroplacental blood flow. This has led to the idea of using Doppler ultrasonography to assess the velocity of uterine artery blood flow as part of routine ultrasound screening[25].

Low end-diastolic velocities and an early diastolic notch characterize the waveforms of uterine artery blood flow in women who are not pregnant or are in their first trimester. Persistence of a diastolic notch (beyond 24 weeks' gestation) or abnormal flow velocity ratios have been associated with inadequate trophoblast invasion [26].



*Uterine artery Doppler ultrasound scan showing early diastolic notch (arrow). The presence of diastolic notches is associated with an increased risk of pre-eclampsia and intrauterine growth restriction[30]

Accurate prediction of pre-eclampsia and intrauterine growth restriction is crucial to allow judicious allocation of resources for monitoring

and preventive treatment to improve maternal and perinatal outcomes. However, studies investigating the predictive accuracy of uterine artery Doppler indices have revealed considerably varied results[27]. According to Myatt L et al, the second trimester uterine artery Doppler ultrasound shows poor sensitivity for the prediction of preeclampsia overall in a well-characterized, low-risk, nulliparous population. Moreover the high negative predictive value of this technique is useful only as a rule out test. Doppler interrogation of uteroplacental blood flow may not identify all women at risk of preeclampsia. Thus the technique has poor predictive power when applied to the overall population of low risk women[28].

As pregnancy induced hypertension can cause major complications like eclampsia, HELLP syndrome, ischemic or hemorrhagic stroke, liver damage and dysfunction, acute kidney injury and acute respiratory distress syndrome(ARDS), increased frequency of Caesarian section, preterm delivery and placental abruption in mother and intrauterine growth restriction(IUGR)[3] and potential perinatal death in the fetus, a more reliable biochemical marker for prediction and diagnosis can be used for a better impact on maternal health rather than Doppler ultrasound of uterine artery.

AIM AND OBJECTIVES

AIM

To look for the association of Ischemia Modified Albumin (IMA) and Uterine artery notching by Doppler Ultrasound in pregnancy induced hypertension.

OBJECTIVES

- To estimate the serum IMA levels in women with pre-eclampsia and normal healthy pregnant women.
- To look for the Uterine artery notching in women with pre-eclampsia and normal healthy pregnant women.
- To compare the serum IMA levels with Uterine artery notching between them.

METHODOLOGY:

STUDY DESIGN: Case-Control study.

STUDY CENTRE: Department of Obstetrics and Gynaecology and Biochemistry in our Institution.

STUDY PERIOD: April-June 2016.

STUDY POPULATION: Total sample size 60 (30 cases and 30 controls).

CALCULATION OF SAMPLE SIZE

$N = \frac{r+1\ (S.D)^2(Z\beta + Z\alpha/2)^2}{r\ (\text{mean difference})^2}$

To estimate a mean difference of 21between the two groups, with pooled standard deviation of 22, with 1:1 case control ratio, at 80% power and 5%α-level, we need 30 Pre-eclampsia cases and 30 normal healthy pregnant women.

CASES

Inclusion criteria

Known pre-eclamptic pregnant women with blood pressure 140/90 mm of Hg and proteinuria ≥ 0.3 grams (300 mg) or more of protein in a 24-hour urine sample.

Exclusion criteria

Known pre-gestational hypertensive patients, bad obstetric history, twin pregnancy,

Previous medical diseases like diabetes mellitus, ischemic heart disease, peripheral vascular diseases.

CONTROL: Normal healthy gestational age matched pregnant women.

INVSTIGATIONS

Under strict aspetic conditions 5ml of blood sample is collected by venipuncture, into labeled plain polystyrene tubes. Blood samples are centrifuged at 5000 rpm for10 min and the serum is stored at -20◦ C until further analysis.

ROUTINE INVESTIGATIONS

1) MEASUREMENT OF BLOOD PRESSURE:

PROCEDURE

Measured by a standard protocol in accordance to JNC-8.

Blood pressure should be measured after the patient has emptied their bladder and has been seated for five minutes with back supported and legs rested on the ground (not crossed).

Arm used for measurement should rest on a table, at heart level.

Use a sphygmomanometer/ stethoscope or automated electronic device (preferred) with correct size arm cuff.

Take two readings one to two minutes apart, and average the readings (preferred).

Measure blood pressure in both arms at initial evaluation. Use the higher reading for measurements thereafter.

Blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic on two separate readings taken at least four to six hours apart after 20 weeks gestation in an individual with previously normal blood pressure.

In a woman with essential hypertension beginning before 20 weeks gestational age, the diagnostic criteria are: an increase in systolic blood pressure (SBP) of ≥30mmHg or an increase in diastolic blood pressure (DBP) of ≥15mmHg.

2) PROTEINURIA

Proteinuria ≥ 0.3 grams (300 mg) or more of protein in a 24-hour urine sample or a SPOT urinary protein to creatinine ratio ≥ 0.3 or a urine dipstick reading of 1+ or greater.

3) Fasting blood sugar

METHOD: GOD/POD method (Enzymatic end point method)

PRINCIPLE: Glucose present in the plasma is oxidized by the enzyme glucose oxidase (GOD) to gluconic acid with the liberation of hydrogen peroxide, which is converted to water and oxygen by the enzyme peroxidase (POD). 4-aminophenazone, an oxygen acceptor, takes up the oxygen and together with phenol forms a pink coloured chromogen which can be measured at 515nm.

Reference range:
Fasting: 70-100 mg/dl
Random : 80-120 mg/dl
Post prandial: 90-140 mg/dl

4) Urea:

METHOD: UV-GLDH method

PRINCIPLE: Urea is hydrolysed in presence of urease to produce ammonia and CO2.The ammonia produced combines with 2 – oxoglutarate and NADH in presence of GLDH to yield glutamate and NAD. The decrease in absorbance due to the decrease of NADH concentration in unit time is proportional to the urea concentration.

Reference range: 15-40 mg / dl.

5) Creatinine:

METHOD: Modified Jaffe's Reaction

PRINCIPLE: Creatinine reacts with sodium picrate in the presence of an alkali to produce yellow-orange creatinine-picrate complex that is measured colorimetrically at 520nm. Reference range: Females: 0.6-0.9 mg/dl;

CHIEF INVESTIGATIONS

1) DOPPLER ULTRASOUND

Doppler ultrasound of uterine artery has a high negative predictive value in high risk population in predicting preeclampsia, and hence it can be used as a screening test to rule out preeclampsia[28]. Doppler ultrasound cannot be used to identify all women at the risk of preeclampsia according to the study done by Myatt L et al. So assessing the uterine artery notching may not be significant in predicting preeclampsia, and the attempt in not made in this study[28].

2) MEASUREMENT OF ISCHEMIA MODIFIED ALBUMIN (IMA):

ALBUMIN COBALT BINDING COLORIME-TRIC ASSAY (ACB)

Principle

Serum albumin loses its ability to bind with the heavy metals like Co+2 at its N-terminal end due the damage caused by the "oxidative stress" is case of hypoxia and ischemia reperfusion in pre eclampsia. In ACB method a known amount of cobalt is added to serum and the unbound cobalt is measured by the intensity of colored complex with dithiothreitol by spectrophotometer at
470nm. IMA is expressed as U/ml. One IMA unit is defined as μ-gm of free cobalt in the reaction mixture per ml of serum sample.

DATA COLLECTION PROCEDURES AND INSTRUMENTS USED

Data collection will be done using standardized proforma by the principal investigator. All the biochemical analyses will be performed using automated (robonik - Autora) and semi-automated (MERCK) clinical chemistry analyzer.

QUALITY CONTROL

All biochemical analyses will be done with adequate internal and external quality checks, and within run and between run CV's will be maintained.

CONFIDENTIALITY

Informed consent will be obtained from all patients. Confidentiality and safety of the subjects will be taken care of.

STATISTICAL ANALYSIS

Coded data was entered in excel. It was analyzed with SPSS 20.0

The IMA in both groups was expressed as mean with standard deviation.

The correlation between IMA values and Doppler notching was expressed in terms of correlation coefficient- Pearson/Spearman.

The difference in IMA between the two groups was expressed as mean with standard deviation.

$p \leq 0.05$ was considered as statistically significant for two tailed test.

RESULTS

This case -control study conducted in the Department of Obstetrics & Gynaecology and Department of Biochemistry with 30 individuals in each group matched for gestational age, in an attempt to find an association of Ischemia modified albumin (IMA) with pregnancy-induced hypertension.

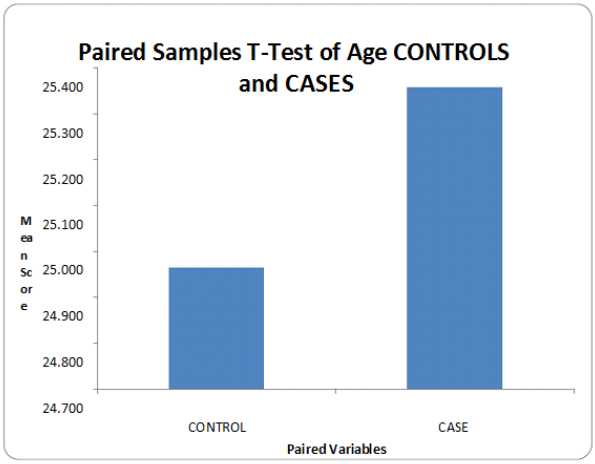
But 2 cases and 2 controls were found to have a high glucose levels which doesn't fit in the inclusion criteria. So this study was done with 28 cases and 28 controls.

COMPARISON OF AGE BETWEEN CASES AND CONTROLS

	CONTROLS	CASES
MEAN	24.964	25.357
STD. DEVIATION	3.294	3.889

p value: 0 .703(p value<0.05)

The p values is not significant, hence the controls and cases are age matched.

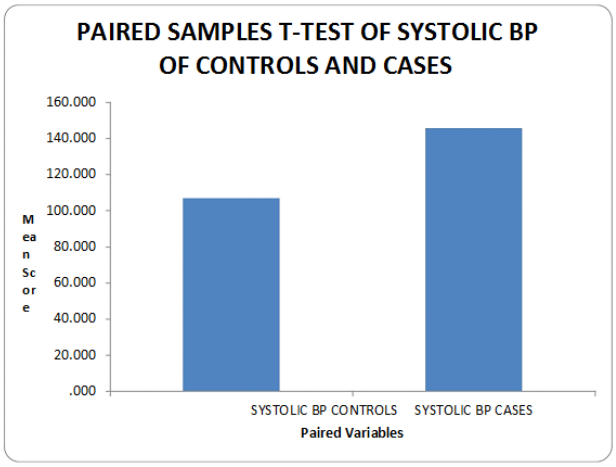


COMPARISON OF SYSTOLIC BP BETWEEN CONTROLS AND CASES

	CONTROLS	CASES
MEAN	106.786	145.714
STD. DEVIATION	9.833	12.599

Mean systolic BP of controls: 106.786
Mean systolic BP of cases: 145.714
p value: 0.000

Since the p value is <0.05, it is statistically significant. Hence the systolic BP in cases was found to be higher than in controls.

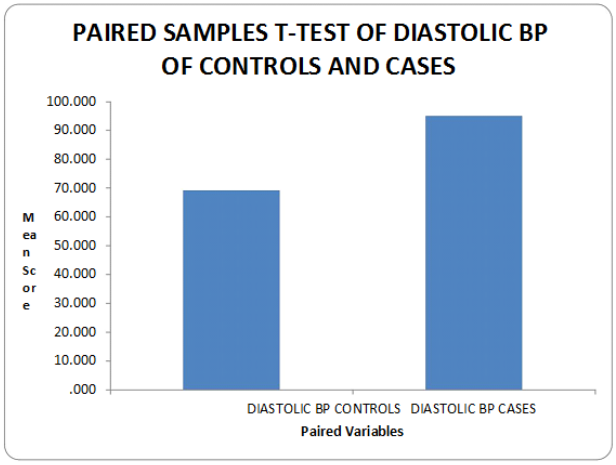


COMPARISON OF DIASTOLIC BP BETWEEN CONTROLS AND CASES

	CONTROLS	CASES
MEAN	69.286	95.000
STD. DEVIATION	9.400	6.383

Mean systolic BP of controls: 69.286
Mean systolic BP of cases: 95.000
p value: 0.000

Since the p value is <0.05, it is statistically significant. Hence the diastolic BP in cases was found to be higher than in controls.

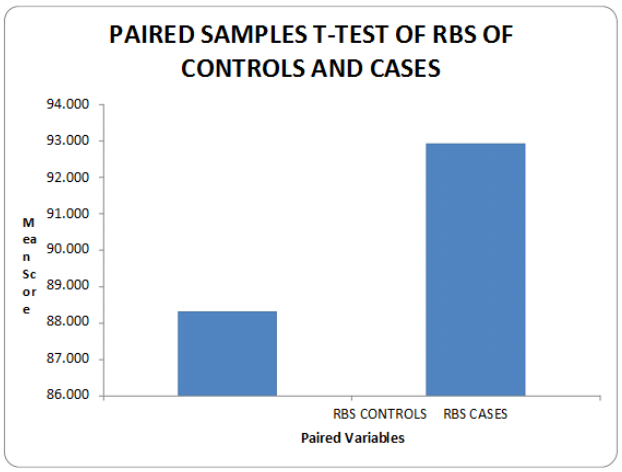


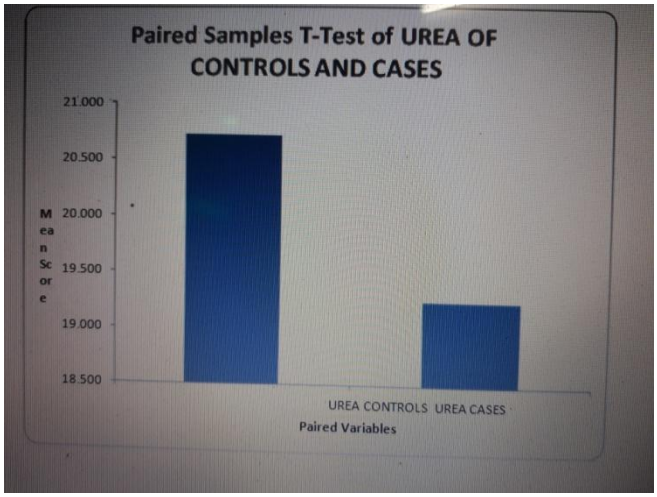
COMPARISON OF BLOOD SUGAR, UREA AND CREATININE BETWEEN THE STUDY GROUPS

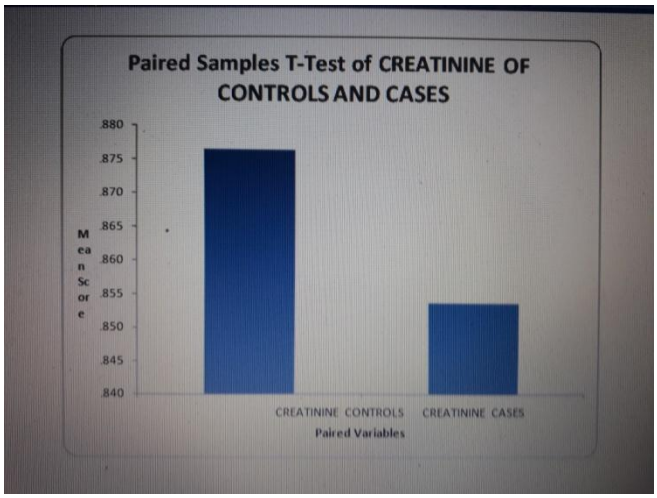
ASSAY	GROUP	N	MEAN	S.D.	P
RANDOM BLOOD SUGAR	Controls	30	88.321	13.982	0.315
	Cases	30	92.929	19.164	
UREA	Controls	30	20.714	5.442	0.315
	Cases	30	19.250	4.088	
CREATININE	Controls	30	0.876	0.230	0.592
	Cases	30	0.854	0.110	

The urea and creatinine levels of controls is increased when compared to cases Random blood sugar levels of controls is decreased when compared to cases

P values of all the 3 parameters are not significant.







COMPARISON OF ISCHEMIA MODIFIED ALBUMIN (IMA) BETWEEN CONTROLS AND CASES

	CONTROLS	CASES
MEAN	624.001	646.443
STD. DEVIATION	88.346	67.476

p value: 0.355

Although the values are statistically insignificant, an increasing trend is seen in cases when compared to controls.

DISTRIBUTION OF URINE ALBUMIN LEVELS AMONG THE CASES

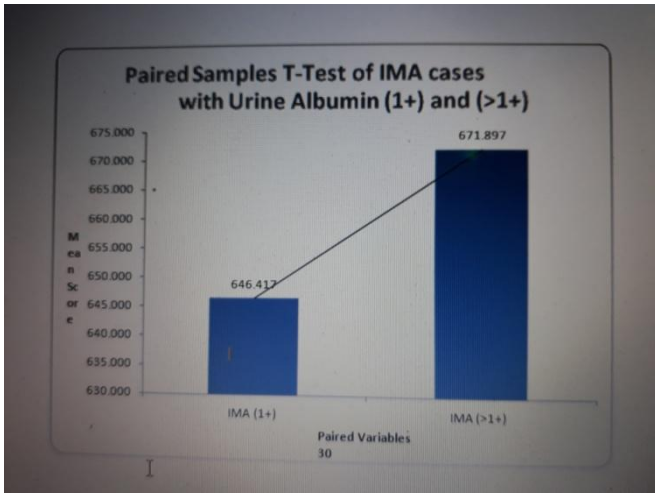
LEVEL OF ALBUMIN IN URINE	FREQUENCY	PERCENTAGE
1+	19	67.857
2+	5	17.857
3+	3	10.714
4+	1	3.571

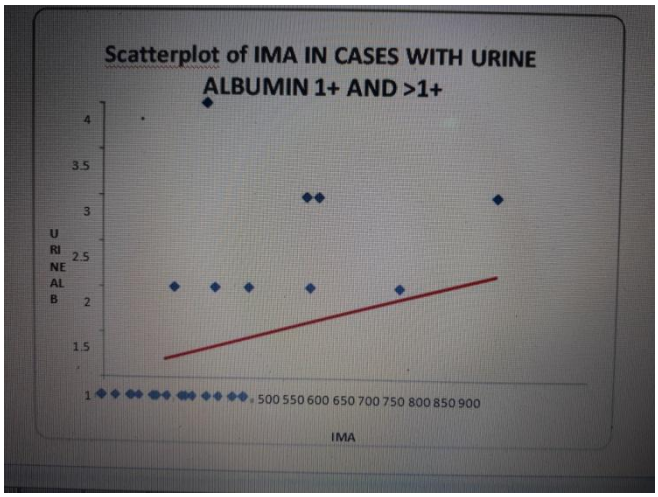
COMPARISON OF IMA IN CASES WITH URINE ALBUMIN OF 1+ AND >1+ :

	URINE ALBUMIN 1+	URINE ALBUMIN >1+
MEAN	646.417	671.897
STANDARD DEVIATION	50.565	90.019

p value: 0.282

The difference between IMA in cases having urine albumin 1+ and >1+ is not statistically significant but an increasing trend is seen between them.





DISCUSSION

The purpose of this study was to find the association of ischemia modified albumin with pregnancy induced hypertension. Hence a case-control study, which included 30 known cases of preeclampsia and 30 healthy pregnant women, was undertaken. The study was conducted in the Department of Obstetrics and Gynaecology and the Department of Biochemistry of our institution.

The exclusion criteria included known pre-gestational hypertensive patients, and those with bad obstetrics history, multiple pregnancies and previous medical conditions like diabetes mellitus, ischemic heart disease and peripheral vascular disease.

The cases and the controls in the study are age matched with mean value of 25.357 and24.964 respectively (p =0.703).

The systolic and diastolic blood pressure were significantly increased in cases as compared to controls with a mean of 145.714 and 95.000 respectively, with a p value 0.000(p<0.05).

The urea and creatinine levels of controls was increased when compared to cases with a mean of20.714 (p=0.315) and 0.876 (p=0.592) in controls and a mean of 19.250 and 0.854 in cases, respectively. Random blood sugar levels of controls was decreased when compared to cases with a mean of 92.929in casesand a mean of 88.321 in controls (p=0.315). However, all the 3 parameters were statistically insignificant in the study.

The serum ischemia modified albumin (IMA) was increased in cases as compared to controls, but a statistical correlation was not observed which was contrary to the study done by Jyotirmayee Bahinipati et al[23].

Mean levels of IMA in cases and controls were 646.44 and 624.001(p=0.355) respectively. Although statistically significant values were not observed, a clinically significant trend in the IMA levels was obtained .Moreover, first trimester IMA measurement may help in assessing the adverse outcomes in pregnancy as stated by Federico Prefumo et al[32].

Papageorghiou et al. observed that defective endovascular trophoblast invasion during the first trimester was associated with increased maternal serum IMA before the onset of clinically evident preeclampsia[34]. They suggested that serum IMA level in first trimester of pregnancy might be a potential biomarker for abnormal placental development related to preeclampsia.

Rossi A et al. analyzed serum levels of IMA during the first and second trimesters and in the immediate postpartum period[35] and associated it with preeclampsia and found it to be positively correlated.

The study case population was divided into two groups with their urine albumin levels as 1+ and >1+. An increase in serum ischemia modified albumin (IMA) was seen in patients with urine albumin of(>1+) as compared with patients with urine albumin of (1+) as seen in the study by Sapna Vyakaranam et al.[31].Mean value of cases with urine albumin 1+ was 646.417 and with urine albumin (>1+) was 671.897(p=0.282). Once again a statistically significant result was not obtained, but a clinically significant trend was observed which could be used in assessing the prognosis of the disease.

Uterine artery doppler ultrasound had revealed a considerably varied results in investigating the predictive accuracy of pregnancy related hypertensive disorders[27]. According to Myatt L, the second trimester uterine artery Doppler ultrasound shows poor sensitivity for the prediction of preeclampsia. Moreover the high negative predictive value of this technique is useful only as a screening test. Doppler interrogation of uteroplacental blood flow may not identify all women at risk of preeclampsia. Thus the technique has poor predictive power when applied to the overall population of low risk women[28] and hence an attempt was not made in this study.

Keziban Doğan et al. demonstrated that maternal serum IMA levels at 20–24weeks' gestation might be a novel predictive biomarker for preeclampsia independent of abnormal uterine artery Doppler findings, including notching, maternal characteristics and laboratory findings[36].

Studies have revealed that maternal serum IMA levels appear to be elevated in women with early recurrent pregnancy loss in the first trimester[33].Hence an assessment of Ischemia Modified Albumin (IMA) in maternal serum,

early in pregnancy, might help in reducing fetal and maternal morbidity and mortality rate.

Conclusion

IMA in maternal serum was found to be elevated in cases than the controls but a statistical significance was not found.

Serum IMA indicates the level of ischemia/hypoxia existing in the placenta and can be used to assess the adverse outcomes in pregnancy.

Measurement of the oxidative stress by this biomarker may be useful in monitoring the patients with preeclampsia.

SCOPE AND LIMITATIONS

The study population was small to assess the statistically significant outcomes in the above project.

Follow up of the patients was not done in this study which could give a better idea of the exact gestational age to measure the ischemia modified albumin in serum.

Early measurement and prophylactic treatment of the patients could reduce the fetal and maternal morbidity and mortality.

SUMMARY

This case-control study performed with the aim of suggesting that Ischemia Modified Albumin can be used as a biomarker or a predictor of pregnancy induced hypertensive disorders with other available techniques like Doppler ultrasound. But in this study, the levels of serum IMA was not significantly elevated but its levels are clinically raised in cases. Further research on this field is necessary.

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36. Ischemia-Modified Albumin (IMA): A Novel Markerfor Preeclampsia Independent of Uterine ArteryNotching Identified by Doppler Ultrasound
37. Keziban Doğan, Hakan Guraslan, Atilla Çankaya, Hediye Dağdeviren & Murat Ekin

PROFORMA:
Name: OP/IP No:
Age: Date:
Address:
Obstetric score:
LMP:
EDD:
GESTATIONAL AGE:
VITALS:
Body weight: Temperature:
Pulse Rate: Blood Pressure:
INVESTIGATIONS:
Serum IMA:
Urine Albumin:
Random blood sugar level:
Serum Urea:
Serum creatinine: