A STUDY OF MATERNAL SERUM CYSTATIN C AND SERUM CREATININE LEVELS IN PREECLAMPTIC AND NORMOTENSIVE PREGNANCIES - A CASE CONTROL STUDY

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY OF MATERNAL SERUM CYSTATIN C AND SERUM CREATININE LEVELS IN PREECLAMPTIC AND NORMOTENSIVE PREGNANCIES - A CASE CONTROL STUDY"** is the bonafide original work of **Dr.S.NASREEN SHAFIEQA,** under the guidance of **Prof.Dr.T.K.SHAANTHY GUNASINGH, MD., DGO.,** Department of Obstetrics and Gynaecology, KMCH, Chennai in partial fulfillment of the requirements for MS Obstetrics and Gynaecology branch II examination of the Tamilnadu Dr.MGR Medical university to be held in April 2017. The period of Postgraduate study and training from June 2014 to April 2017.

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DECLARATION

I solemnly declare that this dissertation **"A STUDY OF MATERNAL SERUM CYSTATINC AND SERUM CREATININE LEVELS IN PREECLAMPTIC AND NORMOTENSIVE PREGNANCIES – CASE CONTROL STUDY"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr.T.K.SHAANTHY GUNASINGH, MD., DGO.,** Professor, Dept of Obstetrics and Gynecology, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr.M.G.R.Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.S. (Obstetrics and Gynecology).**

Place: Chennai

Date: **(Dr.S.NASREEN SHAFIEQA)**

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ABBREVIATIONS

CrCl	-	Creatinine Clearance
GFR	-	Glomerular Filtration Rate
eGFR	-	Estimated GFR
MPGN	–	Membrano Proliferative Glomerulo Nephritis
AST	-	Aspartate Transaminases
ALT	-	Alanine Transaminases
LDH	–	Lactate Dehydrogenase
PT	–	Prothrombin Time
PTTK	–	Partial Thromboplastin Time with Kaolin
NST	-	Non-Stress Test
BMI	–	Body Mass Index
AFI	–	Amniotic Fluid Index

CONTENTS

INTRODUCTION

PREECLAMPSIA

Preeclampsia is a multisystem disorder that is specific to human pregnancy. It is characterized by the development of hypertension to the extent of 140/90 mm Hg or more on atleast two occasions 4 hours apart with proteinuria more than 300mg for 24hrs or urine proteinuria more than 1+ that occurs after 20 weeks of gestation in a previously normotensive and nonproteinuric woman [17]. It is associated with high maternal mortality and morbidity and increased risk of perinatal death, preterm birth, and intrauterine growth restriction. It has been reported to complicate 4–7% of pregnancies worldwide.

There is extensive evidence that the reduction of uteroplacental blood flow in this syndrome results from the toxic combination of hypoxia, imbalance of angiogenic and antiangiogenic factors, inflammation, deranged immunity and oxidative stress.

CYSTATIN C

Cystatin C is a low molecular weight non glycosylated basic protein of 12.8kDa made of 120 amino acid residues expressed in all nucleated cells[20]. It is a potent inhibitor of lysosomal proteinases and probably one of the most important extracellular inhibitors of cysteine proteases. Cystatin C belongs to the type 2 cystatin gene family.

It is extremely sensitive to minor changes in GFR in the earliest changes of kidney disease.

CREATININE

Creatinine is a breakdown product of creatinine phosphate in muscle, and is usually produced at a constant rate by the body. Serum creatinine is an important indicator of renal health because it is an easily measured byproduct of muscle metabolism that is excreted unchanged by the kidneys[9].

Creatinine is removed from the blood chiefly by the kidneys primarily by glomerular filtration but also by proximal tubular secretion. Little or no tubular reabsorption of creatinine occurs. If the filtration in the kidney is deficient, creatinine blood levels rise. Therefore, creatinine levels in blood and urine may be used to calculate the creatinine clearance (CrCl), which correlates with the glomerular filtration rate (GFR). Blood creatinine levels may also be used alone to calculate the estimated GFR (eGFR)[11].

The GFR is clinically important because it is a measurement of renal function. However, in cases of severe renal dysfunction, the creatinine clearance rate will overestimate the GFR because hypersecretion of creatinine by the proximal tubules will account for a larger fraction of the total creatinine cleared.

REVIEW OF LITERATURE

Pre-eclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90mm Hg or more with proteinuria after the 20th week in a previously normotensive non – proteinuric woman. It complicates 4%–7% of pregnancies worldwide and constitutes a major source of morbidity and mortality. Overall, 10%–15% of maternal deaths are directly associated with pre-eclampsia and eclampsia. The risk of pre-eclampsia is 2-fold to 5-fold higher in pregnant women with a maternal history of this disorder. Depending on ethnicity, the incidence of pre-eclampsia ranges from 3% to 7% in healthy nulliparas and 1% to 3% in multiparas. Moreover, nulliparity and a new partner have been shown to be important risk factors.

Diagnosis of Hypertension:

Hypertension in pregnancy should be defined as:

- Systolic blood pressure greater than or equal to 140 mmHg
- Diastolic blood pressure of greater than or equal to 90 mmHg

These measurements should be based on the average of at least two measurements, taken using the same arm, 4-6 hours apart. Elevations of both systolic and diastolic blood pressures have been associated with adverse fetal outcome and therefore both are important. Detecting a rise

in blood pressure from booking or preconception blood pressure, rather than relying on an absolute value, has in the past been considered useful in diagnosing preeclampsia in women who do not reach blood pressure of 140 or 90 mmHg. Available evidence does not suggest that these women have an increased risk of adverse outcome. However, such a rise may be significant in women with other complications such as proteinuria and closer monitoring of such women is recommended. Severe hypertension should be defined as a systolic BP of >160 mmHg or a diastolic BP of >110 mmHg.

MEASUREMENT OF PROTEINURIA:

All pregnant women should be assessed for proteinuria. Urinary dipstick testing may be used for screening for proteinuria when the suspicion of preeclampsia is low. Approximate equivalence is:

- 1+ = 0.3 g/l
- 2+ = 1 g/l
- 3+ = 3 g/l
- 4+ = 10g/l

There is considerable observer error with visual dipstick assessment[17]. This can be overcome by the use of automated dipstick readers, which significantly improve both false positive and negative

rates. In the presence of hypertension, a reading of 1+ or more should prompt further evaluation.

Diagnosis of Clinically Significant Proteinuria:

The upper limit of a normal 24-hour urine protein excretion is 0.3g and is based on a 95% CI for urinary protein in pregnancy. However, there is considerable variation between laboratory assays for the quantification of proteinuria[9]. This combined with unknown errors and the delay associated with obtaining a 24-hour collection means that newer tests have potential advantages. An elevated protein creatinine ratio of greater than 30 mg/mmol correlates with a 24-hour urine excretion greater than 300mg and should be used to check for significant proteinuria.

CLASSIFICATION OF HYPERTENSION IN PREGNANCY:

American Congress of Obstetricians and Gynecologists (ACOG) classification of severity [2]

- **Mild-moderate:**
    - Systolic BP of 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and proteinuria is 300 mg/24 hours or ≥1+ (on 2 random urine samples, collected at least 4 hours apart); or protein:creatinine ratio is ≥0.3 mg/dL.

* BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and, in the absence of proteinuria, any of the following is present:

* Thrombocytopenia, platelets count <100,000/Ul

* Serum creatinine ≥1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease

* Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration

* Pulmonary oedema

* Cerebral or visual disturbances.

- **Severe:**

* BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is lying on bed) and proteinuria is 300 mg/24 hours or ≥1+ (on 2 random urine samples, collected at least 4 hours apart) or protein:creatinine ratio is ≥0.3 mg/dL.

* BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and in the absence of proteinuria, any of the following is present:

* Thrombocytopenia, platelets count <100,000/uL

* Serum creatinine ≥1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease
* Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration
* Pulmonary oedema
* Cerebral or visual disturbances.

HELLP syndrome is a subtype of severe pre-eclampsia characterised by haemolysis (H), elevated liver enzymes (EL), and low platelets (LP).

National Institute for Health and Care Excellence (NICE, UK): classification of severity[4]:

Severity of hypertension in pregnancy is based on BP measurement alone.

- Mild: BP is 140 to 149 mmHg systolic and/or 90 to 99 mmHg diastolic.
- Moderate: BP is 150 to 159 mmHg systolic and/or 100 to 109 mmHg diastolic.
- Severe: BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic.

National High Blood Pressure Education Program (NHBPEP) Working Group, the classification is as follows[3] :

- Gestational hypertension
- Chronic hypertension
- Preeclampsia/eclampsia
- Superimposed preeclampsia (on chronic hypertension)

Although each of these disorders can appear in isolation, they are thought of as progressive manifestations of a single process and are believed to share a common etiology.

Gestational hypertension :

The characteristics of gestational hypertension are as follows[3]:

- BP of 140/90 mm Hg or greater for the first time during pregnancy
- No proteinuria
- BP returns to normal less than 12 weeks' postpartum
- Final diagnosis made only postpartum

Chronic hypertension :

Chronic hypertension is characterized by either

(1) BP 140/90 mm Hg or greater before pregnancy or diagnosed before 20 weeks' gestation; not attributable to gestational trophoblastic disease or

(2) Hypertension first diagnosed after 20 weeks gestation and persistent after 12 weeks postpartum.

Preexisting chronic hypertension may present with superimposed preeclampsia presenting as new-onset proteinuria after 20 weeks gestation[3].

Preeclampsia / eclampsia

Preeclampsia/eclampsia is characterized by a BP of 140/90 mm Hg or greater after 20 weeks gestation in a women with previously normal BP and who have proteinuria (≥0.3 g protein in 24-h urine specimen).

Eclampsia is defined as seizures that cannot be attributable to other causes, in a woman with preeclampsia[4].

Superimposed preeclampsia :

Superimposed preeclampsia (on chronic hypertension) is characterized by

(1) New onset proteinuria (≥300 mg/24 h) in a woman with hypertension but no proteinuria before 20 weeks gestation and

(2) A sudden increase in proteinuria or BP, or a platelet count of less than 100,000/mm^3, in a woman with hypertension and proteinuria before 20 weeks gestation[4].

Risk Factors :

Risk factors for preeclampsia are as follows :

- Nulliparity
- Age older than 40 years
- Black race
- Family history
- Chronic renal disease
- Chronic hypertension
- Antiphospholipid antibody syndrome
- Diabetes mellitus
- Twin gestation (but unaffected by zygosity)
- High body mass index
- Homozygosity for angiotensinogen gene T235
- Heterozygosity for angiotensinogen gene T235

Pathophysiology:

During normal pregnancy, the following changes occur[19]:

- The villous cytotrophoblast invades into the inner third of the myometrium
- Spiral arteries lose their endothelium and most of their muscle fibers.

These structural changes are associated with functional alterations, such that spiral arteries become low-resistance vessels, and thus less sensitive, or even insensitive, to vasoconstrictive substances.

Pre-eclampsia has a complex pathophysiology, the primary cause being abnormal placentation. Defective invasion of the spiral arteries by cytotrophoblast cells is observed during pre-eclampsia.

The following may be the abnormalities in preeclampsia[18]:

1. Thecytotrophoblast invasion of the uterus is actually a unique differentiation pathway in which the fetal cells adopt certain attributes of the maternal endothelium they normally replace. In pre-eclampsia, this differentiation process goes awry.
2. The abnormalities may be related to the nitric oxide pathway, which contributes substantially to the control of vascular tone. Inhibition of maternal synthesis of nitric oxide prevents embryo implantation. Increased uterine arterial resistance induces higher sensitivity to vasoconstriction and thus chronic placental ischemia

and oxidative stress. This chronic placental ischemia causes fetal complications, including intrauterine growth retardation and intrauterine death. In parallel, oxidative stress induces release into the maternal circulation of substances such as free radicals, oxidized lipids, cytokines, and serum soluble vascular endothelial growth factor 1[34]. These abnormalities are responsible for endothelial dysfunction with vascular hyperpermeability, thrombophilia, and hypertension, so as to compensate for the decreased flow in the uterine arteries due to peripheral vasoconstriction.

Endothelial dysfunction is responsible for the clinical signs observed in the mother, like,

- Impairment of the hepatic endothelium contributing to onset of the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome
- Impairment of the cerebral endothelium inducing refractory neurological disorders
- Eclampsia.

3. Depletion of vascular endothelial growth factor in the podocytes makes the endotheliosis more able to block the slit diaphragms in the basement membrane, adding to decreased glomerular filtration and causing proteinuria[16].

4. Endothelial dysfunction promotes microangiopathic hemolytic anemia and vascular hyperpermeability associated with low serum albumin causes edema.
5. Impairment of the maternal immune system prevents it from recognizing the fetoplacental unit. Excessive production of immune cells causes secretion of tumor necrosis factor alpha which induces apoptosis of the extravillous cytotrophoblast.
6. The human leukocyte antigen (HLA) system also appears to play a role in the defective invasion of the spiral arteries. Women with pre-eclampsia show reduced levels of HLA-G and HLA-E[16].
7. High levels of soluble fms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor and placental growth factor, have been found in women with pre-eclampsia. Accordingly, assays of sFlt-1, placental growth factor, endoglin, and vascular endothelial growth factor, all of which increase 4–8 weeks before onset of the disease, may be useful predictors of pre-eclampsia.

The crucial issue to understand is that the prime mover of pre-eclampsia is abnormal placentation. Two common theories appear to be interlinked, i.e., a genetic theory and an immunological theory. Several susceptibility genes may exist for pre-eclampsia. These genes probably interact in the hemostatic and cardiovascular systems, as well as in the

inflammatory response. Some have been identified, and in candidate gene studies they have provided evidence of linkage to several genes, like

- Angiotensinogen on 1-q42–43
- eNOS on 7q36

Other main important loci are 2p12, 2p25, 9p13, and 10q22.

Abnormalities in renal system in preeclampsia[7]:

For some reasons known and unknown renal system bears an unique challenge in preeclampsia.

In normal pregnancies changes observed in renal system are:

- The glomerular filtration rate (GFR) is increased. This leads to a series of changes including the increase in urine output. Increase in blood volume in pregnancy and increase in renal circulation are both contributing to increased urine output.
- There is more blood filtered in pregnancy therefore the renal system goes into an unstressed overdrive.

During preeclampsia, the blood volume that is increased in pregnancy is constricted. Also, in preeclampsia the renal vascular system undergoes vasoconstriction as does the entire vascular system of the pregnant mother. The renal system which is all geared up to handle the increased load actually faces a reduced load due to vasoconstriction. As a result it gets precariously poised and has a tendency to get dried up. The

intensity and frequency with which this occurs depends on the severity of preeclampsia. It also depends on the intrinsic robustness of the renal system to bear the alterations.

While many biochemical markers have been used to assess renal function in non pregnant subjects many of them become incompetent in pregnancy more so in preeclampsia.

Serum uric acid assessment in preeclampsia has been done by different workers at different times to assess renal function. Over a period of time it has been recognized that uric acid is a strong reducing substance in the body. It has therefore a very limited role in reflecting the renal function in a preeclamptic subject.

Pathological changes in kidneys occur in preeclampsia. The changes are due to vasospasm[13].

While one is examining the pathological changes that are taking place in the kidneys – one cannot help but salute the pioneering work done by Sheehan and his team in the same. This group diligently studied and documented renal changes in subjects who died in pregnancy on postmortem. They compared 112 non- preeclamptic subjects who died of preeclampsia or eclampsia with those who died of other causes. They performed postmortems on these subjects within two hours of death. In this way, they successfully deduced the changes occurring as an aftermath of death. Thus their results were very accurate. Their accuracy

in the results could be understood from the fact that modern imaging techniques have also corroborated with the changes described by Sheehan and colleagues. Therefore even to date no discussion and pathology of preeclampsia is complete without taking into account the description of these workers.

Gross changes in the kidneys:

The kidneys appear pale and have a relatively enlarged cortex[13].

Microscopic changes in kidneys:

1. The most characteristic glomerular feature is endotheliosis which is nothing but prominent glomerular endothelial swelling. Occlusion of glomerular capillary lumina occurs without any increase in cellularity and it gives a lobularly accentuated appearance to the glomerular tuft[22].

2. Swelling of naïve endothelial cells and to a lesser extent mesangial cells result in narrowed or occluded capillary lumen. Glomeruli are enlarged and solidified.

3. Volume of glomeruli is slightly increased, yet since its cellularity remains relatively unchanged, an appearance of somewhat hypocellular glomeruli that has a “bloodless” appearance is classically described in preeclampsia due to the endotheliosis[22].

4. Mesangial hypercellularity or mesangial matrix wideningis not typically present but variable degrees of mesangiolysis is commonly noted.

5. Due to hypoperfusion of the glomeruli from compromised arteriolar blood flow the glomerular tuft may have wrinkling of capillary loop with mild collapse/shrinkage. This change is often seen in the afferent arterioles.

6. Prominence of visceral epithelial cells may be observed due to proteinuria; However, this finding depends on the severity of the proteinuria. The glomeruli can be either segmentally or globally involved, and kidney may be focally or diffusely affected, depending on severity of the disease.

7. There is extensive glomerular capillary basement membrane replication in chronic hypertension. This feature is similar to the "tram track appearance" seen in membranoproliferative glomerulonephritis (MPGN) or in transplant nephropathy of renal allografts. These changes are the result of long term glomerular endothelial cell injury and are non specific. But unlike MPGN there is no immune complex mediated process in chronic hypertension

8. The narrowed lumina may have fibrin platelet thrombi within them. This feature reduces blood flow in the afferent arterioles in the glomeruli causing glomerular ischemia .in the subacute phase,

resulting in scarring in the intima due to inflammation. This intimal concentric scarring give it an “onion skin appearance”[11].

Renal changes in preeclampsia on immunofluorescence microscopy:

Thre are no specific features for preeclampsia.

In the acute stages of the disease, thre may be deposition of fibrin and IgM, complement components along the capillary walls of glomeruli in the arterioles and the mesangium.The intensity of immunofluorescence somewhat correlates with the severity of activity of the disease.

Renal changes in preeclampsia on electron microscopy:

- Thickening of glomerular capillary walls due to endothelial cell swelling & subendothelial widening
- Expanded lamina rara interna gives a pale flocculant appearance with collections of electron dense material.
- Endothelial cells lose their fenestrations
- Focal or widespred effacement of podocyte foot processes
- Non specific glomerular capillary basement membrane wrinkling and thickening
- Variable mesangial cell interposition
- Appearance of basementmembrane redup lication due to presence of new glomerular basement membrane material.

Clinical presentation of preeclampsia:

Diagnosis of preeclampsia may not be straightforward due to heterogeneity of symptoms and signs.

Patients with mild preeclampsia may be asymptomatic

Many patients are diagnosed only through routine screening

Clinical and laboratory tests are done to identify severity of preeclampsia and its complications.

Symptoms of imminent eclampsia[19]:

1. Reduced urine output due to acute renal failure
2. Headache due to cerebral edema
3. Visual disturbances due to cerebral edema
4. Tinnitus
5. Vomiting
6. Uterine contractions, bleeding per vaginum due to placental abruption
7. Band like epigastric pain due to hepatic hematoma
8. Difficulty in breathing and cough with expectoration due to pulmonary edema

Clinical examination:

1. Check consciousness and orientation
2. Look for pallor

3. Measurement of blood pressure in resting state with the patient in sitting position or semi recumbent position, using an appropriate sized cuff
4. Look for pedal edema and generalized edema
5. Check height, weight and BMI
6. Screen for weight gain
7. Monitor pulse rate, temperature and respiratory rate
8. Monitor urine output
9. Obstetric examination: Fundal height should correspond to the period of gestation. Fundal height more than period of gestation suggests twins, hydramnios, molar pregnancy and these conditions are more commonly associated with hypertension in pregnancy. Fundal height less than the period of gestation is suggestive of fetal growth restriction and also may be associated with hypertension.
10. Assess fetal well being by electrocardiotocography

Laboratory tests :

1. Complete blood count including platelet count
2. Urine albumin by dipstick method or24 hour urinary protein
3. Liver function test including enzymes aspartate transaminases (AST) and alanine transaminases (ALT) levels.
4. Kidney function tests including serum creatinine and uric acid levels. In severe cases it is advisable to do protein creatinine ratio and creatinine clearance.

5. Lactate dehydrogenase (LDH) for the diagnosis of HELLP syndrome
6. PT and PTTK-Only if platelet count is abnormal
7. Fundus examination to rule out severity of the disease.
8. Blood grouping and Rh typing

All investigations are repeated once a week or fortnightly depending on the severity except urine albumin and blood pressure measurement which should be done daily[18].

Fetal monitoring:

In addition to maternal investigations, fetal monitoring is also required.

Fetal assessment includes

1. Daily fetal movement count by the patient which should be more than 10 in 24 hours or more than 3 in one hour thrice a day
2. Non-stress test(NST)
3. Biophysical profile
4. Umbilical artery and middle cerebral artery Doppler.

These investigations are performed between 28-30 weeks of gestation initially and the biophysical profile/NST is repeated at least once a week till patient delivers.

The frequency may increase if hypertension becomes severe or Doppler shows changes suggestive of fetal growth restriction.

Characteristics of severe and non-severe preeclampsia[36]:

Abnormality	*Non-severe*	*Severe*
Diastolic blood pressure	<110 mm Hg	≥110 mm Hg
Systolic blood pressure	<160 mm Hg	≥ 160 mm Hg
Proteinuria	≤2+	≥3+
Headache	Absent	Present
Visual disturbances	Absent	Present
Oliguria	Absent	Present
Upper abdominal pain	Absent	Present
Convulsions	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present
Papilledema	Absent	Present
Hyper-reflexia	Absent	Present
Signs of CCF	Absent	Present
Signs of multi organ dysfunction	Absent	Present

Initial evaluation:

Elevated blood pressure readings should be confirmed

Quantification of urine proteinuria should be done

Laboratory tests:

1. Full blood counts
2. Renal function tests
3. Liver function tests
4. Serum electrolytes
5. PT and PTTK-Only if platelet count is abnormal

Fetal assessment with ultrasound to monitor AFI, fetal growth, Doppler velocimetry

This should be done once every month and thereafter at frequent intervals if any abnormalities are identified.

Management:

Pregnancy complicated by gestational hypertension is managed according to severity, gestational age and presence of preeclampsia.

Indications for admission to a hospital and further evaluation:

- The Development of proteinuria
- Elevation of the blood pressure above 150/100 mm of Hg threshold
- Decreased fetal movements
- Abnormal symphisio fundal height
- Development of maternal symptoms suggestive of end organ damage

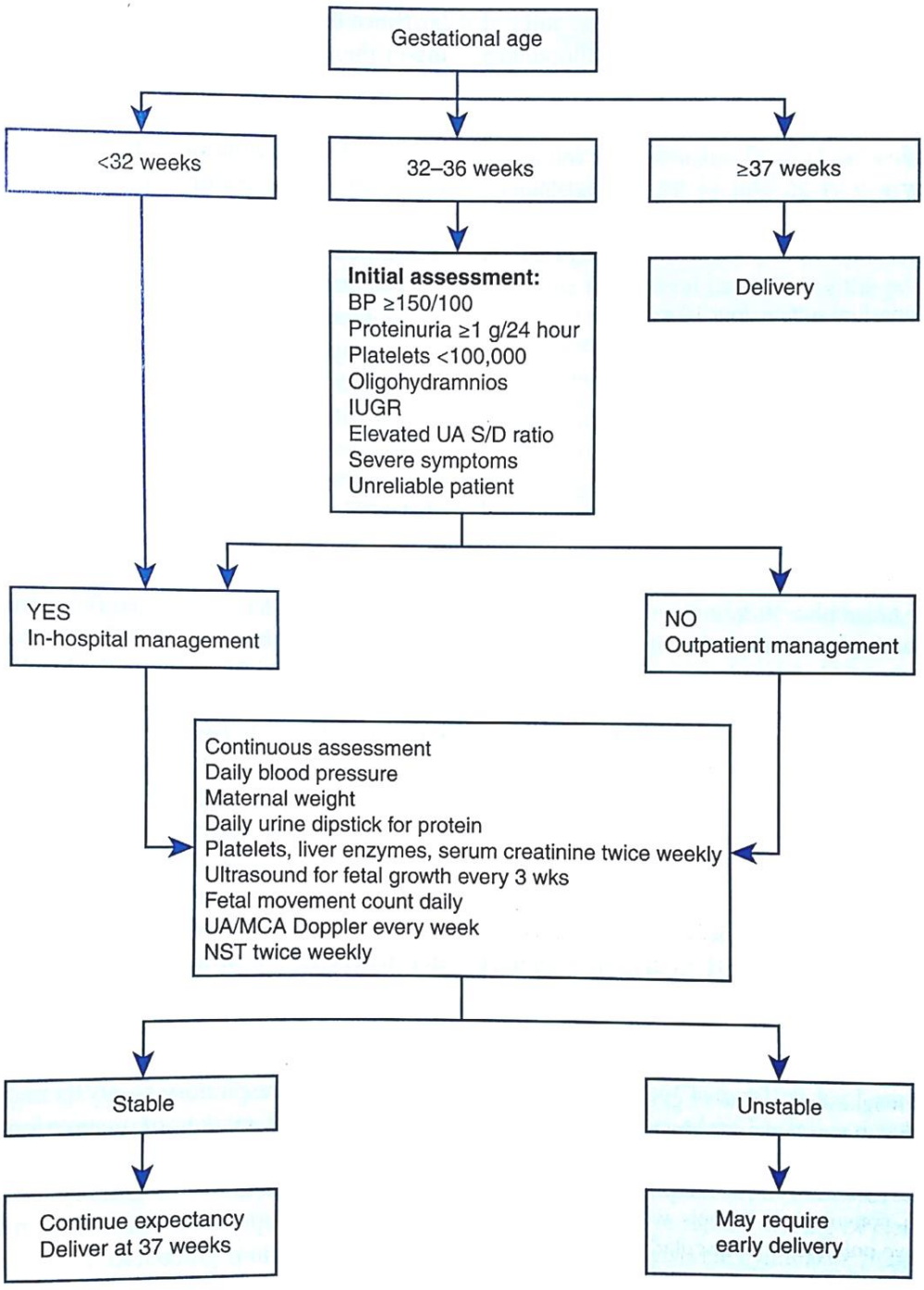
Patients with negative findings for abnormality in their weekly assessment may continue with the pregnancy until they reach 38 weeks of gestation. At this time labor induction is performed with the help of cervical ripening agents like dinoprostone/ oxytocin/artificial rupture of membrane or caesarean section offered to the patient depending on modified Bishop’s score.

Anti hypertensives should be given to maintain systolic blood pressure at 130-155mmhg and diastolic blood pressure at 80 – 105mmhg.

The first line antihypertensive agent of choice is oral labetalol. It may be given orally in doses of 100 – 400mg every 8-12 hours.

Alternatives are methyldopa, nifedipine, the choice of which have been left on the clinician as per their familiarity of use.

Management of mild preeclampsia (ACOG 2014)



Management of severe preeclampsia:

The objectives for management are[10]:

1. Termination of pregnancy with the least possible trauma to mother and fetus. As of now, the only cure for preeclampsia is termination of pregnancy. At best, it may be controlled only when it is of mild variety. It is dangerous tocontinue pregnancy in severe preeclampsia for more than 1-2 weeks.
2. Birth of an infant who subsequently thrives
3. Complete restoration of health to the mother

Aims for the immediate management are:

- To bring down the blood pressure to safe levels
- Assess general condition for presence of immediate risk factors for convulsions.
- Assessment of the fetal wellbeing and reasonable maturity
- With the help of investigations and monitoring of urine output assess the patient for presence or absence of multiorgan involvement and HELLP syndrome.

Antihypertensive treatment for acute management of severe hypertension[3]:

Labetalol:

- It is the medication of choice for treatment of acute severe hypertension in pregnancy and for maintenance treatment of hypertensive disorders during pregnancy.
- It is an alpha and beta adrenergic blocker.
- The ratio of alpha to beta blockade is approximately 1:3 for oral form and 1:7 for intravenous form.
- It should be avoided in asthmatics and in patients with cardiac failure.
- It is effective in the treatment of severe hypertension and can be given by continuous or intermittent intravenous infusion.
- Oral dose - 100-400mg every 6-12 hours
- For intermittent dosing, 20mg should be given intravenous bolus initially over a two minute period. Additional doses of 40 – 80mg may be given at 20minute intervals. The maximum effect of IV labetalol is reached 5 minute after injection.
- For continuous IV use, 500mg of labetalol is added to 400ml normal saline solution and administered at an initial rate of 20mg/hour. If the blood pressure does not fall to the expected range in 20 minutes, the dose is doubled and continued to be doubled every 20 minutes until the expected range is obtained or a maximum dose of 220mg/hour is given. The effective dose range is between 50 and 200mg/hour.

Hydralazine:

- It acts directly on the arteriolar smooth muscle to reduce peripheral vascular resistance.
- It is administered in intravenous boluses starting at 5mg and increasing by 5mg every 20 minutes upto 20mg.
- The most frequent side effects are: decreased uteroplacental perfusion and hyperdynamic circulation. Recovery from these side effects can be seen after the drug is discontinued and the blood pressure rises.

Nifedipine:

- It is a calcium channel blocker.
- It is an excellent peripheral vasodilator and a good tocolytic agent.
- It lowers blood pressure by inhibiting the intracellular influx of calcium into cardiac and vascular smooth muscles and by decreasing peripheral vascular resistance.
- It is rapidly absorbed after oral administration and reaches peak levels 30 minutes after ingestion.
- The NHBEP and RCOG recommend a 10mg initial oral dose to be repeated after 30 minutes if necessary. If there are no side effects the medication may be given in 10-30mg doses every 4-6 hours according to the blood pressure response.Doses above 120mg/day are rarely necessary.

Management of eclampsia[46]:

Management includes following:

1. Check vitals
2. Place patient in lateral decubitus position to prevent aspiration. The bed rails should be elevated to prevent maternal injury. Padded tongue blade should be inserted between teeth to avoid injury to the tongue.
3. Quick history and examination.
4. Keep airway clean and patent by frequent oral suctioning.
5. Give oxygen by mask at 8-10 litres/minute, if convulsion occurs or pulse oximetry show shypoxia
6. Prevent convulsions further by maintaining silence, dim lights, and minimal noise
7. Give loading dose of magnesium sulphate, 4 gm of 20% solution intravenously slowly over 5minutes and 5 gm of 50% solution intramuscularly in each buttock followed by a maintenance dose of 5 gms IM in alternate buttocks every 4 hourly till 24 hours after delivery.
8. Intravenous labetalol or oral nifedipine to bring down the blood pressure to moderate level.

9. Pulse oximetry: There is possibility of help from anesthetist if patient is not maintaining oxygen saturation on pulse oximeter or is having frequent convulsions.

10. After the patient is stabilized, do per vaginum examination and decide on termination, preferably vaginal delivery by instilling dinoprostone gel if cervix is too unfavorable or oxytocin augmentation.

11. It should be noted that cesarean section in eclampsia has higher morbidity and mortality than vaginal delivery. However, indications for cesarean delivery in eclampsia sometimes can be, though rarely (1) obstetric indication like transverse lie, malpresentation, placenta previa, cephalo pelvic disproportion (2) uncontrolled fits not responding to the anticonvulsants treatment and for termination of pregnancy if there is no immediate prospect of vaginal delivery despite induction of labor.

The various regimens available for administration of magnesium sulphate in eclampsia are:

1. PRITCHARD REGIMEN : 4 gm of 20% MgSo4 IV slowly over 5-10 min followed by 5 gm50% MgSo4 IM into each buttock followed by5 gm 50% MgSo4 IM 4hrly to alternate buttock.
2. SIBAI REGIMEN[46]: 6 gm MgSo4 intravenously over 20 min followed by 2 gm MgSO4 IV infusion.

3. ZUSPANREGIMEN: 4 gm MgSo4 intravenously over 5-10 min followed by 1gm/hr MgSO4 IV infusion.

Monitoring for magnesium toxicity:

- Urine output should be atleast 30ml/hour or 100ml in 4 hours
- Deep tendon reflexes should be present
- Respiration rate should be >14 breaths /minute
- Pulse oximetry should be >96%

Any change in these indices makes it necessary to reevaluate the rate of administration.

Cystatin C:

Cystatin C was first discovered in 1961 as an alkaline protein in normal cerebrospinal fluid. It is low molecular weight (13.3KDa) protein having renal excretion. The Cystatin C gene is so called “housekeeping gene“[12]. Unique among cystatins, it seems to be produced by all human nucleated cells. It is produced at a stable rate, which is unaffected by inflammatory processes, sex, age, diet, and nutritional status .The first correlation between GFR and Cystatin C was in the year 1985 .The synthesis is significantly increased by hyperthyroidism and by high doses of corticosteroids.

Serum levels of cystatin C are less dependent on age, sex, race and muscle mass compared to serum creatinine levels. Cross-sectional studies have shown that serum levels of cystatin C are more precise in estimating

kidney functions than serum creatinine. This may be because creatinine is actively secreted by proximal renal tubules and hence glomerular filtration rate, calculated by creatinine clearance, is overestimated in severe renal dysfunction. Newman et al in the study concluded that cystatin C was more sensitive marker for small changes in GFR. In a systematic review, Roos et al reported that Cystatin C was a reliable marker of GFR in patients with mild to moderate renal function impairment and also had higher chance of detecting true renal impairment.

Serum levels of Cystatin C are increased in normal pregnancy, especially in the third trimester. This has been attributed to renal handling of low molecular weight proteins in conjunction with decreased GFR and increased synthesis by feto-placental unit or generalized phenomenon.

The levels of Cystatin C are further increased in pre-eclampsia, correlating with functional and structural changes in kidneys. A study by Strevens et al. demonstrated that maternal serum levels of Cystatin C was a good marker for most onsets and severity of pre-eclampsia. In a renal biopsy study Cystatin C levels were shown to correlate with degree of glomerular endotheliosis, a typical histologic feature of pre-eclampsia. Since degree of endotheliosis has been considered to determine the severity of pre-eclampsia, it has been hypothesized that serum levels of Cystatin C can offer information regarding severity of pre-eclampsia. In the normal kidney, cystatin C is freely filtered through glomerular

membrane and then almost completely reabsorbed and degraded by proximal tubular cells. Therefore, the plasma concentration of cystatin C is almost exclusively determined by GFR, making cystatin C an excellent indicator of GFR. Studies of the serum level of cystatin C in large patient cohorts have failed to correlate serum level to any pathophysiological states besides those affecting GFR.

Characteristics of an ideal GFR marker [51]:

- Demonstrates the early and potentially reversible decrease of GFR
- Independent of diet and hormonal or inflammatory changes
- No tubular secretion
- Low influence by muscle mass, gender and race
- Independent of age for children above 1 year and adults
- Demonstrates the decrease of GFR in old persons
- Mirrors the diurnal GFR variation
- Elucidates filtration quality and life expectancy

Cystatin C as a marker of GFR:

The interest in cystatin C as a marker of renal function has increased tremendously over the last few years and the number of articles and reviews about cystatin C continues to grow. Numerous studies and a meta-analysis incorporating 4,492 subject samples, comparing the use of serum cystatin C and creatinine as markers of GFR have shown that

serum cystatin C is clearly superior to serum creatinine as a marker of GFR.

Advantages of Cystatin C as a marker of GFR than creatinine[38]:

1. Cystatin C responds more quickly to changes in the GFR than creatinine, which is not a sensitive marker for early decline in GFR.
2. A substantial proportion of patients with reduced GFR display serum creatinine levels within the normal range and even a 50% reduction of GFR is not infrequently associated with a normal concentration of serum creatinine. Cystatin C is accurate in this "creatinine-blind area" helping the clinician to get an earlier indication of deteriorating renal function, and thus allowing the possibility of taking preventive action.
3. Cystatin C does not have the previously mentioned limitations of creatinine, and its measurement is a much simpler way of assessing renal function than methods such as iohexol clearance.
4. A particularly important advantage of cystatin C as a marker of GFR is that it can also be used to evaluate GFR in patient populations for whom it is difficult to obtain an accurate assessment of GFR based on the creatinine value.
5. Estimation of GFR from cystatin C helps clinicians when a fast estimate of a patient's renal function is needed to calculate the

correct amount of antibiotics or cytotoxic drugs for the individual patient, for instance, before initiating treatment, and also for monitoring patient response during and after therapy. Cancer therapeutics, in particular, have the potential to inflict severe damage to the kidneys. An early indication of renal dysfunction would allow the oncologist to adjust the drug dosage before irreparable kidney damage had occurred.

6. In contrast to serum creatinine, serum cystatin C is unaffected by muscle mass. This means that selected patient groups, whose muscle mass is either reduced or undergoes rapid change, may particularly benefit from the use of cystatin C for estimating the GFR. This is true for children and the elderly.

7. The reference range for serum creatinine increases with age up to the end of puberty and has to be adjusted for gender from puberty onwards. In contrast, the reference range for serum cystatin C is identical for men, women and children as the cystatin C level is constant after the age of one and virtually identical to the reference range for adults.

8. In the first years of life, renal function matures physiologically. Accordingly high cystatin C concentrations have been found at birth, followed by a rapid decline after birth reflecting maturation of kidney function. Unlike serum creatinine, cystatin C can thus be used to assess the GFR of newborns and even of the foetus.

9. GFR decreases with age as the nephrons start to decrease from about the age of 50. At approximately the same age, muscle mass also begins to decline. In the elderly, serum creatinine is notoriously unreliable as an indicator of GFR because the daily production of creatinine is diminished as a result of the reduced muscle mass.

10. In certain clinical situations, the influence of muscle mass can be essential, for instance when diagnosing reduced GFR in paralysed patients. This has been investigated in patients with spinal cord injury who have varying degrees of muscle atrophy. The results show that cystatin C is much more reliable as a marker of renal function for group of patients compared to creatinine .

11. Diabetes is a highly complex disorder with many ramifications and is the commonest cause of kidney failure in younger people globally. Treatment comprises dialysis or kidney transplantation. If early damage to the kidneys can be detected, preventive action can then be taken. Cystatin C has been reported to be advantageous compared with serum creatinine for the detection of mild diabetic nephropathy, whereas the two markers were equally efficient in detecting advanced diabetic nephropathy.

12. Cystatin C has been measured before and after chemotherapy in cancer patients. The results show that serum cystatin C is a superior marker to serum creatinine for the estimation of GFR,

independent of the presence of metastases, and independent of chemotherapy.

13. Cystatin C can be used to characterise glomerular function in children with cancer. In multiple myeloma, a study has demonstrated no correlation between cystatin C and tumour burden.

14. Cystatin C could be used as a valuable parameter in the monitoring of pregnancies complicated by pre-eclampsia. There is a real need for sensitive and specific diagnostic tests for pre-eclampsia. During uncomplicated pregnancy, the renal-flow progressively increases, leading to about 40% higher GFR than in a non-pregnant woman. Because pre-eclampsia is characterised by a decrease in GFR, kidney function needs to be monitored closely to ensure timely delivery before the development of toxaemia and serious kidney tissue injury. Cystatin C has been shown to provide superior diagnostic accuracy for pre-eclampsia compared to serum urate and creatinine, and cannot only be used as a marker for impaired renal function, but also for the degree of glomerular endotheliosis (the only consistently found pathological lesion in pre-eclampsia). Thus, cystatin C seems to be useful for optimising the timing of delivery.

Cystatin C Immunoassay:

Cystatin C Immunoassay is intended for the quantitative determination of cystatin C in human serum and plasma by turbidimetry and nephelometry. The assay is based on particle-enhanced immune turbidimetry. The measuring range is optimised to 0.4 - 7.5 mg/L, which covers the concentration range in normal and diseased states[42]. The assay can be performed in most clinical chemistry analysers available in the market and the total assay time is approximately 10 minutes. This enables cystatin C to be measured 24 hours/day in most clinical chemistry laboratories. The reagents on board the instrument and the calibration curve stored in the instrument remain stable for up to 90 days.

There is currently no international reference material available for cystatin C, but the International Federation of Clinical Chemistry (IFCC) has recently established a working group on standardisation of Cystatin C.

PREDICTION OF PREECLAMPSIA:

Uterine artery Doppler:

A well-known mechanism of pathophysiology of preeclampsia is impaired trophoblastic invasion of the spiral arteries which increases impedance of flow to uterine arteries[24]. Several studies have shown that evidence of reduced uterine flow, is associated with the development of preeclampsia.

Elevated level of second trimester β-human chorionic gonadotropin (β-HCG) have been identified in patients at risk for hypertensive disorders during pregnancy. Another study demonstrated that in presence of a diastolic notch, the association of serum screening with alfa-feto-protein and human chorionic gonadotropin, improves sensitivity and positive predictive value to 91% and 41% respectively.

Regarding the placental protein-13 (PP-13), initial studies showed significantly decrease in preeclamptic women, recently another study did not show any relationship betweenPP-13 levels and preeclampsia. Akolekar *et al* studied placental protein-13 (PP-13) associated with pregnancy associated pregnancy protein-A (PAPP-A) and uterineartery Doppler in first trimester in 200 preeclamptic patients and in 410normal pregnancies showing reduction in PP-13 levels during early preeclampsia but not in latepreeclampsia with positive predictive value for early preeclampsia of 75%, while for late preeclampsia of 49%. Though in preeclampsia PAPP-A was reduced and uterine velocimetry Doppler was elevated, combination of these parameters with PP-13 does not look to improve sensitivity of PP-13[39].

Inspite of the promising results, heterogeneity between studies regarding gestational age at the time of study or selected population has lead us to incline towards the combination of ultra sonographic and biochemical markers as screening procedure for preeclampsia.

Maternal echocardiography:

In pregnancy changes happen in haemodynamic and cardiovascular system within intial vasodilatative adaptation of the maternal cardiovascular system which begins in Ist trimester as a result of invasion by spiral arteries by the trophoblast. Indeed remodelling in the spiral arteries contributes to 20% to 26% to the total reduction of systemic vascular resistance in the second trimester. Another change is in body composition with increase in blood volume. An analysis on multi frequency bioelectrical impedance, documented that the body water, extracellular water increased significantly and increasing from first half to the later half of pregnancy.

Cardiovacular and haemodynamic modifications include elevated pre-load, reduced after-load, an increased compliance of vascular tree and a ventricular remodelling at the level of heart. We have therefore increase in blood volume to occupy the enlarged vascular bed. On the other hand, inadequate placentation and failure of haemodynamic adaptation was identified to base of pathologic process that leads to complications of pregnancy. Already in a study concluded that in preeclamptic women, along with the cardiac output, a high peripheral resistance can be observed and in those subjects with a reduced cardiac output low birth weight could occur. Another study observed that patients with fetal growth restriction (FGR) had a smaller diameter of left atrium and failure of cardiac output in early pregnancy.

The study group of Valensise designed a different thesis to evaluate the predictive value of some echocardiographic parameters for abnormalities in uterine artery Doppler and its relation to maternal and fetal complications.

Echoparameters of cardiac changes in pregnancy may be, in normotensive women, an important marker of pregnancy complications & of predispostion to cardiac diseases.

Provocative pressor tests:

These are tests which assess blood pressure increase in response to a stimulus. They are cumbersome and time consuming. Sensitivities of all these tests range from 55 to 70% with specificity of 85%. They include:

1. Angiotensin sensitivity test:

The abnormal vascular reactivity of patients destined to develop preeclampsia may be detected several weeks before the development of clinical signs and symptoms and the degree of sensitivity to angiotensin II may be used as a screening test to identify the patients at risk.

2. Roll over test:

It measures the hypertensive response in women at 28 to 32 weeks who are resting in the left lateral decubitus position and then roll over to a supine position. A positive test is an elevation of 20mmHg or more of blood pressure when patients roll over from the lateral to the supine position

3. Urinary calcium:

Several studies have demonstrated that preeclampsia is associated with hypocalciuria. A urinary calcium concentration equal to or less than 12mg/dl in a 24 hour collection has positive and negative predictive values of 85 and 91% respectively, for the diagnosis of preeclampsia. Determination of calcium creatinine ratio in a randomly obtained urine sample seems to be accurate as 24 hour collection.

New biochemical markers:

In obstetrical practice a long-term objective is to identify ideal maternal biomarkers for preeclampsia, but it is very difficult because the "ideal marker" requires the coexistence of different characteristics: non invasiveness, high sensitivity and specificity, high positive predictive value to predict disease prognosis. Currently we have a plethora of studies intended to identify an ideal biomarker, however differences in the studied populations, in the methodologies and in the results interpretations, make it difficult to perform a systematic analysis of all the markers.

Research of these new emerging biomarkers arises from the new model of pathogenesis of preeclampsia which places the focus not longer on vasoconstrictive phenomenon but on the angiogenesis process.

Among proangiogenic factors there are vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), among antiangiogenic

factor there are soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 receptor (sFlt-1).

Cells expressing VEGF are located near fenestrated endothelia and the inhibition of VEGF leads to pathological conditions in many organs with fenestrated endothelia (*e.g.*, liver, kidney, choroid plexus *etc.*) as observed in severe preeclampsia. PlGF is expressed mainly by placental cells and its levels increase from the second to third trimester. Both VEGF and PlGF bind VEGF receptor family, named Flt-1 and KDR. PlGF binds more actively Flt-1, while VEGF binds KDR. It has been suggested that sFlt-1 acts modulating VEGF availability.

This evidence confirms the antiagiogenic role of soluble form of VEGF-PlGF receptor sFlt-1.

sFlt-1bindsthese angiogenic factors and inhibits their vasodilatory effect. Other anti-angiogenic factor is sEng. In animal studies it allows the formation of endothelial tube and increases capillary permeability and could be responsible of hypertension, nephrotic syndrome and liver dysfunction during preeclampsia.

A recent review reported significant changes in levels of sFlt-1, PlGF and sEng in preeclamptic patients, but with a different time course, earliest in the first trimester for PlGF and later for sFlt-1 and sEng.

More recently the level of placental growth factor (PIGF) is evaluated in pregnancy complicated by hypertension disease and it has

been found that a positive PIGF test can predict delivery before 37 weeks in over 90% of pregnant women with hypertensive disease. Therefore a low level of PIGF could be used before 35 weeks, in hypertensive women, to evaluate the risk of pregnancy complications. Also sEng level seems to be a prognostic, and its level appears correlated with severe preeclampsia or eclampsia. Despite this evidence, there aren't yet conclusive data on their diagnostic capability, on the cut-off of normality and on the time or the strategy to measure these markers.

Regarding diagnostic capability, a recent extensive study conducted on 2200 patients reported for PlGF and sFlt-1 at first trimester, a sensitivity of 55% and 57% respectively and a specificity of 43% and 40% respectively and this result doesn't improve later in pregnancy. It is evident that the predictive positive value is too low to use this marker at first trimester as screening of preeclampsia. Other strategies in measuring the angiogenic factors have been proposed: a longitudinal evaluation and ratio between two factors.

Indeed in preeclamptic women it has been demonstrated an increase from first to second trimester of sFlt-1, sEng and PlGF, on the other hand several studies, based on the observation that levels of PlGF and sFlt-1 are altered together in preeclampsia, proposed a ratio between sFlt-1 and PlGF (sFlt-1:PlGF) and between PlGF and sEng (PlGF:sEng) reporting an important improvement in sensitivity (88.5% and 100% respectively)

and in specificity (88.5% and 98% respectively). Despite these promising results, larger studies are needed to confirm these finding.

Biomarkers in preeclampsia:

Autoantibodies:

Gant et al identified hypersensitivity to infused Angiotensin II in preeclamptic patients. However, circulating levels of Angiotensin II are not increased in preeclampsia. Instead, immunoglobulins from preeclamptic women increased the beating rate of neonatal rat cardiomyocytes. These immunoglobulins contained Angiotensin II type 1 (AT1) autoantibodies that stimulate the Angiotensin-receptor. The increased heartbeat rate could be blocked by treatment with losartan and it could be demonstrated that the autoantibodies bind to the second extracellular loop of the AT1 receptor. AT1 agonistic autoantibodies are not only found in preeclampsia but also in antibody mediated kidney transplant rejection. In kidney-transplant recipients who had severe allograft dysfunction without anti-HLA antibodies but detection of AT1 agonistic autoantibodies rejection was accompanied by accelerated hypertension and convulsions. It is proposed that similar mechanisms might be involved in preeclampsia and refractory allograft rejection and it was found that one rejecting kidney-transplant recipient had had preeclampsia 16 years earlier.

Adrenomedullin:

Pregnancy is associated with high concentrations of adrenomedullin in maternal and foetal blood and in the amniotic fluid. Adrenomedullin has a potent and long-lasting hypotensive effect when injected intravenously in anaesthetised rats. Hata et al measured circulating adrenomedullin concentrations in preeclampsia and normotensive pregnant women and showed that adrenomedullin concentrations are significantly lower in preeclamptic women.

Podocyturia:

Renal involvement in preeclampsia can be at least partly explained by impaired podocyte function. Podocytes are the major source of VEGF in the glomerulus. Podocyte-derived VEGF has paracrine functions on endothelial cells as well as autocrine functions on the podocytes themselves. New data suggest that detection of podocyturia might serve as an early diagnostic marker for preeclampsia prior to the development of proteinuria and hypertension. Garovic et al showed that podocyturia is present at delivery in women with preeclampsia[53]. Podocyturia also had a significantly greater sensitivity and specificity for the subsequent diagnosis of preeclampsia than any single angiogenic marker or a combination thereof in the second trimester. A strong correlation was found by Aita et al between the number of podocytes lost in urine and blood pressure, but no correlation with proteinuria. Several markers have been used in different studies to detect podocyturia. Nevertheless, it is

important to keep in mind that the expression of marker proteins does not allow a definite allocation of the involved glomerular cell types. De- or transdifferentiation and detachment of cells as well as changes in the urine milieu have a direct effect on marker protein expression. According to Skoberne et al, the urine markers most reliable for assessing disease activity of certain glomerular diseases are PDX- or CD68-positive cells.

mRNA:

Recently, quantitative polymerase chain reaction for podocyte-specific markers was found to be a rapid method to detect preeclampsia. Significantly elevated mRNA levels of nephrin, podocin, and VEGF were detected in preeclamptic women compared with healthy controls.

Placental protein 13:

Placental protein 13 (PP13) is a member of the galectin super family and is important for differentiation and proliferation. Than et al[47] found reduced PP13 mRNA levels in placentas obtained from patients with preeclampsia and HELLP syndrome in the first trimester compared to controls. Blood levels of PP13 mRNA were also significantly lower in preeclampsia compared to controls.

Pregnancy associated plasma protein-A:

Pregnancy associated plasma protein-A (PAPP-A) is mainly produced by the placental trophoblasts. PAPP-A and PP13 serum levels were significantly lower in the first and second trimesters in women who

developed preeclampsia. First-trimester PAPP-A provided a prediction for preeclamspia when combined with uterine artery pulsatility measured by Doppler velocimetry.

Activin A and inhibin A:

During the first trimester of pregnancy, the foeto-placental unit is the main source of circulating activin A and inhibin A. Activin A enhances Follicle-stimulating hormone (FSH) biosynthesis and secretion and is involved in the control of trophoblast cell differentiation in the first trimester. Inhibin A down regulates FSH synthesis and inhibits FSH secretion. Activin A seems to be a sensitive marker for the risk of later development of preeclampsia at 21-25 weeks of gestation. Inhibin A is thought to be more sensitive than activin A in predicting cases of early-onset preeclampsia at 15-19 weeks of gestation.

P-selectin:

P-selectin belongs to the group of cell adhesion molecules. It is expressed in granules of platelets and the Weibel-Palade bodies of endothelial cells and is involved in leukocyte-endothelial interactions. The P-selectin concentration was found to have a negative predictive value of almost 99% for preeclampsia. Mean plasma P-selectin concentrations were significantly elevated at 10-14 weeks of gestation in women who later developed preeclampsia. Wang et al suggested that the increase in neutrophil-endothelial adhesion and activation seen in

preeclampsia is at least in part due to up-regulation of P-selectin. This would be in line with the theory that preeclampsia reflects an excessive maternal inflammatory response to pregnancy.

Pentraxin 3:

Another inflammatory molecule involved in preeclampsia is Pentraxin 3. It is expressed in response to inflammatory stimuli by endothelial cells, monocytes, macrophages and fibroblasts. Elevated maternal plasma levels of pentraxin 3 in preeclamptic in comparison to normal pregnancies could represent altered endothelial function. The increase in maternal plasma develops from 11^{th} to 13^{th} week of gestation in women with subsequent preeclampsia.

Fibronectin:

Maternal plasma fibronectin levels of patients with preeclampsia were significantly higher than those of healthy pregnant women. Significant elevations in fibronectin levels with an extra type III domain occurred in the first trimester before clinical evidence of preeclampsia. Fibronectin plays a major role in embryonic development, cell adhesion, growth, migration and differentiation.

Heat-shock proteins:

Heat-shock proteins (Hsps) are highly conserved molecules that have chaperone functions. Circulating Hsps may also be cytoprotective, as exogenous Hsp70 increases the survival and protects from apoptosis in

stressed arterial smooth muscle cells. Fukushima et al reported significantly higher Hsp70 serum levels in preeclampsia. Higher serum levels of Hsp70 were also found in patients with early onset of severe preeclampsia. The difference in serum Hsp70 concentration between preeclamptic patients and the control group was statistically significant in each gestational age. Thus, Hsp70 might not only be a marker but also play a role in the pathogenesis of preeclampsia.

Fms-like tyrosine kinase 1/ placental growth factor:

Gene expression profile studies identified the regulation of soluble fms-like tyrosine kinase 1 (sFlt-1) in preeclampsia. SFlt-1 binds and antagonises vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).

The described functions of VEGF include induction of matrix metalloproteinases, regulation of angiogenesis, lymphangiogenesis and hematopoiesis and cell signalling. Serum concentration of sFlt-1 decreases from 8-12 weeks to 16-20 weeks of gestation, gradually increases at 26-30 weeks of gestation and rapidly elevates at 35-39 weeks of gestation in normal pregnancy.

SFlt1 concentrations increased gradually throughout pregnancy in women with preeclampsia and was significantly higher between 25 and 28 weeks of gestation in women with preeclampsia than in women with normal pregnancies or isolated hypertension. Of note, sFlt1 are high 5-6

weeks prior to the onset of preeclampsia and correlate with the severity of disease. In rats sFlt-1 infusion increased vascular and placental oxidative stress, decreased maternal circulating VEGF and nitric oxide and reduced fetal weight.

Serum concentration of PlGF increases gradually from 8 weeks until 29-32 weeks of gestation and then decreases at 33-40 week of gestation in normal pregnancy. PlGF levels in women who later developed preeclampsia were significant lower than those of controls from 13-16 weeks of gestation until delivery. As the change of PlGF occurs earlier than that of sFlt-1, it might be the better angiogenic factor for predicting preeclampsia. Serum sFlt-1 to PlGF ratio (sFLT-1/PIGF) was also suggested as screening parameter. An adenovirus-expressing sFlt-1 in rodents caused a clinical syndrome with glomerular endotheliosis, proteinuria, and hypertension. Glomerular capillary endotheliosis is another typical lesion in preeclampsia.

Soluble endoglin:

Serum levels of sEng in normal pregnancy are quite stable and slightly increase by 33-42 weeks of gestation. Placental endoglin is up-regulated in preeclampsia and released in the circulation. Rising levels of circulating soluble endoglin (sEng) herald the onset of preeclampsia. Women with higher sEng levels at 21 through 32 weeks of gestation had an increased risk of preterm preeclampsia and an increased risk for a small-for-gestational-age infant.

Cellfree fetal DNA:

Cellfree fetal DNA (cffDNA) is increased at 11-13 weeks of gestation in pregnancies that experience preeclampsia. Hypoxia within the intervillous space of the placenta leads to tissue oxidative stress and increases placental apoptosis and necrosis. This might be the cause of increased levels of cffDNA. Elevated cffDNA is not specific for preeclampsia and is also seen in other conditions associated with placental pathology.

WHO recommendations for prevention and treatment of preeclampsia [10]:

Rest for Prevention and Treatment of Preeclampsia

1. Advice to rest at home is not recommended as an intervention for the primary prevention of preeclampsia and hypertensive disorders of pregnancy in women considered to be at risk of developing those conditions.

2. Strict bedrest is not recommended for improving pregnancy outcomes in women with hypertension (with or without proteinuria) in pregnancy.

Dietary Salt Restriction for Prevention of Pre-eclampsia

3. Restriction in dietary salt intake during pregnancy with the aim of preventing the development of pre-eclampsia and its complications is not recommended.

Calcium Supplementation during Pregnancy to Prevent Preeclampsia and Its Complications

4. In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of preeclampsia in all women, but especially in those at high risk of developing preeclampsia.

Vitamin D Supplementation

5. Vitamin D supplementation during pregnancy is not recommended to prevent the development of preeclampsia and its complications.

Antioxidants for Prevention of Preeclampsia and Its Complications

6. Individual or combined vitamin C and vitamin E supplementation during pregnancy is not recommended to prevent the development of preeclampsia and its complications.

Antiplatelets for Prevention of Preeclampsia

7. Low-dose acetylsalicylic acid (aspirin, 75 mg/day) is recommended for the prevention of preeclampsia in women at high risk of developing the condition.

8. Low-dose acetylsalicylic acid (aspirin, 75 mg/day) for the prevention of preeclampsia and its related complications should be initiated before 20 weeks of pregnancy.

Antihypertensive Drugs and Diuretics

9. Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs.

10. The choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician's experience with that particular drug, its cost and local availability.

11. Diuretics, particularly thiazides, are not recommended for the prevention of preeclampsia and its complications.

Magnesium Sulfate for Prevention and Treatment of Eclampsia

12. Magnesium sulfate is recommended for the prevention of eclampsia in women with severe preeclampsia in preference to other anticonvulsants.

13. Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants.

14. The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia.

15. In settings where it is not possible to administer the full magnesium sulfate regimen, the use of magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended for women with severe preeclampsia and eclampsia.

Corticosteroids for HELLP (haemolysis, elevated liver enzymes, low platelet count) Syndrome

16. The use of corticosteroids for the specific purpose of treating women with HELLP syndrome is not recommended.

Interventional versus Expectant Care for Severe Preeclampsia before Term

17. Induction of labour is recommended for women with severe pre-eclampsia at a gestational age when the fetus is not viable or unlikely to achieve viability within one or two weeks.

18. In women with severe preeclampsia, a viable fetus, and before 34 weeks of gestation, a policy of expectant management is recommended, provided that uncontrolled maternal hypertension,

increasing maternal organ dysfunction or fetal distress are absent and can be monitored.

19. In women with severe preeclampsia, a viable fetus and between 34 and 36 (plus 6 days) weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.

Induction of Labour for Preeclampsia at Term

20. In women with severe preeclampsia at term, a policy of early delivery is recommended.

21. In women with mild preeclampsia or gestational hypertension at term, induction of labour is recommended.

Prevention and Treatment of Postpartum Hypertension

22. In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended.

23. Treatment with antihypertensive drugs is recommended for severe postpartum hypertension.

AIMS & OBJECTIVES

- To estimate serum cystatin C and serum creatinine level in pre-eclamptic primigravidae and compare it with controls.
- To assess the diagnostic performance of serum Cystatin C in early detection of renal dysfunction in pre-eclamptic primigravidae by comparing it with serum Creatinine.

BENEFITS OF THE STUDY

The better marker of renal dysfunction in preeclampsia can be used in clinical settings –serum cystatin C / serum creatinine

METHODOLOGY

1) Term primigravidae attending AN OPD who are diagnosed to have preeclampsia are included and compared to equal number of healthy matched normotensive pregnant women
2) Detailed history, general examination, obstetric examination are performed
3) Withdrawal of 5ml blood for serum cystatin C& serum creatinine estimation

Cases - pre-eclampticprimigravidae in third trimester ofpregnancy

Controls - healthyprimigravidae in third trimester

Inpatients and outpatients of O & G Department, GovtKilpauk medical college & Hospital, Chennai

Estimation of serum Creatinine by Jaffe's method.

Estimation of Cystatin C by Nephelometric method

STUDY DESIGN:-

Case control study

PLACE OF STUDY:

Antenatal Outpatient Department, LABOR WARD AND ANTENATAL WARD Dept of Obstetrics & Gynaecology, Govt Kilpauk medical college & Hospital, Chennai

DURATION OF STUDY: 6 Months

SAMPLE SIZE

$n=(r+1/r)\sigma^2(Zb+Za/2)^2/difference^2$

n-sample size,

r-ratio of cases to controls = 1

Zb-the desired power of the study = 80% = 0.84

Za/2-represents the desired level of statistical significance – 1.96

σ -standard deviation= 0.4

difference-effect size(the difference in means)= 0.52

n = 10

cases – 40

control - 40

INCLUSION CRITERIA:-

- Pre-eclamptic primigravidaein third trimester as cases
- Healthy matched primigravidae in third trimester as controls

EXCLUSION CRITERIA:

- Pre-eclamptic multigravidae
- Healthy multigravidae

- Known case of diabetes mellitus, renal disease and chronic hypertension
- Multiple pregnancy
- Liver disease
- Connective tissue disorders
- Smoking
- Alcoholism

STATISTICAL ANALYSIS:

The mean and standard deviation of serum cystatin C& serum creatinine in both cases and controls will be compared by student t test

STATISTICAL ANALYSIS:

Serum Cystatin C and Serum creatinine were considered as the primary outcome variables. Presence or absence of Preeclampsia was considered as primary exposure variable. Age and gender are considered as other explanatory variables. Descriptive analysis of all the variables was done using mean and standard deviation for quantitative variables, frequency and percentage for categorical variables. The association between Preeclampsia and primary outcome variables was assessed by Independent Sample T-Test. Mean differences, their confidence intervals and p-value were calculated and presented. P value < 0.05 was considered as statistically significant.IBM SPSS version 21 was used for statistical analysis.

RESULTS

A total of 80 participants were included in the final analysis.

TABLE 1:

DESCRIPTIVE ANALYSIS OF AGE IN STUDY GROUP (N=50)

Parameter	Mean±STD	Median	Max	Min	95% C.I.for EXP(B)	
					Lower	Upper
AGE	23.71 ± 2.710	23.00	29.00	20.00	23.11	24.32

The mean age was 23.71 ± 2.710 in the study population. (Table 1)

FIGURE 1: BOX-WHISKER PLOT OF AGE

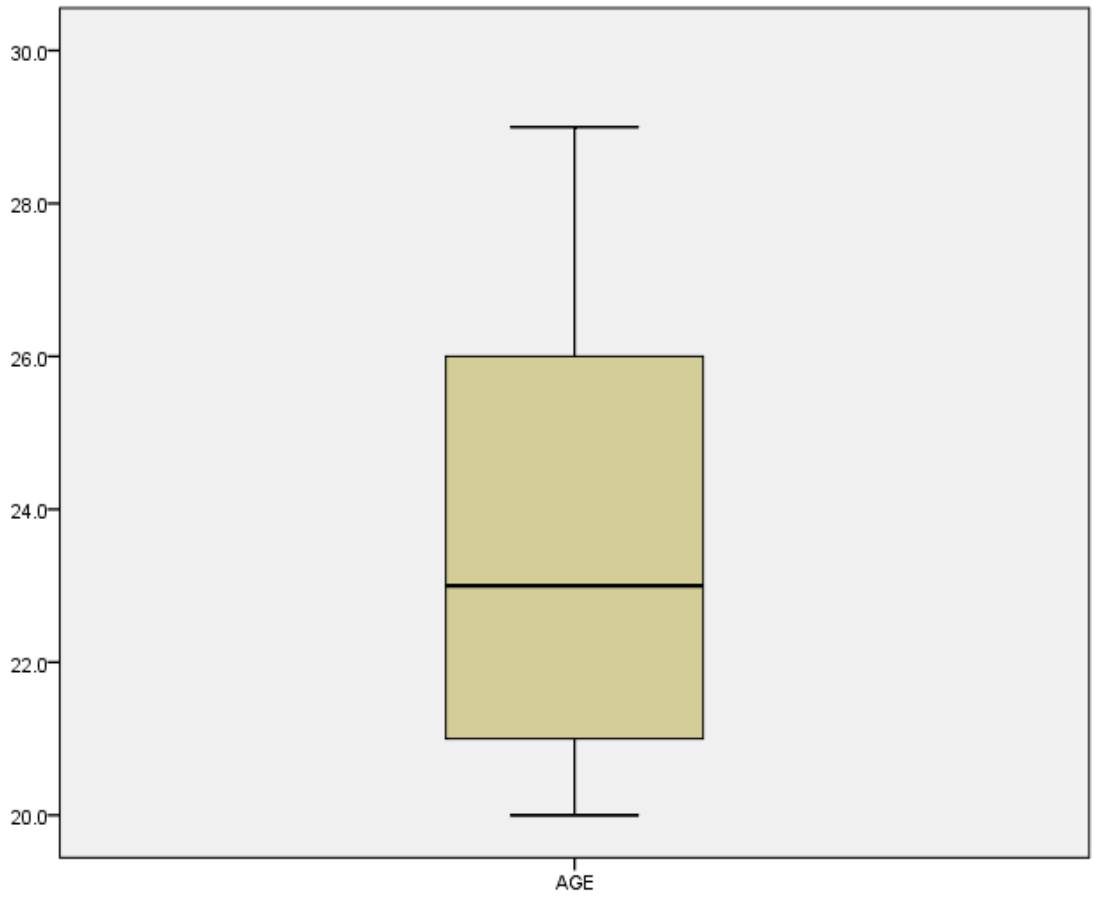


TABLE 2:

DESCRIPTIVE ANALYSIS OF AGE GROUP IN STUDY GROUP

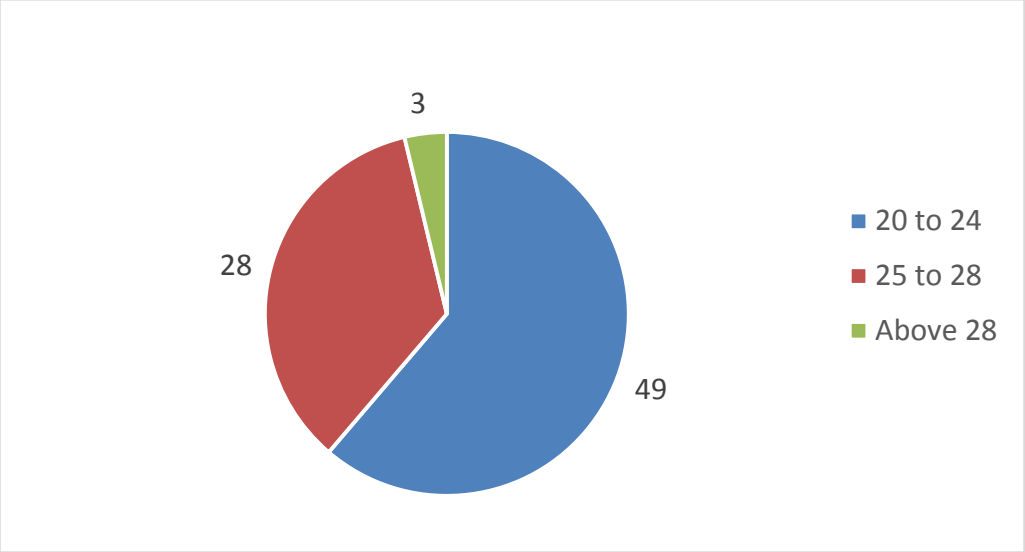
(N=80)

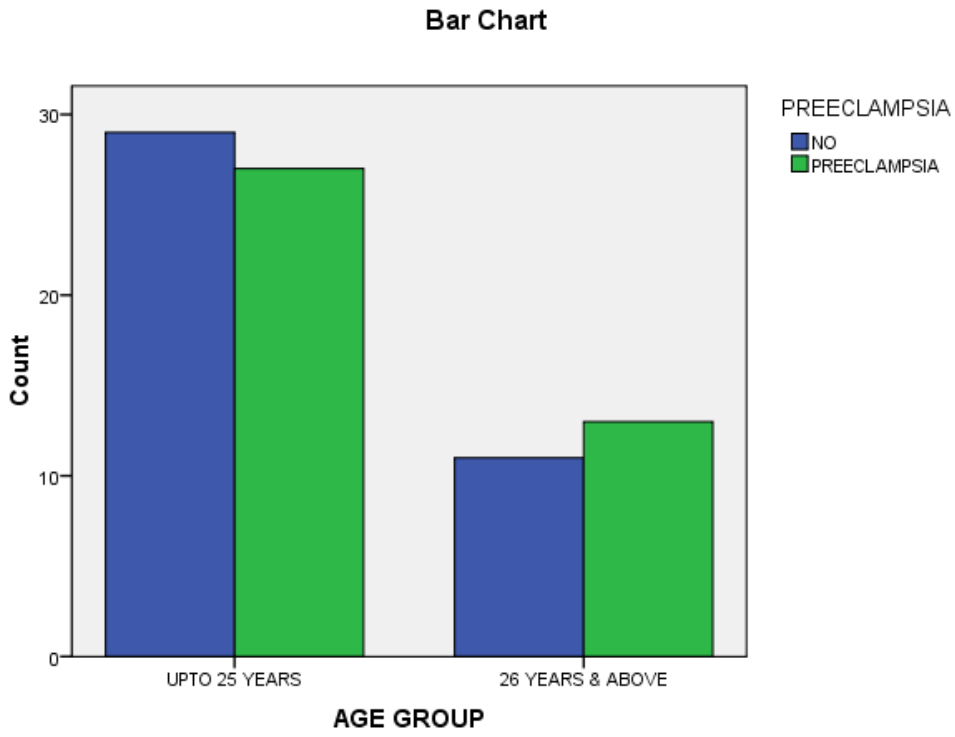
Age group	Frequency	Percent
20 to 24	49	61.25%
25 to 28	28	35%
Above 28	3	3.75%
Total	80	100%

The number of people in the age group 20 to 24 were 49 (61.25%), age group 25 to 28 were 28 (35%) and above 28 years were 3 (3.75%). (Table 2)

FIGURE 2:

PIE CHART OF AGE GROUP DISTRIBUTION IN STUDY GROUP (N=80)





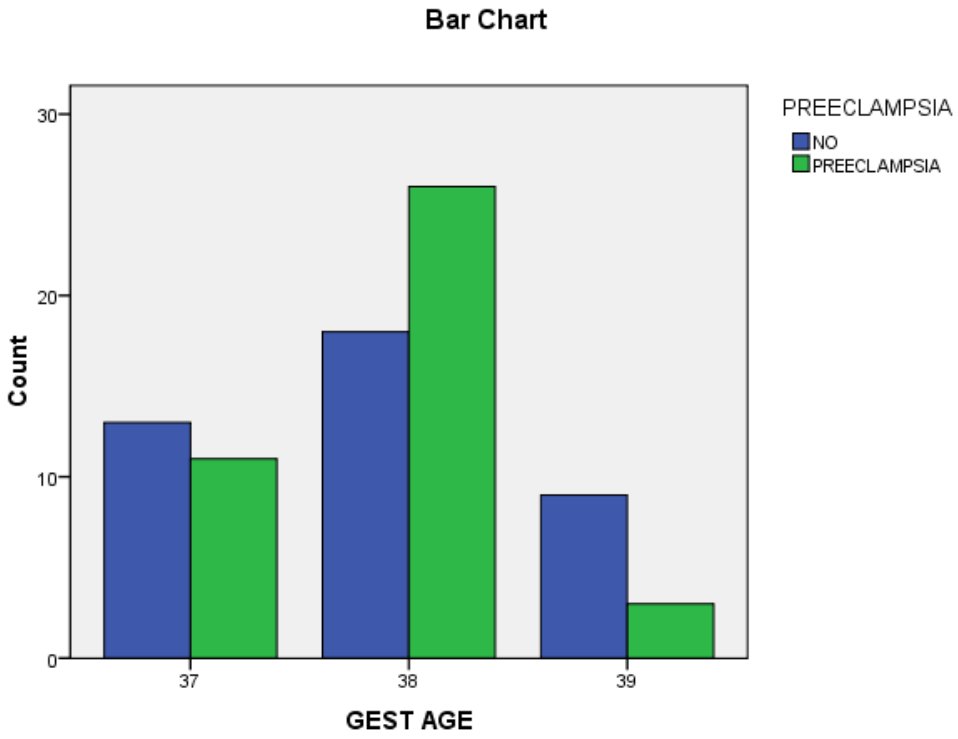

Bar Chart
PREECLAMPSIA
NO
PREECLAMPSIA
Count
30
20
10
0
37
38
39
GEST AGE

TABLE 3:

DESCRIPTIVE ANALYSIS OF SYSTOLIC BP AND DIASTOLIC BP IN STUDY GROUP (N=80)

Parameter	Mean±STD	Median	Max	Min	95% C.I.for EXP(B)	
					Lower	Upper
Systolic BP	134 ± 26.22	130.00	180.00	100.00	128.16	139.84
Diastolic BP	83 ± 19.31	85.00	120.00	60.00	78.70	87.30

The mean Systolic BP was 134 ± 26.22 and mean Diastolic BP was 83 ± 19.31in the study population. (Table 3)

FIGURE 3:

BOX-WHISKER PLOT OF SYSTOLIC BLOOD PRESSURE

FIGURE 4:

BOX-WHISKER PLOT OF DIASTOLIC BLOOD PRESSURE

TABLE 4:

DESCRIPTIVE ANALYSIS OF PREECLAMPSIA IN STUDY GROUP (N=80)

PREECLAMPSIA	Frequency	Percent
Yes	40	50.00%
No	40	50.00%
Total	80	100.00%

Out of 80 subjects, 40 (50.00%) has preeclampsia and 40 (50.00%) has no preeclampsia. (Table 3)

FIGURE 3:

BAR CHART OF PREECLAMPSIA DISTRIBUTION IN STUDY GROUP (N=80)

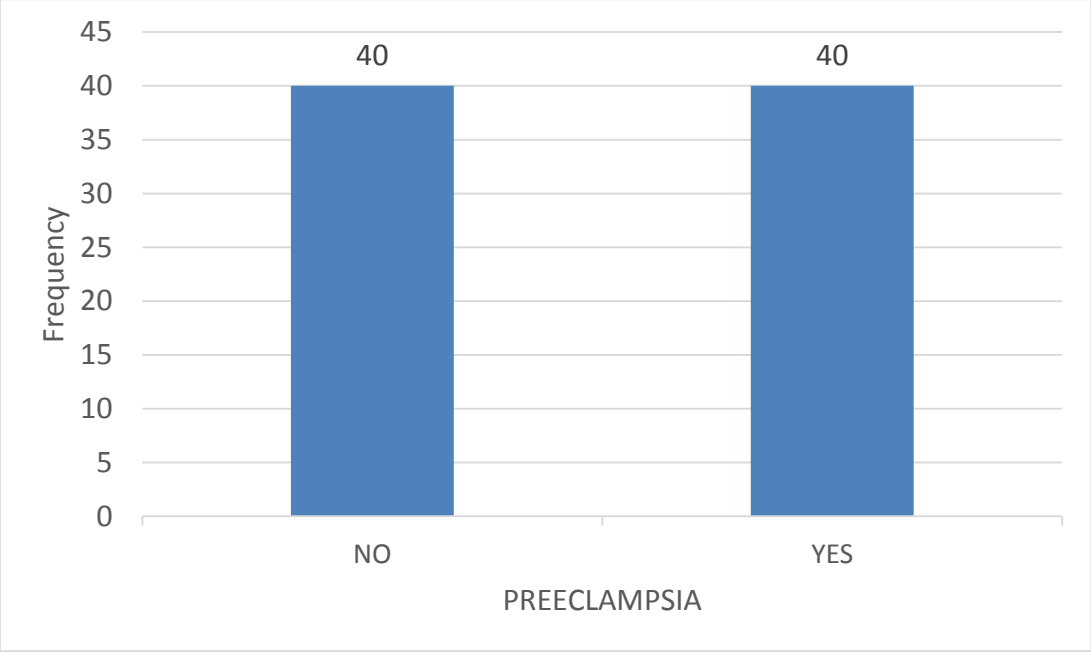


TABLE 5:

DESCRIPTIVE ANALYSIS OF SERUM CYSTATIN C AND SERUM CREATININE IN STUDY GROUP (N=80)

Parameter	Mean±STD	Median	Max	Min	95% C.I.for EXP(B)	
					Lower	Upper
SerumCYSTATINC	0.692 ± 0.302	0.55	1.64	0.40	0.62	0.76
SerumCREATININE	0.707 ± 0.236	0.60	1.40	0.30	0.65	0.76

The mean serum cystatin C was0.692 ± 0.302 and the mean Serum creatinine was 0.707 ± 0.236.(table5)

FIGURE 5:

BOX-WHISKER PLOT OF SERUM CYSTATIN C

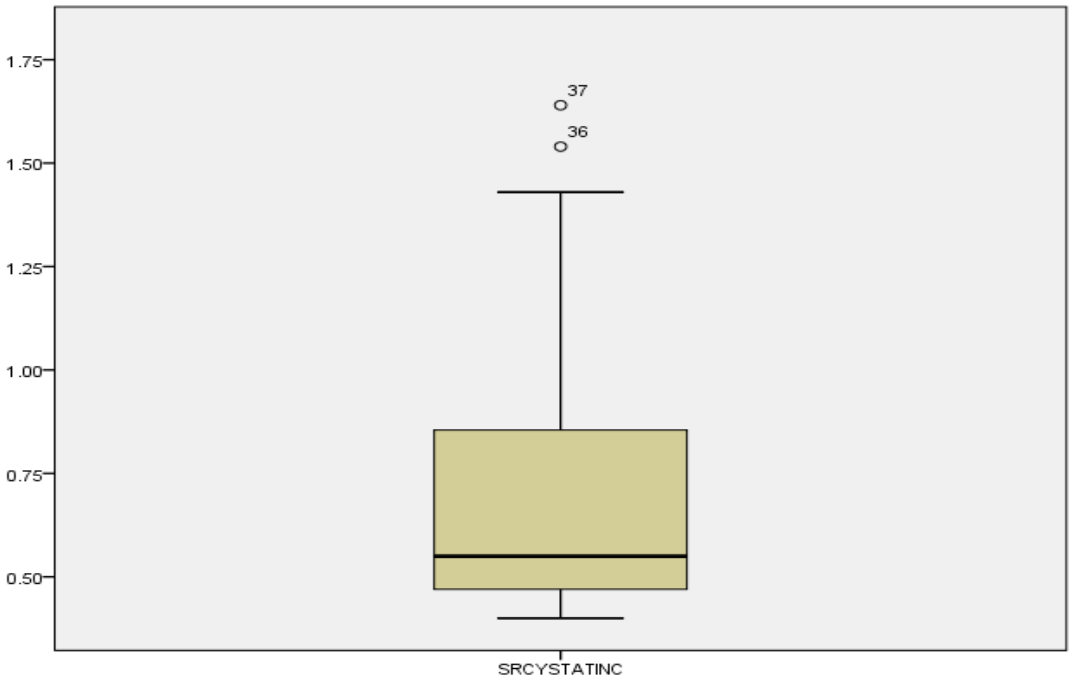


FIGURE 5(a):

BOX-WHISKER PLOT OF SERUM CREATININE

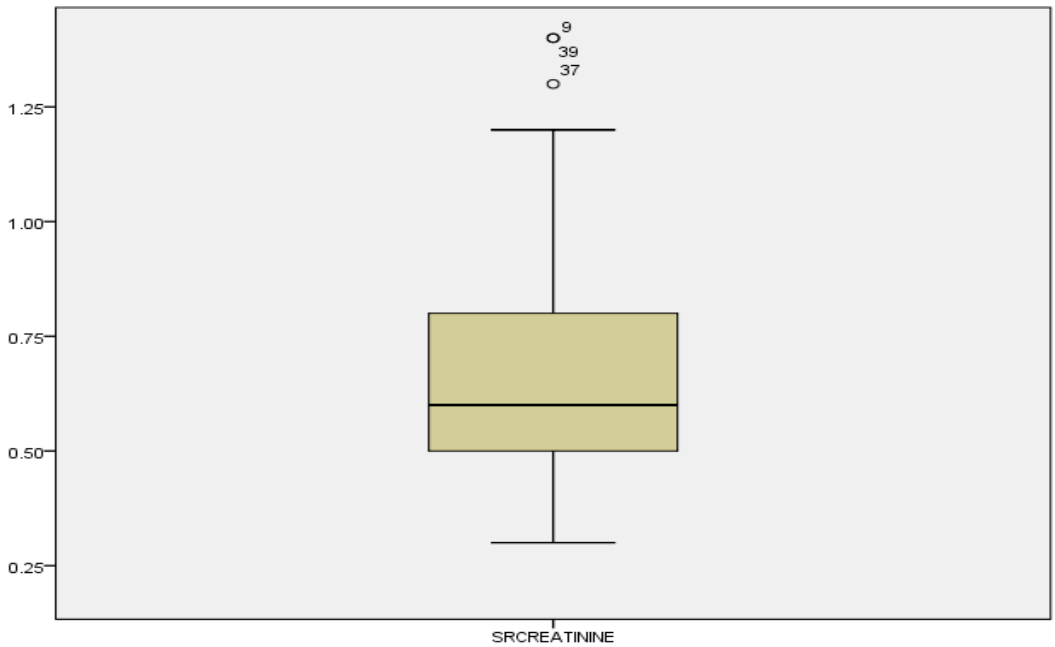


TABLE 6:

DESCRIPTIVE ANALYSIS OF URINE ALBUMIN IN STUDY GROUP (N=80)

URINEALB	Frequency	Percent
1+	7	8.75%
2+	16	20%
3+	10	12.5%
4+	7	8.75%
NIL	40	50%
Total	80	100%

The number of subjects with Urine albumin 1+ was 7 (8.75%), with Urine albumin 2+ was 14 (20%), with Urine albumin 3+ was 10 (12.5%), with Urine albumin 4+ was 7 (8.75%) and without Urine albumin was 42 (50%). (Table 6)

FIGURE6:

PIE CHART OF URINE ALBUMIN DISTRIBUTION IN STUDY GROUP (N=80)

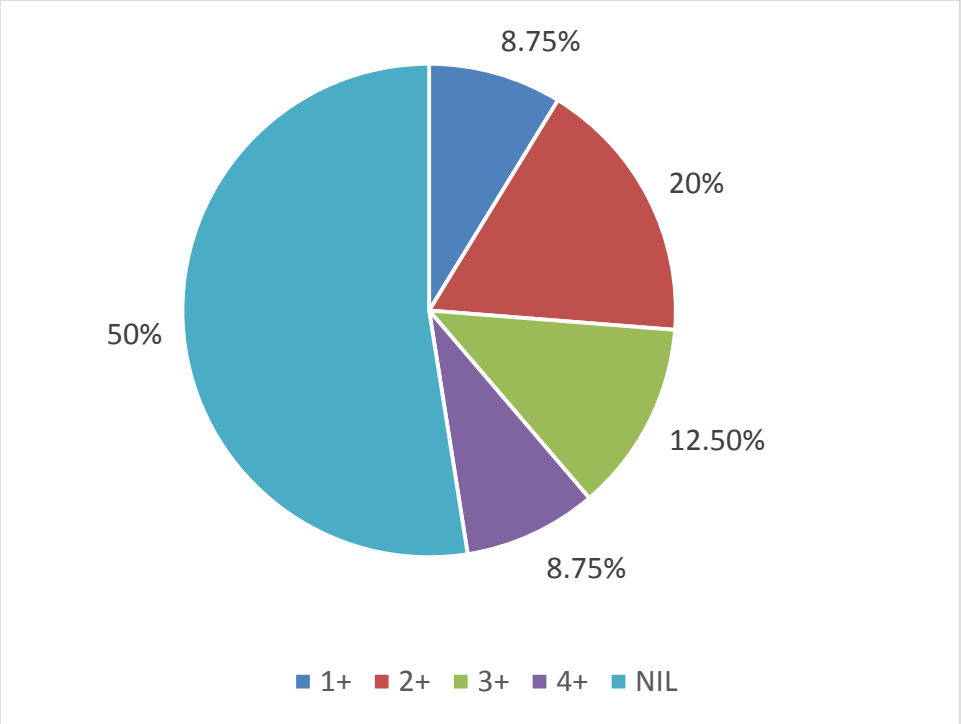


TABLE 7:

COMPARISON OF MEAN SERUM CYSTATIN C ACROSS STUDY GROUPS (N=80)

Pre-eclampsia	Serumcystatin C Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
YES	0.895 ± 0.310	0.41	0.30	0.50	<0.001
NO	0.489 ± 0.064				

The mean of serum cystatin C among people with preeclampsia was 0.895 ± 0.310 and the mean serum cystatin C among people without preeclampsia was 0.489 ± 0.064 in the study population. Hence Serum Cystatin C was 0.41 units higher (95% CI 0.30 to 0.50, p value <0.00) in people with preeclampsia (Table 7)

ROC curve

Variable	Serum.CYSTATINC Serum.CYSTATIN C
Classification variable	PREECLAMPSIA

Sample size		80
Positive group :	PREECLAMPSIA = 1	40
Negative group :	PREECLAMPSIA = 0	40

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.941875
Standard Error[a]	0.0259
95% Confidence interval[b]	0.865947 to 0.981859
z statistic	17.031
Significance level P (Area=0.5)	<0.0001

[a] Hanley & McNeil, 1982

[b] Binomial exact

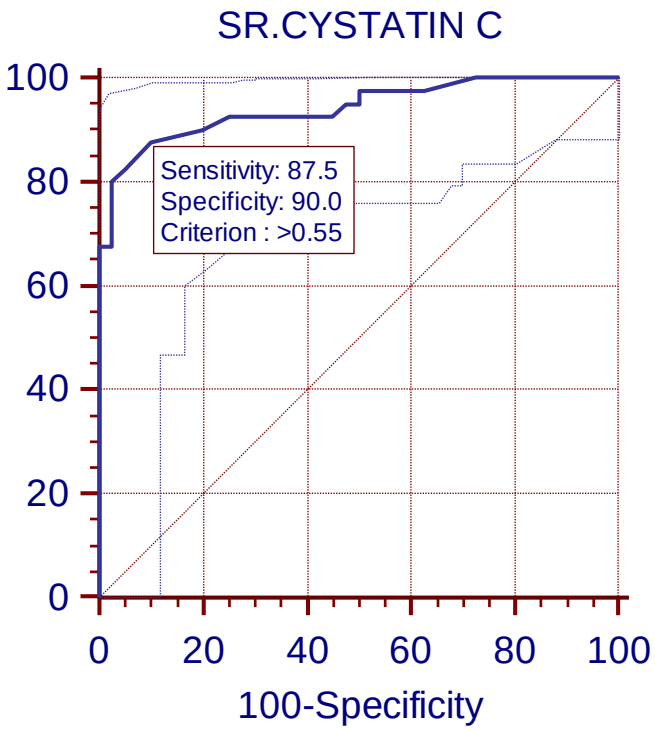

SR.CYSTATIN C
100
80
60
40
20
0
Sensitivity: 87.5
Specificity: 90.0
Criterion : >0.55
0
20
40
60
80
100
100-Specificity

FIGURE 7:

COMPARISON OF SERUM CYSTATINC ACROSS STUDY GROUP (N=80)

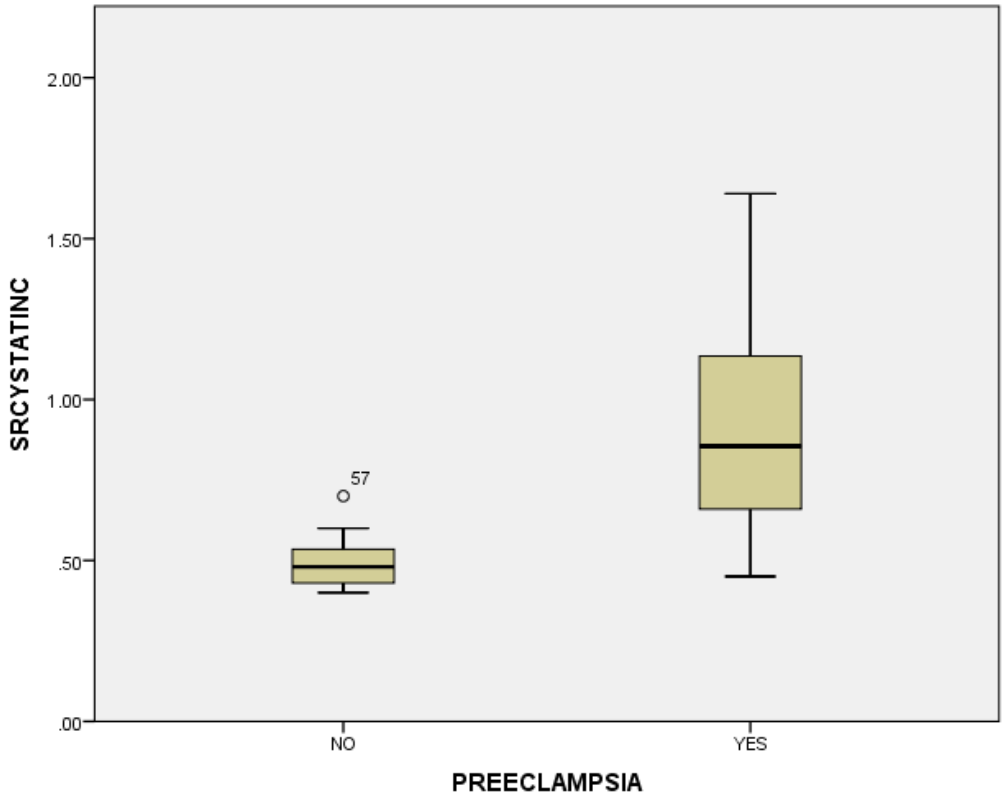


TABLE 8:

COMPARISON OF SERUM CREATININE ACROSS STUDY GROUPS (N=80)

Pre-eclampsia	**Serum creatinine Mean ± STD**	**Mean difference**	**95% CI**		**P value**
			Lower	**Upper**	
YES	0.856 ± 0.215	0.30	0.21715	0.38085	<0.001
NO	0.557 ± 0.144				

The mean of serum creatinine among people with preeclampsia was 0.856 ± 0.215 and the mean serum creatinine among people without preeclampsia was 0.557 ± 0.14in the study population. Hence Serum Creatinine was 0.30 units higher (95% CI 0.21 to 0.38, p value <0.001) in people with preeclampsia (Table 8)

ROC curve

Variable	Serum.CREATININE
Classification variable	PREECLAMPSIA

Sample size		80
Positive group :	PREECLAMPSIA = 1	40
Negative group :	PREECLAMPSIA = 0	40

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.875313
Standard Error[a]	0.0387
95% Confidence interval[b]	0.782484 to 0.938622
z statistic	9.692
Significance level P (Area=0.5)	<0.0001

[a] Hanley & McNeil, 1982

[b] Binomial exact

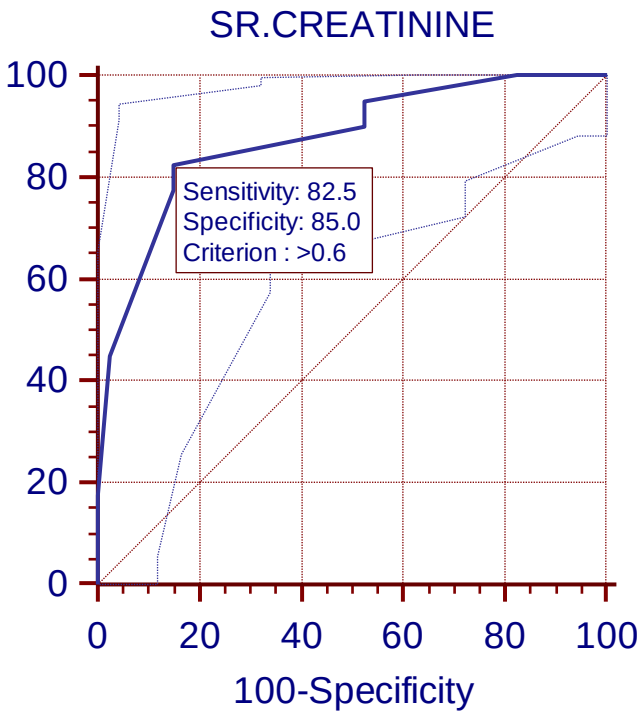

SR.CREATININE
100
80
60
40
20
0
Sensitivity: 82.5
Specificity: 85.0
Criterion : >0.6
0
20
40
60
80
100
100-Specificity

FIGURE 8:

COMPARISON OF SERUM CREATININE ACROSS STUDY GROUP (N=80)

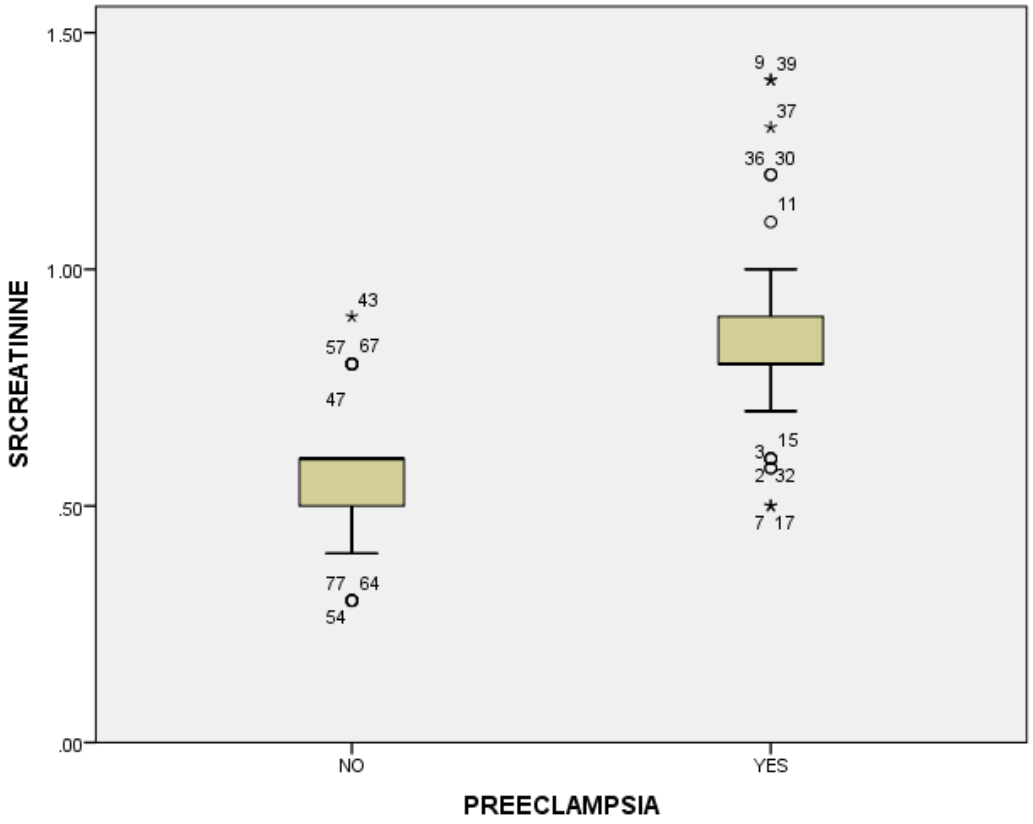


TABLE 8:

ASSOCIATION OF PREECLAMPSIA WITH URINEALBUMIN OF STUDY POPULATION (N=80)

URINEALB	PREECLAMPSIA		Chi square value	P value
	NO	YES		
1+	0	7	72.381	.000
	0.00%	20%		
2+	0	16		
	0.00%	35.00%		
3+	0	10		
	0.00%	25.00%		
4+	0	7		
	0.00%	17.5%		
NIL	40	nil		
	95.24%	50%		

None of the study subjects without preeclampsia had albuminuria. The proportion of subjects with 1+, 2+, 3+ and 4+ albuminuria was 17.5%, 35%, 25% and 17.5% respectively in the study.

DISCUSSION

Pre-eclampsia, a syndrome characterized by hypertension, proteinuria and systemic vasoconstriction, is one of the leading causes of maternal and fetal morbidity. Although the exact etiology of pre-eclampsia is not clear, insufficient placental function is thought to play a pivotal role. Studies have shown the association of pre-eclampsia with deficiency in the trophoblast invasion of maternal spinal arteries, leading to poor perfusion of feto-placental unit. Cathepsins (cysteine-proteases) are considered to be important for trophoblast invasion while their inhibitor, cystatin C, regulates this invasion to prevent formation of placenta accreta or percreta.

Cystatin C is a low molecular weight (13.3KDa) protein having renal excretion. Serum levels of cystatin C are less dependent on age, sex, race and muscle mass compared to serum creatinine levels. Cross-sectional studies have shown that serum levels of cystatin C are more precise in estimating kidney functions than serum creatinine. This may be because creatinine is actively secreted by proximal renal tubules and hence glomerular filtration rate, calculated by creatinine clearance, is overestimated in severe renal dysfunction. Serum levels of cystatin C are increased in normal pregnancy, especially in the third trimester. This has been attributed to altered renal handling of low molecular weight proteins in conjunction with a decreased GFR and increased synthesis by the feto-placental unit or generalized phenomenon.

A study concerning serum levels of cystatin C in preeclampsia and normal pregnancy was published by Strevens et al[48]. These investigators have found serum cystatin C concentrations to be significantly elevated in preeclamptic patients compared to normal pregnant women.

Our data regarding both cystatin C and creatinine levels are consistent with the previous studies of Shalvi Sharma et al[19] and Fauzia Jumaat et al. Karl Kristensen[21] et al, which showed elevated plasma concentrations of cystatin C in patients with preeclampsia at the time of diagnosis.

In my study, the mean age group, gestational age and parity of both controls and cases was similar. Serum cystatin C concentrations were significantly higher in pre-eclamptic patients (0.895 ±0.310mg/L) compared to the healthy pregnant females (0.489 ± 0.064 mg/L) with p value of *<0.001* (highly significant). Serum levels of cystatin C are increased in normal pregnancy, especially in the third trimester. This has been attributed to renal handling of low molecular weight proteins in conjunction with a decreased GFR and increased synthesis by the fetoplacental unit or generalized phenomenon.

The levels of Cystatin C are further increased in pre-eclampsia, correlating with the functional and structural changes in kidneys. In a renal biopsy study Cystatin C levels were shown to correlate with the degree of glomerular endotheliosis, a typical histologic feature of pre-

eclampsia. Since degree of endotheliosis has been considered to determine the severity of pre-eclampsia, it has been hypothesized that serum levels of Cystatin C can offer information regarding the severity of pre-eclampsia.

In the present study also, serum Cystatin C levels were significantly higher in patients with pre-eclampsia than healthy pregnant females. On the other hand, serum creatinine levels did not show significant difference between the two groups. These results confirm the previous observations of Cystatin C being superior to serum creatinine for estimation of renal function in pre-eclampsia patients.

CONCLUSION

Serum cystatin C appears to be a superior marker of renal function compared to serum creatinine in patients with preeclampsia and should be routinely included in the investigative work-up of these patients.

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PROFORMA

NAME HUSBAND NAME

AGE PH NO.

IP NO QUALIFICATION

ADDRESS OCCUPATION

SOCIOECONOMIC STATUS

OBSTETRIC HISTORY :-

1. PARITY
2. GESTATIONAL AGE
3. LMP EDD
4. COMORBID ILLNESS
5. COMPLAINTS IF ANY

H/O HEADACHE

H/O VISUAL DISTURBANCES

H/O EPIGASTRIC PAIN

H/O VOMITING

H/O REDUCED URINE OUTPUT

H/O DIFFICULTY IN BREATHING

H/O BLEEDING PV

MENSTRUAL HISTORY

MARITAL HISTORY

PAST HISTORY :-

1) DIABETES MELLITUS
2) HYPERTENSION
3) CHRONIC RENAL FAILURE
4) HEART DISESE
5) TUBERCULOSIS
6) DRUG INTAKE
7) EPILEPSY

GENERAL EXAMINATION:-

PALLOR: HEIGHT

PEDAL EDEMA WEIGHT

BMI BREAST

THYROID

VITALS:

TEMPERATURE:

PULSE:

BP:

CVS:

RS:

PER ABDOMEN:

INVESTIGATIONS:-

SERUM CREATININE

URINE ALBUMIN

SERUM CYSTATIN C

FOR CASES

S.NO	NAME	AGE	GESTATIONAL AGE	BLOOD PRESSURE	SERUM CREATININE	SERUM CYSTATIN C

FOR CONTROLS

S.NO	NAME	AGE	GESTATIONAL AGE	BLOOD PRESSURE	SERUM CREATININE	SERUM CYSTATIN C

SIGNATURE OF THE GUIDE SIGNATURE OF THE INVESTIGATOR

INSTITUTIONAL ETHICS COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 2/2016 Dt: 11.02.2016
CERTIFICATE OF APPROVAL

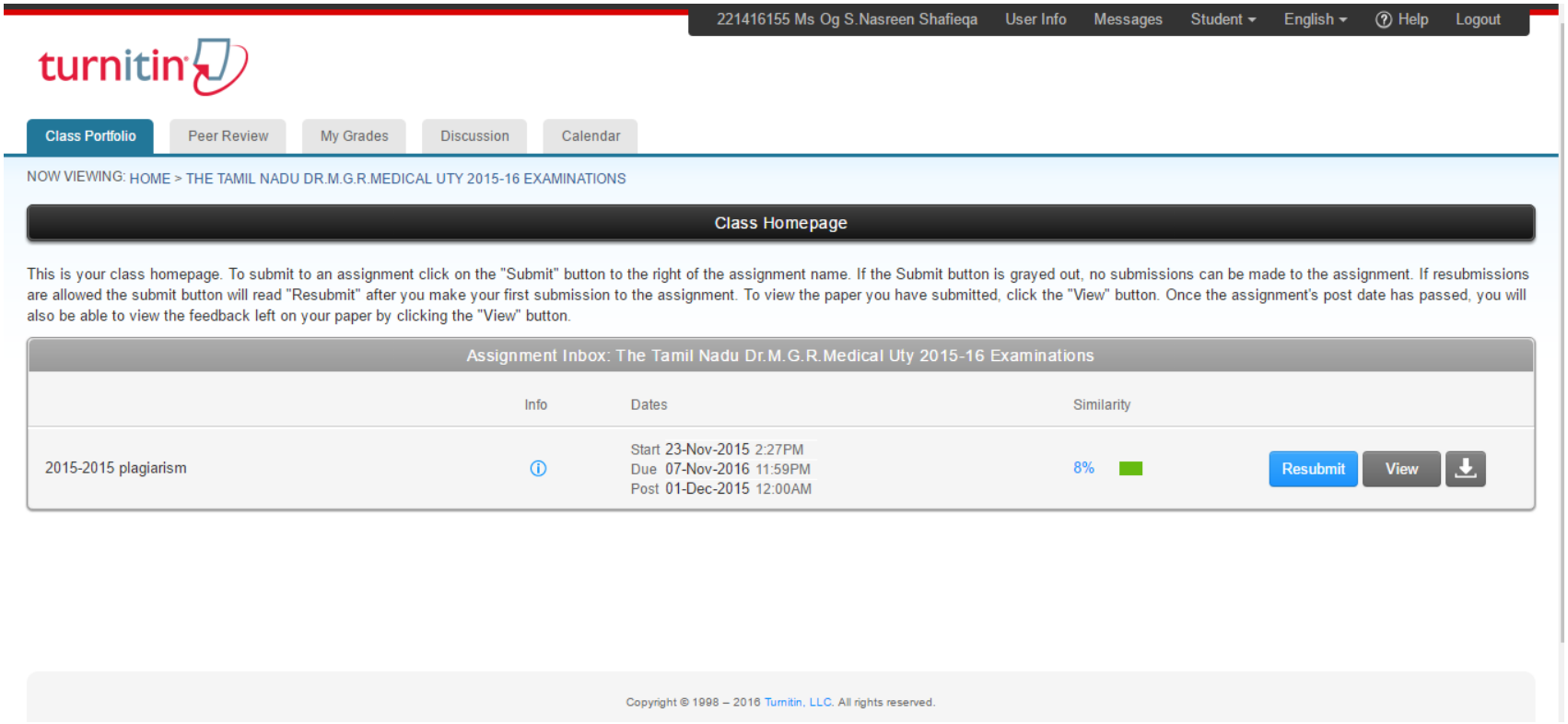
The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study of maternal serum Cystatin C and serum Creatinine levels in preeclamptic and normotensirc pregnancies A Case – Control study" - For Project Work submitted by Dr.S.Nareen Shafiega, PG MS., (O&G), Govt. Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

24/2/16

DEAN
Govt.Kilpauk Medical College,
Chennai – 10.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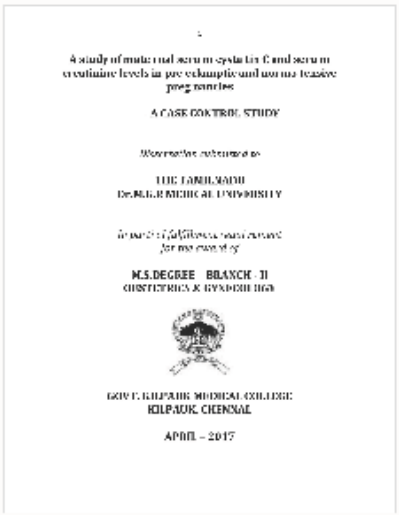

A study of maternal serum cystatin C and serum creatinine levels in pre eclamptic and normotensive pregnancies

A CASE CONTROL STUDY

Dissertation submitted to

THE TAMILNADU
Dr.M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the requirement
for the award of

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OBSTETRICS & GYNAECOLOGY

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