Calcium Creatinine ratio and Microalbuminuria as a recommendation for screening of pre-eclampsia

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for the Award of the Degree of

M.S. (OBSTETRICS & GYNAECOLOGY) - BRANCH – II

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GOVERNMENT STANLEY MEDICAL COLLEGE

CHENNAI

CERTIFICATE

This is to certify that this dissertation entitled **"Calcium Creatinine ratio and Microalbuminuria as a recommendation for screening of pre-eclampsia"** submitted by **Dr A. POORNIMA**, appearing for Part II MS, Branch II obstetrics and Gynecology Degree Examination in April 2014, is a Bonafide record of work done by her, under my direct guidance and supervision as per the rules and regulations of the Tamil Nadu Dr. MGR Medical university, Chennai, Tamil Nadu, India. I forward this dissertation to the Tamil Nadu Dr. MGR Medical University Chennai, India.

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DECLARATION

I Dr. A. Poornima solemnly declare that the dissertation titled,**"Calcium Creatinine ratio and Microalbuminuria as a recommendation for screening of pre eclampsia"** is a bonafide work done by me at R.S.R.M. Lying in Hospital. Stanley Medical College, Chennai – during October 2012 –November 2013 under the guidance and supervision of Prof.Dr.V.Kalaivani M.D., D.G.O., Professor and Head of the department.Obstetrics and Gynaecology. The dissertation is submitted to the TamilnaduDr.M.G.R. Medical University, is partial fulfilment of University rules and regulations for the award of M.S. Degree is obstetrics and Gynaecology.

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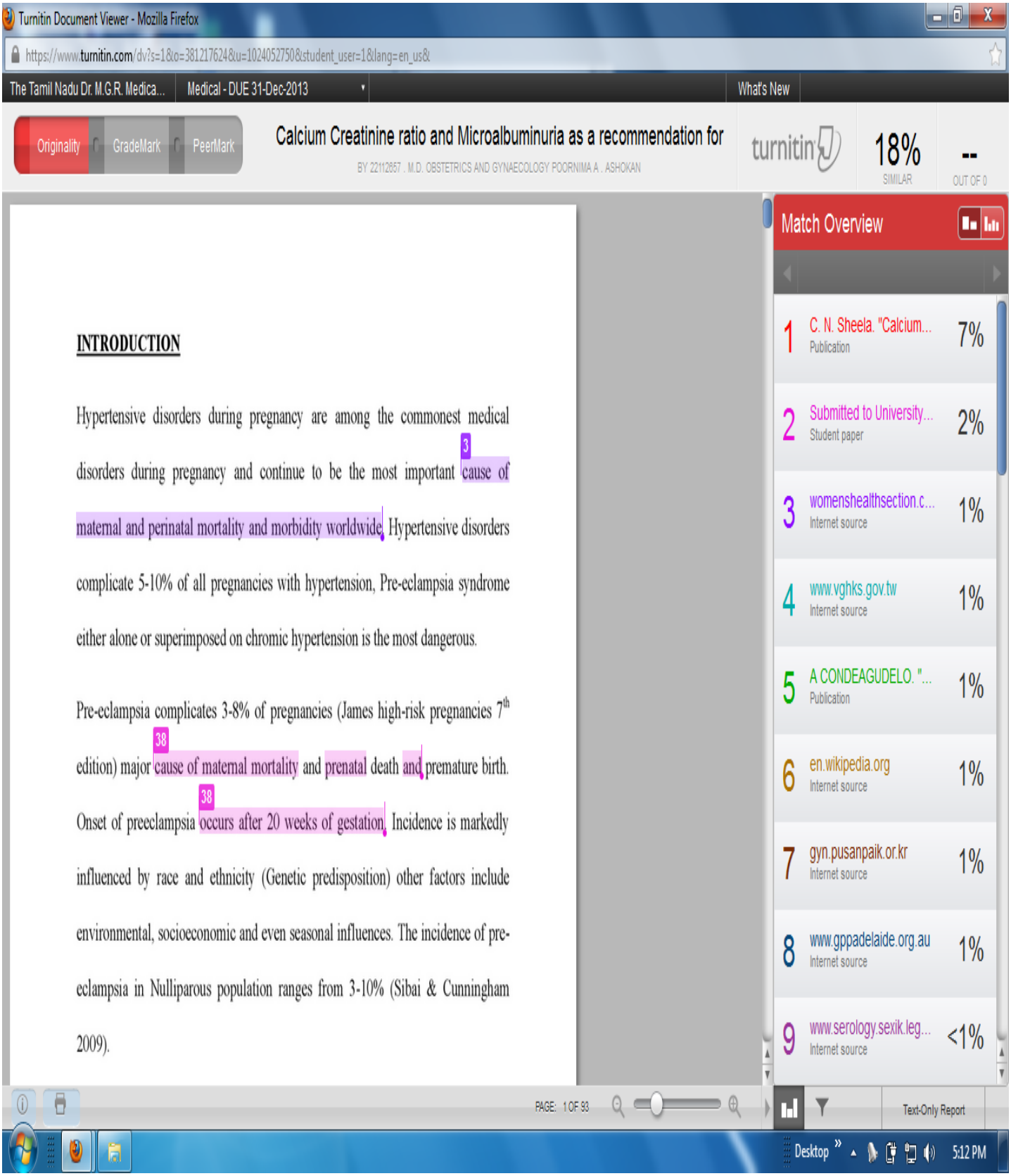
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Hypertensive disorders during pregnancy are among the commonest medical disorders during pregnancy and continue to be the most important cause of maternal and perinatal mortality and morbidity worldwide. Hypertensive disorders complicate 5-10% of all pregnancies with hypertension, Pre-eclampsia syndrome either alone or superimposed on chromic hypertension is the most dangerous.
Pre-eclampsia complicates 3-8% of pregnancies (James high-risk pregnancies 7th edition) major cause of maternal mortality and prenatal death and premature birth. Onset of preeclampsia occurs after 20 weeks of gestation. Incidence is markedly influenced by race and ethnicity (Genetic predisposition) other factors include environmental, socioeconomic and even seasonal influences. The incidence of pre-eclampsia in Nulliparous population ranges from 3-10% (Sibai & Cunningham 2009).
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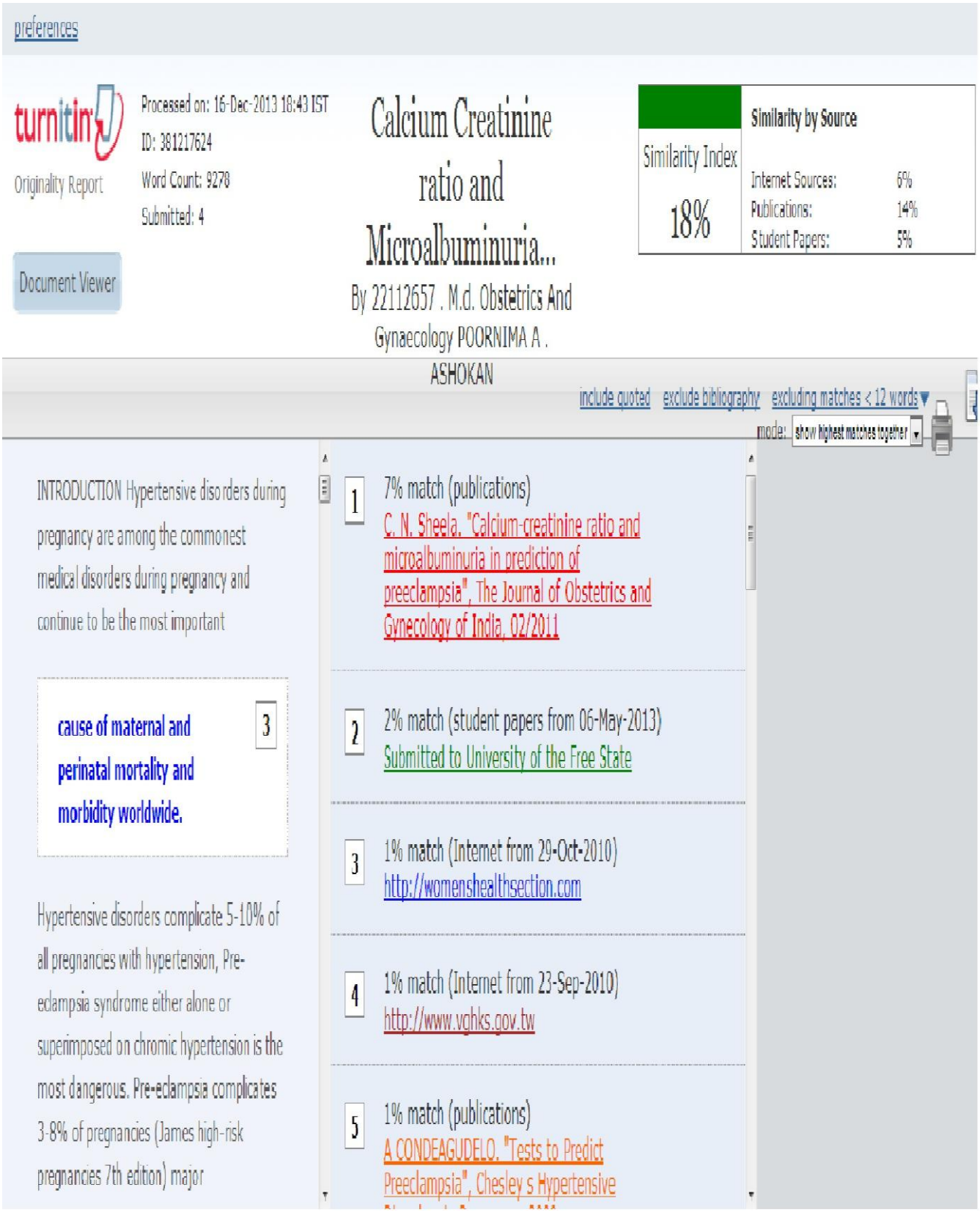
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CONTENTS

INTRODUCTION

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Pre-eclampsia complicates 3-8% of pregnancies (James high-risk pregnancies 7th edition) major cause of maternal mortality and prenatal death and premature birth. Onset of preeclampsia occurs after 20 weeks of gestation. Incidence is markedly influenced by race and ethnicity (Genetic predisposition) other factors include environmental, socioeconomic and even seasonal influences. The incidence of pre-eclampsia in Nulliparous population ranges from 3-10% (Sibai& Cunningham 2009).

To reduce the impact of pre-eclampsia on maternal mortality, it is necessary to establish correct diagnosis of pre-eclampsia and to proceed with early interventions to prevent complications. In the past few decades, several methods have been developed to establish the disease as early as possible, many of these tests could not be used as screening test, due to their false positive results and subjective

interpretation. Hence, there is a need for the screening test to predict pre-eclampsis at the early period of gestation.

Renal function changes may be seen in women preeclampsia, without any symptoms. Several studies have shown that hypocalciuria is associated with preeclampsia. Rodriquez et al in his study has shown that decreasing calcium-creatinine ratio and micro-albuminuria may be used to predict pre-eclampsia and concluded that it may be used as a screening tools.

The purpose of this study is to find out the predictive values of urinary calcium to creatinine ratio and micro-albuminuria in all asymptomatic pregnant women and recommend it as a screening test for pre-eclampsia.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

1. Eclampsia was first noted in the Hippocrates writings (430-330BC)
2. De-La Motte (1726) considered oedema to be benign unless associated with convulsions.
3. DESAVEREGES (1739) wrote, “All convulsions of acute causation iseclampsia”.
4. VOGEL (1764) & GILLEN (1771) formed “Eclampsiaparturientum”
5. Zweifel and Chesley described Preeclampsia as disease of theories.
6. Zweifel first termed pre-eclampsia as “Toxemia”.
7. Bossier (1790) first introduced term eclampsia.
8. Frerichs (1851) published Eclampsia as a form of Uremia.
9. LAHLEIN 1918, FAHR 1920 → described changes in Glomeruli.
10. Farguhar (1959) → demonstrated glomerular capillary endotheliosis by electron microscopy.

11. In 1991, Redmann regarded pre-eclampsia as inadequate response of mother to the presence of conceptus.

12. In 1994, Gill postulated that pre-eclampsia occurs in families and suggested a Recessive Mendelian Trait.

13. Tweedy Duslinstrangnoff in Russia – Conservative expectant management with sedation and Anti-hypertensive, in hope of reducing neonatal mortality occurring due to premature termination.

Definition

According to NHBEP & ACOG (2002), Hypertension in pregnancy is defined as,

- Systolic BP greater than or equal to 140 mm Hg and /or
- Diastolic BP greater than or equal to 90 mm Hg (Korotkoff 5) after 20 weeks of gestation in a woman previously with normal BP (NHBEP 2000 ACOG 2002)

These measurements should be confirmed by repeated readings over 4-6hours.

Where K5 is absent, K4 (muffling) should be accepted.

Severe hypertension in pregnancy is defined as,

- Systolic BP greater than or equal to 160 mm Hg and / or.
- Diastolic BP greater than or equal to110mm Hg.

This BP level represents, the level at which cerebral auto regulation is overcome.

Systolic hypertension as well as Diastolic hypertension increases the risk of cerebral hemorrhage.

Blood pressure measurement

1. Conventional sphygmomanometer is suitable for routine use.
2. Woman should be relaxed and resting for at least half an hour before blood pressure measurement.
3. BP measurement should be done in sitting position with right forearm horizontal and well supported and the upper arm at the level of heart. (Left atrium)
4. The cuff should be long enough to encircle the arm and wide enough to cover at least two thirds of upper arm. It should be firmly applied, and inflated and deflated smoothly.
5. The disappearance of Korotkoff sounds (K5) has been shown to correlate better with direct intra-arterial measurements of Diastolic pressure. Hence it is recommended that K5 should be routinely used in pregnancy.

Classification

Various schemes of classifying hypertensive disorders in pregnancy have been proposed by different obstetric and hypertension societies. A recent classification recommended by the National Institute of Health (NIH) working group on high

Blood Pressure in Pregnancy 2000 – NH BP EP 2000 has categorized hypertensive disorders into 4 types.

1. Gestational hypertension – formerly termed pregnancy induced hypertension. If pre-eclampsia does not develop and hypertension resolves by 12 weeks postpartum, it is re designated as transient hypertension.
2. Pre-eclampsia and eclampsia syndrome
3. Pre-eclampsia syndrome superimposed on chronic hypertension
4. Chronic hypertension

The classification adopted by International Society for the Study of Hypertension in pregnancy (ISSHP) reflecting both the pathophysiology of the condition and the risks and potential outcomes for both mother and baby is

1. Gestational hypertension
2. Pre-eclampsia
3. Chronic hypertension
   - Essential
   - Secondary
4. Pre-eclampsia superimposed on chronic hypertension

DIAGNOSIS OF HYPERTENSIVE DISORDERS IN PREGNANCY	
GESTATIONAL HYPERTENSION	BP >140/90 mm Hg ,first time during pregnancy No proteinuria BP becomes normal before 12wks postpartum Final diagnosis made only in postpartum
PREECLAMPSIA	**Minimum criteria:** BP >140/90 mm Hg after 20 wks Proteinuria >300mg/24hrs or >1+dipstic **Increased certainty of preeclampsia:** BP > 160/110 mmHg Proteinuria 2g/24hrs or >2+ dipstic Serum creatinine>1.2 mg/dl Platelets <100,000 / µl Microangiopathic hemolysis-increased LDH Elevated serum transaminase levels-ALT /AST Persistent headache or other cerebral or visual disturbance Persistent epigastric pain
ECLAMPSIA	Seizures which cannot be attributed to any other cause in a woman with preeclampsia
SUPERIMPOSED PREECLAMPSIA ON CHRONIC HYPERTENSION	New onset proteinuria > 300mg/24hrs before 20 weeks in a hypertensive woman. Sudden rise in proteinuria or BP or platelet count <100,000/ µl before 20 weeks in a women with hypertension and proteinuria
CHRONIC HYPERTENSION	BP >140/90 mmHg before pregnancy or diagnosed before 20 weeks, not attributable to gestational trophoblastic disease OR Hypertension diagnosed first after 20 wks and persistent after 12 wks postpartum

RISK FACTERS

Couple- Related Risk Factors.

- Primi-paternity.
- Limited sperm exposure.
- Pregnancies after donor insemination, oocyte donation, embryo donation.
- Protective effect of "Partner change" in case of previous pre-eclamptic pregnancy.
- Dangerous male partner (Paternal effects).

Maternal or Pregnancy – related risk factors.

- Age: Extremes of maternal age. (< 20years and > 35years).
- Multi-fetal Gestation.
- Pre-eclampsia in a previous pregnancy.
- Chronic hypertension and / or renal disease.
- Maternal chronic inflammatory conditions

(Eg: Rheumatologic disease, SLE).

- Maternal chronic infections.

- Maternal low birth weight.
- Obesity and insulin resistance (with or without the polycystic ovary syndrome, this risk is proportionate to BMI).
- Pre-gestational Diabetes mellitus.
- Pre-existing thrombophilias.
- Maternal susceptibility genes.
- Family history of pre-eclampsia.
- Smoking (reduced risk).
- Hydropic degeneration of the placenta.

ETIOPATHOGENESIS

The exact actiolagy of pre-eclampsir remains unknown.

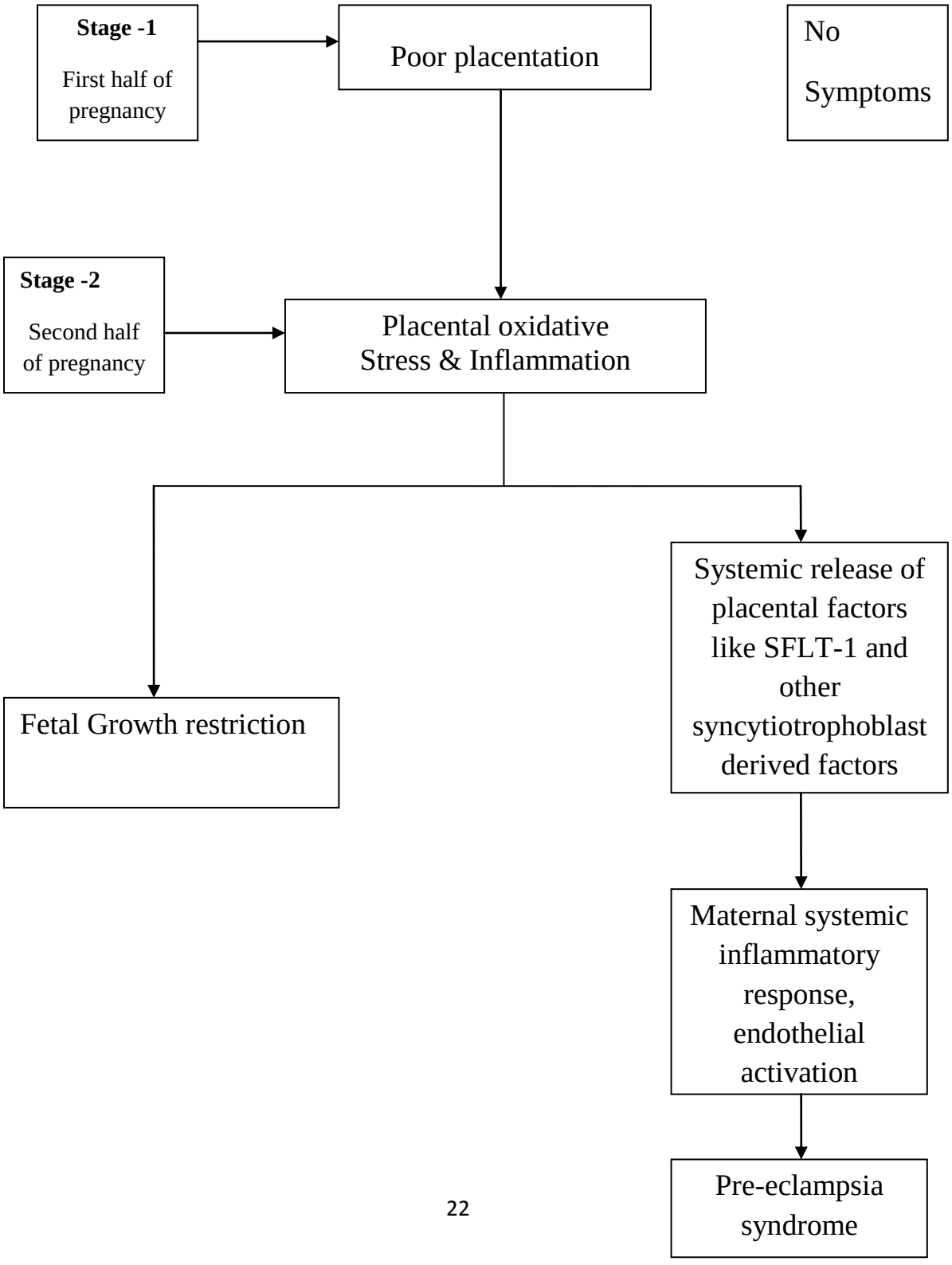
As Boyd stated Pre-eclampsia remains “die krankheit der theorien”- the disease of theories.

Etiology:-

1. Placental implantation with abnormal trophoblastic invasion of uterine vessels.
2. Inappropriate endothelial cell activation.
3. Immunologic maladaptive tolerance between maternal, paternal (placental) and fetal tissues.
4. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy.
5. Exaggerated inflammatory responses.
6. Increased vasopressor response & vasospasm.
7. Genetic factors including inherited predisposing genes and epigenetic influences.

TWO STAGES OF PRE-ECLAMPSIA

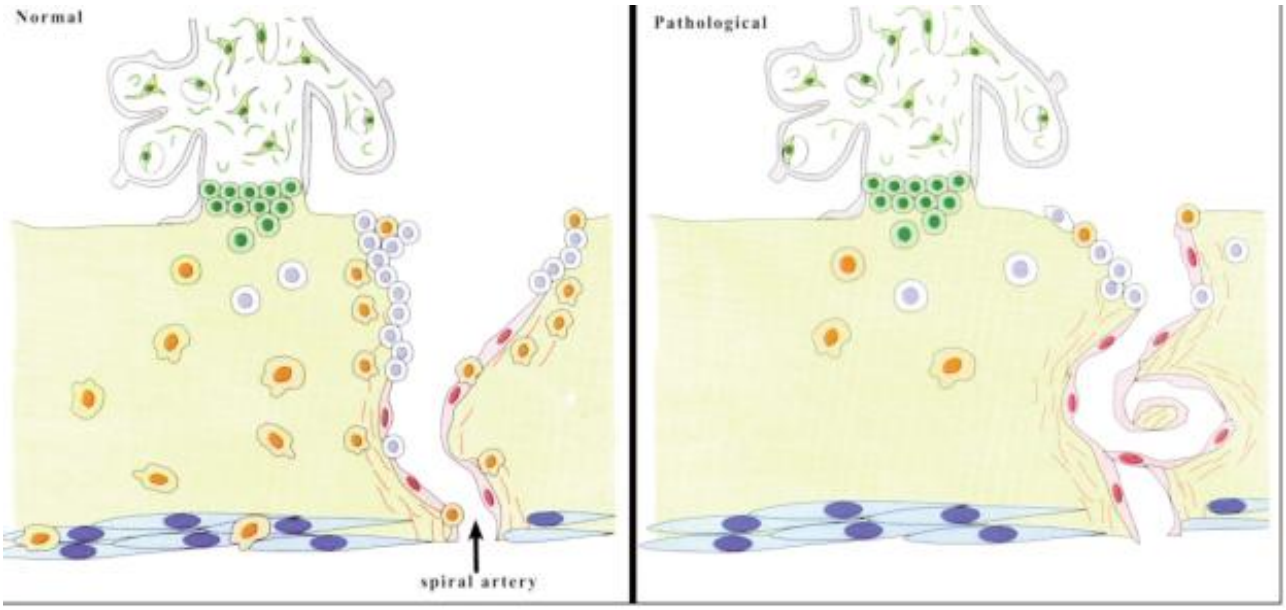
(Borzychowski 2006 & Redman 2009)



Two basic abnormalities seen in pathophysiology of pre-eclampsia are

1. Abnormal placentation.
2. Endothelial dysfunction.

Abnormal Tophoplastic Invasion.



In normal pregnancies, endovascular cytotrophoblasts replace endothelial cells in spiral arteries, this leads to destruction of the medial elastic, muscular and neural tissue. These physiologic changes normally reach the inner third of myometrium. These changes results in an arteriolar system with decreased resistance and without maternal vasomotor control, this allows increased blood supply to the fetus. The end result of these changes is that 100-120 spiral arteries are remodeled by the invading “foreign” CTBs into dilated, inelastic tubes without maternal vasomotor control. This process starts around 10-12 weeks and is completed by 18-20 weeks.

In pre-eclampsia, physiologic changes in many but not all spiral arteries are confirmed to decidual portion. The myometrial segments in these arteries remain anatomically intact, which does not dilate and retains its adrenergic nerve supply. The inner myometrial arterioles retains its endothelial lining and musculoelastic tissues, with mean external diameter half of that of vessels in normal placentas (Fishes & Colleagues 2009).

Magnitude of defective trophoblastic invasion of the spiral arteries correlates with severity of hypertensive disorder (Madazli& associates 2000).

Initially lipids get accumulated in myointimal cells and then within macrophages. Such findings were referred to as atherosis (Hertig 1945).

The abnormal spiral arteriolar lumen leads to decreased placental blood flow with a hypoxic environment, which causes the release of placental debris that incites a systemic inflammatory response as described by Redman & Sargent (2008).

Endothelial cell activation:-

Endothelial activation is a part of the generalized inflammatory reactions involving leucocytes as well as clotting and complement systems. Endothelial cell dysfunction is due to an extreme activated state of leucocytes in maternal circulation (Fars 2000, Gervasi 200, Redman 1999).

Renin-Angiotensin system is not stimulated, despite relative hypovolemia in severe pre-eclampsia, increased vascular sensitivity to vasoconstrictors and increased endothelial cell permeability can be explained in the basis of endothelial cell activation.

Selective platelet activation and consumption (microangiopathic hemolysis) and the resulting reduction in placental blood flow due to spiral artery Thrombosis & placental infarction can be attributed to endothelial cell dysfunction. Cytokines contributes to oxidative stress associated to pre eclampsia.

Reactive oxygen species and free radicals lead to formation of self-propagating lipid peroxides (Manten& associates 2000) which generate highly Toxic radicals, which will injure endothelial cells and modify nitric oxide production and interfere with prostaglandin balance, which promote coagulation and increased sensitivity to vasopressor agents.

Immunological Factors:-

Loss of maternal immune tolerance to paternally derived placental and fetal antigens is cited to account for pre-eclampsia syndrome.

Histological changes at the maternal placental interface are suggestive of acute graft rejection (Labarrere 1988).

The risk of pre-eclampsia is increased in circumstances where formation of blocking antibodies to placental antigenic sites might be impaired – first pregnancy would carry a higher risk.

"Tolerance dysregulation" also explains an increased risk when paternal antigenic load is increased (as with 2 sets of paternal chromosomes). Belo Lah& associates (2006) showed that these women have elevated levels of antiangiogenic factors (SFLTI).

In women likely to become pre-eclampsia, early in gestation, the extra villous trophoblast express reduced amounts of immunosuppressive human leucocytes antigen G (HLA G) which contributes to defective placental vascularisation.

In normal pregnancy, T helper (Th) lymphocytes produced, increases type 2 activity relation to type 1 termed type 2 bias (Redman & Sargent 2008).

Th-2 cells promote humoral immunity; Th-1 cells stimulate cytokine secretion. In pre-eclampsia, at the beginning of second trimester, the Th-1 action is increased and the ratio Th-1 / Th-2 changes. Immunologically mediator inflammatory reactions are stimulated by placental micro particles as well as by adiposities (Redman & Sargent 2008).

Genetic Factors:-

Pre-eclampsia is a multifactorial, polygenic disorder (Ward & Lindheimer-2009).

It is also reported that, risk of pre-eclampsia is 20-40% for daughters of pre-eclamptic mothers, 11-37% for sisters of pre-eclamptic women and 22-47% for twin babies.

Vasospasm:-

Vascular constriction causes increased resistance and subsequent hypertension with decreased blood flow due to mal-distribution and ischemia of surrounding tissues leading to necrosis, hemorrhage and other end organ disturbance characteristic of the syndrome.

Increased Pressure Responses:-

Increased sensitivity to angiotension II clearly precedes the onset of Gestational hypertension. Grant & Colleagues (1974) showed that normotensive nulliparas remained refractory to infused angiotensin II, but those who subsequently became hypertensive lost this refractoriness several weeks before the onset of hypertension.

Prostaglandins:-

- In normal pregnancy, endothelial prostaglandins mediate decreased vascular response to presser agents.

- Endothelial prostaglandins (PGI_2) production is decreased in pre-eclampsia. This action appears to be mediated by phospholipase A_2 (Taylor and Roberts 1999).

- At the same time, thromboxane A_2 secretion by platelets increased and the Prostacyclin: Thromboxane A_2 ratio decreases. The net result favours increased sensitivity to infused angiotensin II & Vasoconstriction (Spitz and colleagues 1988). These changes are apparent as early as 22 weeks in women who later develop pre-eclampsia (Chavarria& Co-workers 2003).

Nitric Oxide:-

- Synthesised in endothelial cells from L-arginine. It is a potent vasodilator. Inhibition of NO synthesis increases mean arterial pressure, decreases heart rate and reverses the pregnancy induced refractoriness to Vasopressors.

- Low-pressure vasodilated state characteristic of fetoplacental perfusion is maintained by nitric oxide (Myatt & Co-worker 1992, Weiner and associates 1992). NO also synthesized from fetal endothelium and is increased in

response to pre-eclampsia, diabetes and infection (Parra & associates 2001, Von Mondach& Co-workers 2003).

- In pre-eclampsia, these is decreased NO synthase expression & increasing NO inactivation.

Endothelins:-

- These are potent Vasoconstrictors, Endothelin 1 (ET-1) is primary isoform produced by endothelium (Mastrogiannis& Co-workers 1991).
- Plasma ET 1 levels are increased in normotensive pregnant woman, woman pre-eclampsia have even high levels. (Ajne 2003, Clark 1992, Nova 1991).
- Placenta is not the only source of increased ET-1 concentrations and they likely arise from systemic endothelial activation (Taylor and Roberts 1991)
- Treatment of pre-eclampsia woman with magnesium sulphate lowers ET-1 concentrations (Sagsoz and Kucukozkan 2003)

Angiogenic and Antiangiogenic Proteins:-

- Vascular endothelial growth factors and angiopoeitins (Ang) gene products are extensively studied in placental vascular development.

- Excessive amounts of antiangiogenic factors are thought to be stimulated by the worsening hypoxic environment at the uteroplacental interface leading to imbalance in angiogenesis.

- Trophoblastic tissue of women who will develop pre-eclampsia overproduces at least two antiangiogenic peptides that enter maternal circulation (Karumanchi and Colleagues 2009).

    a. Soluble Fms like Tyrosine Kinase (SFlT-1) is a variant of flt-1 receptor for placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). Increased SFlt-1 levels may inactivate and decrease circulating PlGF and VEGF concentrations causing endothelial dysfunction (Maynard and associates 2003).

    b. Soluble endoglin (S Eng) is a placenta-derived molecule that blocks endoglin also called CD 105, which is a co-receptor for TGF β family.

- This soluble form of endoglin inhibits TGF β isotopes from binding to endothelial receptors and results in decreased endothelial Nitric oxide dependent vasodilatation (Levine and Co-workers 2006, Venkatesha& associates 2006).

- The soluble forms are not increased in the fetal circulation or amniotic fluid and their levels dissipate after delivery (Staff & Co-workers 2009).

- Research currently focused an immunological mechanisms, oxidative stress, mitochondrial pathology and hypoxic genes (Karumanchi& Colleagues 2009).

- Widner and associates (2007) concluded that retrospective studies showed third trimester elevation of sflt 1 levels and decreased PlGF concentration correlates with development of preeclampsia after 25 weeks.

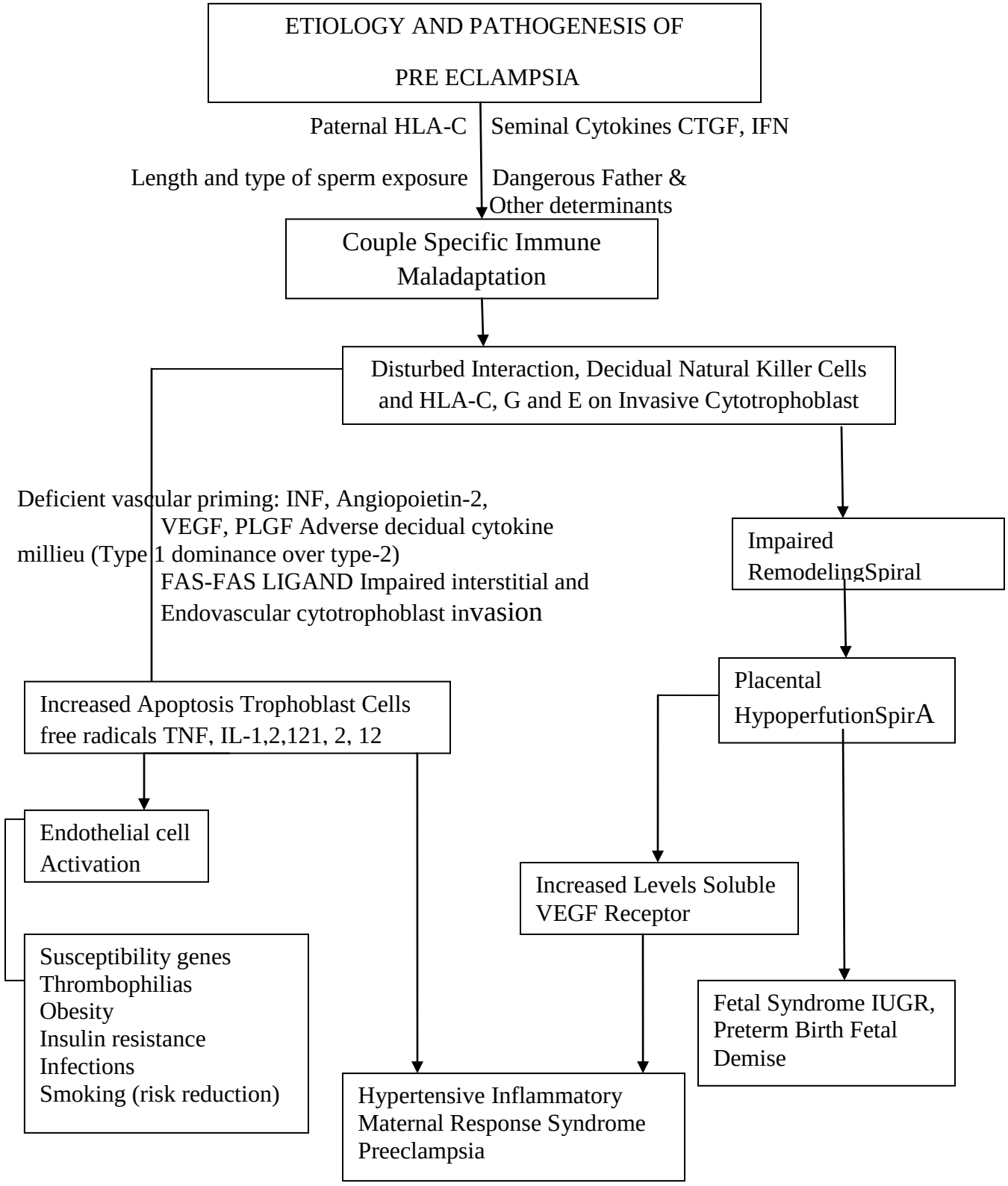
Nutritional Factors:-

- Diet rich in fruits and vegetables that have anti-oxidant activity is associated with decreased blood pressures (John & Co-workers 2002).

- Daily intake of ascorbic acid less than 85mg was associated with increased incidence of preeclampsia (Zhang and associates 2002).

- Calcium supplementation in population with low calcium intake had a small effect to lower perinatal mortality rates (Villar and associates 2006).

ETIOPATHOGENESIS



Pathophysiology

The cause of pre-eclampsia remains unknown and evidence for its manifestation begins early in pregnancy.

Abnormal placentation is thought to be the initial events. Some of the main features include improper trophoblastic invasion of spiral arterioles and accelerated apoptosis of the trophoblasts with abundant release of fetal DNA into maternal circulation. This leads to decreased perfusion of uteroplacental vessels. The disruption of normal placentation may to lead to synthesis of products, which affect angiogenesis, and to abnormal lipid peroxidation.

With advance in gestation, these products will affect the endothelial system with production of signs and symptoms of multiple organ compromise. Not all women with pre-eclampsia exhibit abnormal placentation and not all cases of abnormal placentation result in pre-eclampsia. Pre-eclamptic women who are obese, diabetic, with chromic hypertension multi-fetal gestation may have placentas of normal or large size without the characteristic features of abnormal placentation (Zhang et al., 2006). Thus, pre-eclampsia can be divided into two types namely,

a.) Placental pre-eclampsia → for those cases of pre-eclampsia with evidence of abnormal placentation.

b.) Maternal pre-eclampsia → to those cases where placenta is normal but there is an underlying chronic maternal condition associated to the

Pre-eclampsia (Redman and sergeant 2004)

Here the normal adaptive inflammatory response that occurs with pregnancy is aggravated by maternal medical conditions to a point of decompensation that will manifest clinically as pre-eclampsia.

Irrespective of etiology and mechanism of the disease, there are several pathophysiologic changes in pre-eclampsia, which includes haemodynamic changes due to alteration in blood volume and PVR, alterations of the hemostatic system and abnormal renal functions.

I) Haemodynamic Changes:-

- Maternal cardiac output is increased more than increased PVR in mild

Pre-eclampsia.

- On severe pre-eclampsia, there is a switch to normal or decreased cardiac output and elevated PVR (Hibbard et al 2004) using Doppler, Bosio et al (1998) formed that women with pre-eclampsia initially have increased CO & normal PVR, with worsening of the disease, there was a hemodynamic crossover to low CO and elevated PVR.

A) Changes in Blood Volume

1. In mild pre-eclampsia → normal expansion of intravascular volume.
2. In severe pre-eclampsia → due generalized vasoconstriction of capacitance vessels, the intravascular volume, which increases during normal pregnancy is minimal or completely absent
3. The plasma volume increases and Haemoglobin and Haematocrit values decrease after delivery due to decreased vasospasm, excessive blood loss following delivery and mobilization of fluid from extracellular to intravascular compartment.

B) Changes in PVR

- Normotensive woman will show resistance to pressor effect of angiotensin II and catecholamine.
- Patients destined to develop pre-eclampsia show progressive loss of resistance to pressor effect of angiotensin II & catecholamine.
- In patients with chronic hypertension who may develop superimposed pre-eclampsia, there is decrease in vascular resistance to the pressor effects of angiotensin II

II) Haemostatic abnormalities.

These abnormalities develop in some women with pre-eclampsia. Among these commonly identified are:

Thrombocytopenia (< 10%)

- Some clotting factors are decreased and erythrocytes may show bizarre shapes and may undergo rapid hemolysis
- The intensity and frequency of thrombocytopenia varies with the severity and duration of pre-eclampsia syndrome as well as the frequency with which platelet counts are performed (Heilmann& Colleagues 2007)
- Overt thrombocytopenia <1,00,000 indicates severe disease.
- After delivery, platelet count continues to decrease for the first day and usually increases progressively to reach a normal Level in 3-5 days.

Other platelet abnormalities:-

- Platelet activation with increased degranulation, thromboxane A_2 release and decreased life span (Kenny & associates 2009)
- The cause is unknown, immunological endothelial damage may be implicated

- Platelet bound and circulating platelet bindableimmunoglobulins are increased which suggest platelet surface alterations. (Samuels and Colleagues 1987)

Hemolysis:-

- Severe pre-eclampsia is frequently accompanied by evidence of hemolysis, semi-quantified by elevated LDH levels
- Also from schizocytosis, spherocytosis and reticulocytosis in peripheral blood (Cunningham and associates 1985, Pritchard & Colleagues 1954)
- These derangements results from microangiopathic hemolysis caused by endothelial disruption with platelet adherence and fibrin deposition.
- Sanchez- Ramoz and colleagues described increased erythrocyte membrane fluidity with HELLP syndrome.
- These changes were due to serum lipid alterations (Cunningham & Co-workers 1995)
- Erythrocytic membrane changes, increased adhesiveness and aggregation may also facilitate a hyper-coagulation state (Gamzu and Co-worker 2001)

HELLP Syndrome:-

In addition to hemolysis and thrombocytopenia, elevated serum liver transaminase levels were commonly found with severe pre-eclampsia and were indicative of hepatocellular necrosis (Chesley 1978 & Weinstein 1982) referred this condition as HELLP syndrome.

Coagulation:-

- Increased factor VIII consumption, increased levels of fibrinopeptides A & B and of fibrin degradation products and decreased levels of regulatory proteins – antithrombin III and protein C & S.
- Coagulation aberrations are generally mild.
- Routine laboratory assessment for coagulation is unnecessary in managing pregnancy associated hypertensive disorders (Barron & Colleagues 1999).

Other Clotting Factors:-

- Early onset pre-eclampsia is associated with thrombophilias, clotting factor deficiencies that lead to hyper coagulability. Association has been found between severe pre-eclampsia and thrombophilia particularly factor V Leiden and to a lesser extent MTHFRC67TT mutations (Morrison et al., 2002).

- Fibronectin, a glycoprotein associated with vascular endothelial cell basement membrane, is elevated in women with pre-eclampsia (Brubaker & Colleagues 1992).

III. Volume Homeostasis

Endocrine changes:-

- Plasma level of Renin, angiotensin II angiotensin 1-7, and aldosterone are decreased (Luft and colleagues 2009)
- Secretion of Atrial Natriuretic peptide is increased in women with pre-eclampsia (Borghi& associates 2000, Luf& Colleagues 2009).

Fluid and Electrolyte changes:-

- In severe pre-eclampsia, the volume of extracellular fluid, manifests as edema. The mechanism responsible for pathological fluid retention is thought to be endothelial injury.
- In addition to Edema and proteinuria, these patients have reduced plasma oncotic pressure, which causes a filtration imbalance leading to displacement of intravascular fluid into the surrounding interstitium.
- There is no change in electrolyte concentrations.
- In eclampsia, there is a reduced pH and bicarbonate concentration due to lactic acidosis and compensatory respiratory less of carbon dioxide.

I. Kidney:-

With development of pre-eclampsia, there may be a number of reversible anatomical and pathophysiological changes.

- Glomerular filtration rate, filtration fraction and effective renal plasma flow all decrease in pre-eclampsia.
- Glomerular endotheliosis, swollen intracapillary endothelial cells in the glomeruli, the hallmark of renal lesion of pre-eclampsia, represents the primary renal manifestation. The excess of SFLT-1 probably plays a major role in causation of glomerular endotheliosis.
- The increased renal vascular resistance will cause a reduction in renal blood flow and this leads to decrease in glomerular filtration (Conrad and Co-workers 2009)
- Glomerular endotheliosis leads to block in the filtration barrier. Decreased filtration causes serum creatinine values to rise to 1 mg/ml or more (Linheimer and Colleagues 2008).
- Urine sodium concentration is elevated.
- Plasma uric acid levels are elevated in pre-eclampsia. The elevation exceeds the reduction in glomerular rate and is due to enhanced tubular reabsorption (Chesley& Williams 1945)

- Also from increased placental urate production compensatory to increased oxidative stress.
- Diminished urinary excretion of calcium because of increased tubular reabsorption (Taufield and associates 1987)
- Oliguria / anuria is a most important sign to look for in pre-eclampsia (Mac Gillivray 1983). It is a consequence of combination of glomerular endotheliosis, intrarenal vasoconstriction and hypovolemia.
- Acute renal failure is a rare complication (1 in 10000-150000), It is a major cause of obstetric ARF. It is mostly caused by ATN, but sometimes due to bilateral cortical necrosis.

II. Liver:-

- Pathological changes in the liver are periportalhaemorrhages, ischemic Lessons and fibrin deposition.
- Liver damage may vary from mild hepatocellular necrosis to severe liver injury with marked increase in liver enzymes, sub-capsular rupture and rarely even liver rupture.

Other organs:-

Changes in other organs are involved only in severe cases.

Brain → multiple petechial harmorrhages and larger haemorrhages in the cortex pons or mid brain.

Heart → subendocardial petechial hemorrhages may be present in myocardium and in case of acute left ventricular failure, the left ventricular is dilated.

Lungs → pulmonary edema.

Adrenals → Haemorrhages and necrosis.

Eye → purtscher retinopathy, retinal detachment

Prediction of Pre-eclampsia

Measurement of a various biological, biochemical and biophysical markers associated in the pathophysiology have been proposed to predict preeclampsia.

Studies have been done to identify early markers of defective placentation, decreased placental perfusion, endothelial cell activation and dysfunction, and activation of coagulation.

Unfortunately, most of these tests have poor sensitivity with poor positive predictive values for pre-eclampsia (Conde-Agudelo and Colleagues 2009, Lindheimer and associates 2008 Sibai 2003). There is a constant search for a screening test, which is reliable, accurate and cost effective.

I. Placental perfusion / vascular resistance – Related test

i. Provocative Pressor Tests:-

There are 3 tests extensively evaluated to assess blood pressure increase in response to a stimulus. Sensitivity of all 3 tests range from 55-70% with spasticity of approx 85% (Conde – Agudelo& associates 2009)

a.) The Roll-over test:-

- Measures the hypertence response in women at 28-32 weeks,who are resting in the left lateral decubitus position and then “roll over” to assume a supine position.
- Test is considered positive if there elevation of 20mm Hg or more in diastolic blood pressure when patient rolls over from left lateral position to supine position (Gant et al)
- It has poor sensitivity, poor specificity and is of limited clinical value.

b.) The isometric exercise test :-

- Employs the same principle by squeezing a handball or hand grip test.
- A increase of 15mm Hg in systolic BP during hand grip test predicted the development of gestational hypertension
- It has sensitivity of 81.8% and specificity of 68.4%, but has poor reproducibility.

c.) Angiotensin II infusion test:-

- It is preformed by giving incrementally increasing doses intravenously, and the hypertensive response is quantified.
- It is based on the loss of refractoriness to angiotensin II in pregnant women who later develop pre-eclampsia.

- It has high false negative and false positive results. Test is expensive, time consuming and at times unreliable.

ii. Uterine artery Doppler velocimetry:-

- Faulty trophoblastic invasion of the spiral arteries, results in diminished placental perfusion and upstream increased uterine artery resistance.
- Increase uterine artery velocitmetry determined by Doppler ultrasound in the first or middle trimester should provide indirect evidence of this process & serves as predictive test (Gebb and associates 2009)
- Increased flow resistance results in an abnormal waveform represented by increased Diastolic notch at 16-20 weeks gestation have been found to be useful prediction of pre-eclampsia.

iii.Midtrimester mean arterial pressure:-

- Mean arterial pressure (Systolic + (2/3) × Diastolic) > 90mm Hg in mid trimester was proposed to predict pre-eclampsia.
- Low sensitivity and low specificity.
- Recent review suggests that MAP in mid trimester is a better predictor of gestational hypertension than pre-eclampsia (Conde-Agudelo et al 1993).

iv. 24 hours ambulatory BP monitoring:-

24 hours mean diastolic pressures greater than 71 mm Hg was been used to predict the development of pre-eclampsia or gestational hypertension with a sensitivity of 22% and positive predictive value of 15%.

II. Fetal – Placental unit Endocrine Dysfunction.

A number of serum analysis have been proposed to predict pre-eclampsia however, none of these tests have been shown to be clinically beneficial for hypertension prediction.

III. Endothelial Dysfunction / Oxidative stress.

Fibronectin:-

- These are high molecular weight glycoprotein released from endothelial cells and extracellular matrix following endothelial injury.
- The plasma concentrations of these are elevated in women with pre-eclampsia (Stubbs & Colleagues 1984)
- Recent review concluded that neither cellular nor total fibronectin was clinically useful to predict pre-eclampsia (Leeflang and associates 2007).

IV. Oxidative stress:-

a) Increased levels of lipid peroxides coupled with decreased antioxidant activity have raised the possibility that markers of oxidative stress might predict pre-eclampsia (Walsh 1994)

Eg:-Malondialdehyde - marker of lipid peroxidation.

Other markers are a variety of pro- oxidation or potentiators of pro-oxidants including iron, transferin and ferritin blood lipid and anti oxidants. These are not predictive but treatments to prevent pre-eclampsia with some of these have been studied.

b) Hyperhomocysteinemia causes oxidative stress and endothelial cell dysfunction and is found in pre-eclampsia.

Although women with elevated serum homocysteine levels at mid pregnancy had a 3-4 fold risk of pre-eclampsia, these tests have not shown to be clinically useful predictors (D'Anna 2004) Mignini 2005, Zeeman 2003 and their colleagues.

V. Angiogenic Factors:-

- Imbalance between pro angiogenic and antiangiogenic factors is associated with the pathogenesis of pre-eclampsia.
- Serum levels of pro angiogenic factors such as vascular endothelial growth factor (VEGF & placental growth factor (PlGF) begin to decrease before clinical pre-eclampsia develops.

- At the same time, levels of some antiangiogenic factors such as soluble forms like tyrosine Kinase-1 (SFLT-1) and soluble endoglins (SEng) are increased (Maynard and Colleagues 2008).
- The measurements of these may predict pre-eclampsia. The sensitivity ranged from 59-100% & specificity ranged from 43-100%. (Conde-Agudelo and associates 2009).
- The predictive accuracy was higher for early-onset pre-eclampsia.
- Until better substantiated, their clinical usefulness is not recommended (Widmer& Colleagues)

VI. Free Fetal DNA:-

- Free fetal DNA can be detected in maternal plasma by polymerase chain reaction (Lo and colleagues 1997).
- Fetal – maternal cell trafficking is increased in pregnancies complicated by pre-eclampsia.
- Fetal DNA is released from apoptosis of cytotrophoblast (Difederico& colleagues 1999)
- From these review Conde-Agudelo& associates (2009) → Concluded that free fetal DNA quantification is not useful for prediction purposes.

VII. Renal Dysfunction – Related tests

i. Serum uric acid

- Hyperuricemia may be one among the earliest laboratory manifestations of pre-eclampsia (Powers and associates 2006)
- Excretion of uric acid is reduced due to decreased glomerular filtration, increased tubular reabsorption and decreased secretion (Lindheimer& colleagues 2008).
- Sensitivity ranged from 0-55% & specificity from 77 to 95% (Cnossen& associates)

ii. Microalbuminuria:-

- Sensitivity 7-90% & specificity 29-97% (Conde-Agudelo& associates) indicates poor clinical predictive value.
- Radioimmunoassay can detect the value of > 11µgm/ml which indicate positive test.

iii. Fasting urine albumin - Creatinine ratio:-

- Ratio of ≥ 16 indicates positive screening (Nakamura et al). False positive 57%, False –ve 6%.

iv. Urine kallikrein - Creatinine ratio:-

- Ratio of ≤ 170 may predict future development of pre-eclampsia (Camphell et al 1987, Miller 1996

v. Urinary calcium excretion:-

- Sanchez – Romos 1991 → 24kg urinary calcium excretion less than 12 mg / dl had positive predictive value of 91% sensitivity of 88%.

vi. Urinary calcium - creatinine ratio:-

- Low calcium - creatinine value of < 0.04 is used in prediction of pre-eclampsia (Rodriquez et al).

Similar studies related to urine calcium – creatinines are as follows:

- In 1984, Pederson E.B & Co-workers concluded that the increased renal excretion of calcium during normal pregnancy and decreased calcium excretion in pre-eclampsia might be due to changes in kidney function.

- 1987, Taufield& Co-workers concluded that measurement of urine calcium might be useful to distinguish pre-eclampsia from other forms of Gestational hypertension.

- In 1988, Rodriguez H.M & Co-workers studied first morning Urine sample in pregnant women between 24 and 34 week gestation for the presence of

micro albuminuria and calcium / creatinine ratio was estimated. Ca /Cr ratio < 0.04 and micro albumin < 11µg / dl as predictor for pre-eclampsia.

- Urinary calcium < 12 mg /dl may help to distinguish pre-eclampsia from other hypertensive disorders of pregnancy.

- 1991, Misiani.R and Co-workers → Microalbuminuriapreceeded the onset of hypertension.

- 1991 Annai T and Co-workers → Concluded that determination of the 24hr urinary calcium excretion / Ca /Cr ratio in random urine sample is reliable index of preeclampsia.

- 1992 → Suzuki Y & Co-workers –urinary calcium excretion may be useful marker for preeclampsia.

- 1995 – Ozcan T and co workers: Suggested that single urine calcium to creation ratio might be an effective marker for predicting pre-eclampsia in high risk population.

Prevention

Variety of strategies is used to prevent or modify the severity of pre-eclampsia In general none of these have been found to be clinically efficacious

Dietary Manipulation:-

1) Low Salt diet:-

- One of the earliest effort to prevent pre-eclampsia was salt restriction

(De snoo 1937).

- First Randomised trial was done by knuist& colleagues 1998, showed that sodium restricted diet were ineffective in preventing pre-eclampsia.

2) Calcium Supplementation:-

- Women with low dietary calcium intake were at increased risk for gestational hypertension (Belizan and villar 1980)
- Unless women are calcium deficient, supplementation has no salutary effects (Sibai and Cunningham 2009)

3) Fish oil supplementation:-

- The fatty acids found in some fatty acids have cardio protective effect – EPA Eicosapentaenoia acid & ALA – alpha linoleic acid
- Would prevent inflame amatory – mediated atherogenesis.

- Randomised control trich conducted so far have shown no such benefits. (MAKRIDES 2006)

4)Antioxidants:-

- Naturally, occurring antioxidants are vit C & E.
- Women who developed pre-eclampsia were found to have reduced plasma levels of these two vitamins (Raijimakes and associates 2004).
- Several Randomized studies have been done; none of them showed reduction of pre-eclampsia in women given antioxidant vitamins compared with those given placebo.

Medical measures:-

Antihypertensive drugs:-

Patients with chronic hypertension are at increased risk for pre-eclampsia.

- Several randomized trials have been carried out to evaluate various anti hypertensive drugs in reducing the incidence of superimposed pre-eclampsia
- A critical analysis of these failed to demonstrates such a reduction (Sibai and Cunningham 2009)

Antithrombotic agents:-

Antithrombotc agents might reduce the incidence of pre-eclampsia.

Low dose aspirin

- Oral dose of 50-150 mg per day, aspirin can inhibit effectively the biosynthesis of platelet thromboxane A_2 with minimum effect on vascular prostacyclin production (Wallenburg and associates 1986).
- Due to marginal benefits, it is reasonable to individualisethe use of low dose aspirin to prevent recurrent pre-eclampsia (Sibai and Cunningham 2009).
- Collaborative low dose Aspirin study in pregnancy (CLASP), a large randomized controlled trial reported a reduction of 12% in pre-eclampsia, which was non-significant.
- Some benefit was noted in a small subset of women, who were likely to develop early onset pre-eclampsia.

Calcium

It is the most abundant mineral in body. Adult body contains approximately total calcium of 1 kg. 99% is in the form of calcium phosphate salts, in the skeleton

The rest is present in extra cellular fluid, which contains 22.5m mol of which 9m mol is in the serum. Over a period of 24 hrs, 500m mol of calcium is exchanged between the bone and extra cellular fluid.

Biological functions:-

1) Structural function → supporting material in bone (Calcium phosphate)
2) Signaling functions → Inter cellular calcium function as second messenger for harmones.
3) Enzymatic function → Coenzyme for clotting factors.

- Calcium also helps in transmission of nerve impulse by releasing acetyl choline from pre-synaptic terminal
- Causes contraction of muscles

Normal Range:-

Normal total calcium = 2.2 – 2.6 m mol/L or 9-10.5 mg/dl

Normal ionized calcium = 1.1 to 1.4 m mol/L or (4.5 - 5.6 mg/dl)

The biological activity of calcium is mainly by ionized calcium. Total calcium is bound to Albumin hence its serum concentration varies with concentration of serum Albumin.

Absorption:-

In a normal diet, about 25m mol of calcium enters the body, of this 10m mol is absorbed in small intestine and 5m mol is excreted in the feces. Thus about 5m mol of calcium is available per day.

Calcium may be absorbed by two methods

a) Active process → which is vitamin D dependent

b) Passive process → occurs in jejunum and ileum when calcium intake is high.

Active process:-

Calcium is absorbed by passing through the ion channels. Calbindin is the vit D dependent binding protein present in the epithelial cells of intestine, which along with ion channels and calcium pumps actively transports calcium into the body

This process occurs actively in Duodenum portion when calcium intake is less.

EXCRETION

The Kidneys excrete about 250m mol / day, reabsorbs 245 m mol. Thus, a net loss in urine is about 5m mol / day. The presence of phosphorous decreases calcium excretion.

Regulation:-

Calcium homeostasis mechanism is multifactorial.

Involves calcium itself and other related minerals such as magnesium & phosphorous. And three calcitropic hormones like parathyroid hormone, calcitonin, and active form of vitamin D_3 (1,25 – dihydroxycholecalciferol).

Calcium homeostasis involves 3 principal organs.

→ Gastro intestinal Tract

→ Bone

→ Kidneys

a) Gastro intestinal Tract:-

At high levels of calcium intake, synthesis of calcitrol is decreased, which decreases calbindin synthesis and thus decreases rate of active calcium absorption. The opposite phenomenon occurs with decreased dietary calcium intake.

b) Kidneys:-

Of 250m mol / day plasma calcium filtered through glomeruli, 98% is reabsorbed from proximal tubules.

It is a passive process, not regulated by hormone.

In the distal parts of the nephrons (Distal convoluted tubules, connecting tubules and initial portion of collecting duct) 15% of the filtered load of calcium is reabsorbed.

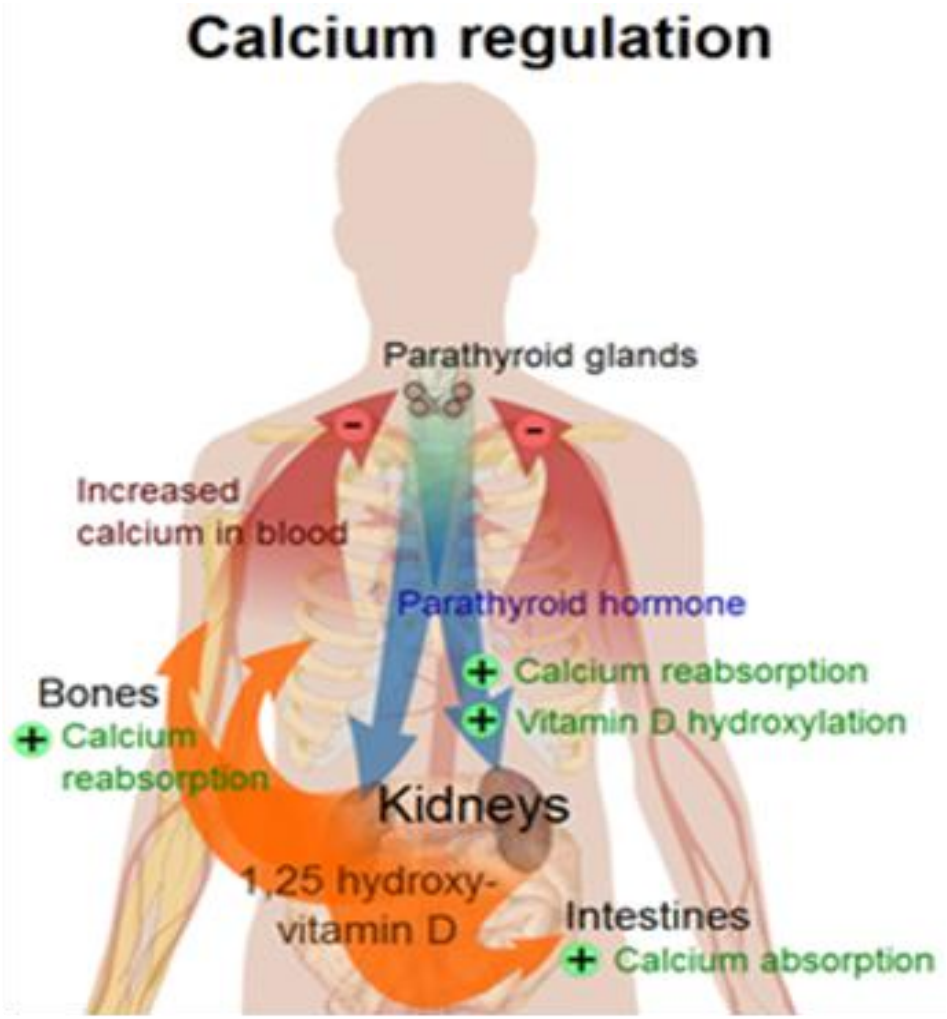
This reabsorption is an active process occurring against electrochemical gradient.

It is subjected to hormonal regulation mainly by parathormone and also by calcium, calcitonin, estrogens and androgen.

c) Bone:-

The calcium influx into bone equals rate of efflux hence bone mass remains constant. Turnover in a day is about 5m mol.

Hormonal Regulation

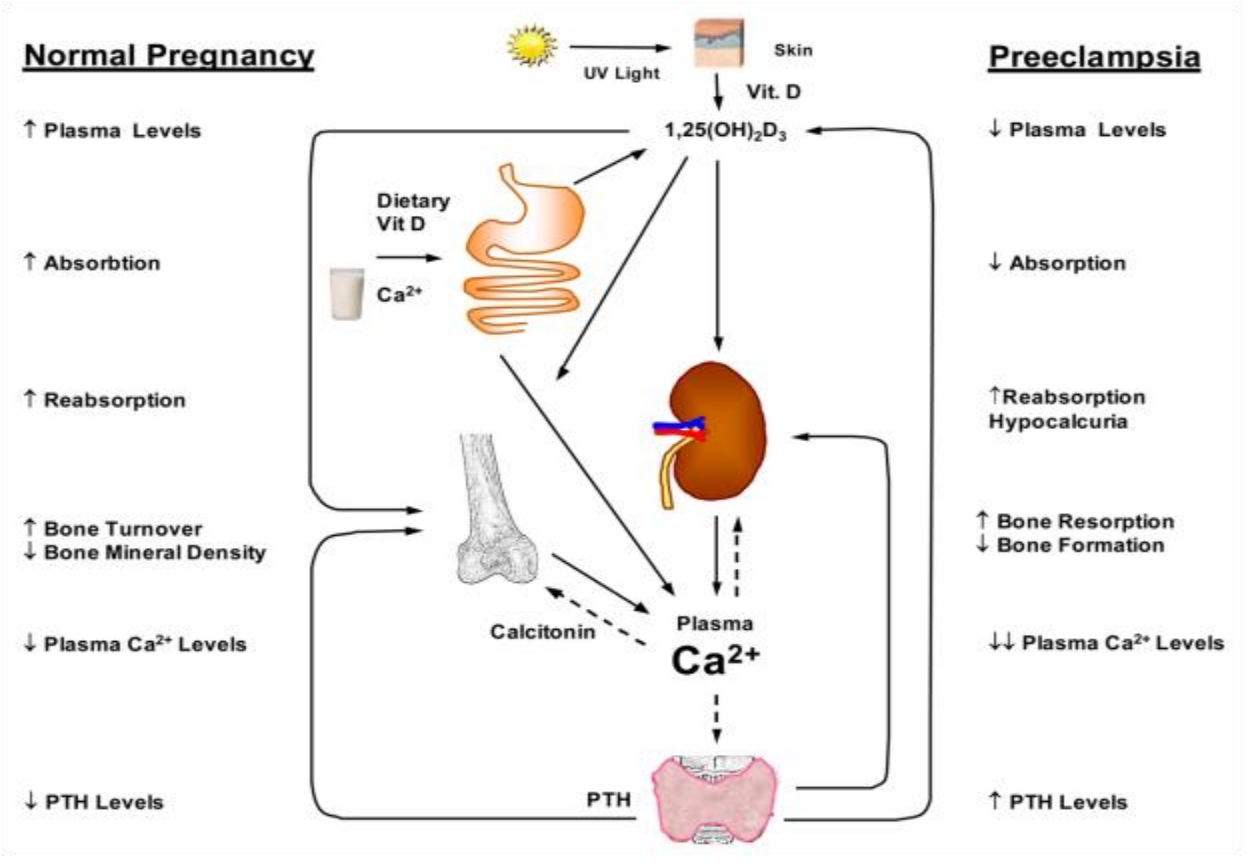


a.) Parathyroid harmone:- In extra cellular fluid, low levels, ionized calcium concentration stimulates PTH secretion, high levels inhibit it. Action of PTH is to increase extracellular calcium levels and decrease phosphate levels mainly by Bone resorption, Intestinal absorption and Kidney reabsorption.

b.) Vitamin D → vit D_3 after ingestion or synthesized from UV light is hydroxylated to 25 hydroxy vitamin D_3 (The principal circulating form of vitamin).

This form is normally hydroxylated at 1α position in Kidney, placenta and decidua to form 1, 25-dihydroxycholecalciferol facilitated by PTH, low calcium levels and phosphate levels & its actions opposed by calcitonin. 1, 25-dihydroxycholecalciferol is the biologically active form. It stimulates resorption of calcium from bone and absorption of calcium from small intestines.

Calcium in normal pregnancy and pre-eclampsia.



The Developing fetus imposes a significant demand on maternal calcium homeostasis. Eg; Fetal skeleton accretes 30g of calcium by term, 80% of which is deposited during the last trimester. The demand of which is met by doubling of intestinal calcium absorption mediated by 1, 25, dihydroxy vitamin D_3 (Kovacs and Fuleihan 2006).

Total calcium levels decline during normal pregnancy due to lowered plasma albumin concentration levels of serum ionized calcium remains unchanged (Power & associates 1999).

Plasma concentrations of parathyroid hormone decrease during first tri mester and then increases progressively throughout the remainder of pregnancy (Pitkin and associates 1979). This increase is due to lowered calcium concentrations as a result of increase in plasma volume, glomerular filtration rate and maternal transfer of calcium to fetus. Estrogen blocks action of PTH on bone resorption thus increases its levels. Thus it results in physiological hyperparathyroidism of pregnancy, which supplies the fetus with adequate calcium.1, 25 dihydroxy vitamin D_3 levels are increased during normal pregnancy (Weisman and co-workers 1979) probably (placental &decidual origin)

In Pre-eclampsia, due to defective placenta, there is decrease in levels of 1, 25 dihydroxyvit D_3 which causes decrease in GI absorption of calcium. Thus there is

low ionized calcium. During pregnancy due to transfer of calcium to fetus from mother, there is increased calcium uptake by placenta resulting in hypocalcemia, this in turn increases PTH. Hence, there is reduced placental perfusion and renal damage which leads to decreased synthesis of 1, 25 dihydroxyvit D_3 which would stimulate PTH to increase reabsorption of Ca^{++} from distal tubules and proximal tubules resulting in hypocalciuria.

Important changes:-

- Serum ionized concentration of calcium is lower in pre-eclampsia.
- Lower calcium excretion.
- Lower 1, 25 dihydroxyvit D_3
- Increased PTH levels.

Lower calcium intake will increase BP due to vasoconstriction by stimulating release of renin from Kidneys and / or PTH.

Creatinine

- It is derived from Greek word Kreas meaning flesh. It is a break down product of muscle creatinine phosphate
- Produced at a constant Rate by the body
- Creatinine constitutes 0.5% of total muscle mass.
- It is filtered by the Kidneys (Glomerular filtration and proximal Tubular secretion)
- There is little or no tubular reabsorption of creatinine. When the filtering by the Kidneys is decreased, creatinine in blood increases.
- Hence creatinine values in blood & urine can be used to estimate the creatinine clearance (Cr Cl) which reflects the glomerular filtration rate.
- Normal urine creatinine levels are 1-2 gm / day.
- Normal plasma creatinine 0.8-1 mg / dl.
- In normal pregnancy, there is decrease in plasma creatinine and increase in 24 hrscreatinine clearance

- In pre-eclampsia, due to diminished renal perfusion and glomerular filtration there is elevation in plasma creatinine.

Micro Albuminuria

- It is a marker for endothelial dysfunction.
- Micro albuminuria occurs when there is small amount of albumin leaks from Kidney into urine suggesting abnormally high permeability for albumin in the renal glomerulus
- Micro albuminuria is defined as urinary excretion of albumin that is persistently above normal but cannot be detected by urine dipstick methods.
- Diagnosed from 24hrs urine collection value of 20-200mg / min or elevated concentrations of 30-300 mg / L on at least two occasions.
- It reflects the presence of generalized vascular damage
- During normal pregnancy, the urine albumin excretion remains within normal range. There may be small increase in albumin excretion during the third trimester due to increased glomerular permeability and due to decreased tubular protein absorption

- In pre-eclampsia there is decrease in GFR and renal blood flow,leading to decreased filtration fraction.
- Glomerular endotheliosis characterized by enlarged and swollen glomeruli, which is mainly due to hypertrophy of the intracapillary cells, which encroach on the capillary lumen resulting in bloodless glomerulus.
- These changes are responsible for the microalbuminuria in initial stages & later proteinuria in pre-eclampsia.

AIM OF THE STUDY

AIM OF THE STUDY

To determine predictive values of decreasing urinary calcium to creatinine ratio and microalbuminuria for preeclampsia, in a spot urine sample, in asymptomatic pregnant women between 20 to 24 weeks of gestation in order to recommend it as screening test for preeclampsia

MATERIALS AND METHODS

MATERIALS AND METHODS

This test was conducted at RSRM Lying in hospital, Royapuram, Chennai. Attached to Stanley Medical College.

STUDY PERIOD

The study period was from October-2012 to November-2013

STUDY DESIGN - Prospective study**.**

200 asymptomatic pregnant women attending routine antenatal care who could be followed until term at RSRM Lying in hospital were selected.

INCLUSION CRITERIA

- 20–24 weeks of gestation age
- Asymptomatic women who attended the antenatal OPD at RSRM Lying in hospital, Royapuram- Chennai.

EXCLUSION CRITERIA

- ✓ Chronic hypertension
- ✓ Renal disease
- ✓ Diabetes
- ✓ Albuminuria in dip-stic method
- ✓ BP >140/90

METHODOLOGY

- Pregnant women included in the study were counseled, given proforma and a written informed consent was obtained.
- Patients detailed history was taken.
- clinical and routine obstetric examination was done
- Blood pressure was recorded in sitting position in right arm. Korotkoff V was used to measure diastolic blood pressure.
- Routine antenatal tests were done.
- Single spot urine sample irrespective of day-time was collected in clean sterile universal bottle without any preservative.
- Urine samples were sent to biochemistry laboratory, RSRM Lying in hospital without delay
- urine tested for microalbumin, calcium and creatinine using commercially available kits(ROBONIK LABORATORIES)
- O Cresolphthalein complex reaction was used to estimate calcium.
- Jaffes method was used to estimate creatinine.
- Microalbumin was detected by immunometric assay.
- Values of urinary calcium - creatinine ratio calculated and value of microalbumin noted.

- After initial workup, patients were followed thereafter in the antenatal clinic till the time of delivery.
- During follow up, they were evaluated by detailed history of symptoms of preeclampsia and imminent eclampsia such as edema, nausea, vomiting, epigastric pain, decreased urine output and visual disturbances. Clinical and routine obstetric examination was done. Blood pressure was measured and urine was tested for protein by dipstick method.
- Pre-eclampsia was defined as systolic arterial blood pressure ≥140mmHg and/or diastolic arterial blood pressure ≥ 90mm Hg with ≥300 mg/24h proteinuria (dipstic method)
- The number of patients who developed preeclampsia was noted and correlation studied
- Based on these criteria the women studied were categorized as those who developed pre-eclampsia and those who remained normotensive.
- Calcium - Creatinine ratio less than or equal to 0.04 were considered test positive and those with a ratio of >0.04 were considered test negative.
- Urine microalbumin levels between 30 to 300mg/L were considered test positive for microalbuminuria and those with levels <30mg/L were considered test negative.

- Predictive values of calcium to creatinine at less than or equal to 0.04 and microalbuminuria determined by statistical analysis.

STATISTICAL METHODS:

Chi square test and Fisher Exact test has been used to find the significant association of findings of preeclampsia and CCR and microalbuminuria.

p value :

a) ≤ 0.01 → strongly significant

b) 0.01- 0.05 → moderately significant

c) 0.05 - 0.1 → significant

Area under Receiver Operator Curve (ROC) was used to find the predictive values of CCR at less than or equal to 0.04 and microalbuminuria for preeclampsia.

a) 0.9 – 1 : Excellent test

b) 0.8 – 0.9 : Good test

c) 0.7 – 0.8 : Fair test

d) 0.6 – 0.7 : Poor test

ESTIMATION OF URINARY CALCIUM BY

ORTHO - CRESOLPHTHALEIN COMPLEXONE REACTION

Principle :

- In alkaline medium, ortho-cresolpthaleincomplexone reacts with calcium forming red violet colour.
- Interference by magnesium is eliminated by addition of 8 hydroxyquinoline in the reagent
- The colour intensity is directly proportional to concentration of calcium in the sample.
- Measurement of calcium is done in coloured complex at wavelength of 570nm -580 nm.

ESTIMATION OF URINARY CREATININE BY JAFFE 'S METHOD

Principle:

Creatinine forms a coloured orange red complex in an alkaline picrate solution.

The colour intensity obtained is directly proportional to the amount of creatinine in the sample.

ESTIMATION OF URINE MICROALBUMIN BY IMMUNOMETRIC ASSAY

Principle:

Microalbumin in urine is measured by turbidimetric immunoassay, which measures the reduction in light transmission caused by particle formation and quantifies the residual light transmitted.

It is based on agglutination reaction. Albumin present in the sample forms an insoluble complex producing a turbidity, which can be measured at wavelength of 340 nm. Turbidity corresponds to the concentration of albumin present in the sample.

RESULTS

RESULTS

DISTRIBUTION OF PREGNANT WOMEN 20 – 24 WEEKS GESTATION IN STUDY GROUP ACCORDING TO AGE

Table-1

Age in years	Number	percentage
< 20	52	26
21 -30	131	65.5
>30	17	8.5
total	200	100

In our study, majority 131 (65.5%) out of 200 women were in the age group of 21 to 30 years, 52 (26%) were in the age group of below 20 years, 17(8.5%) were in the age group of above 30 years of age.

DISTRIBUTION OF PREGNANT WOMEN 20 – 24 WEEKS GESTATION IN STUDY GROUP ACCORDING TO AGE

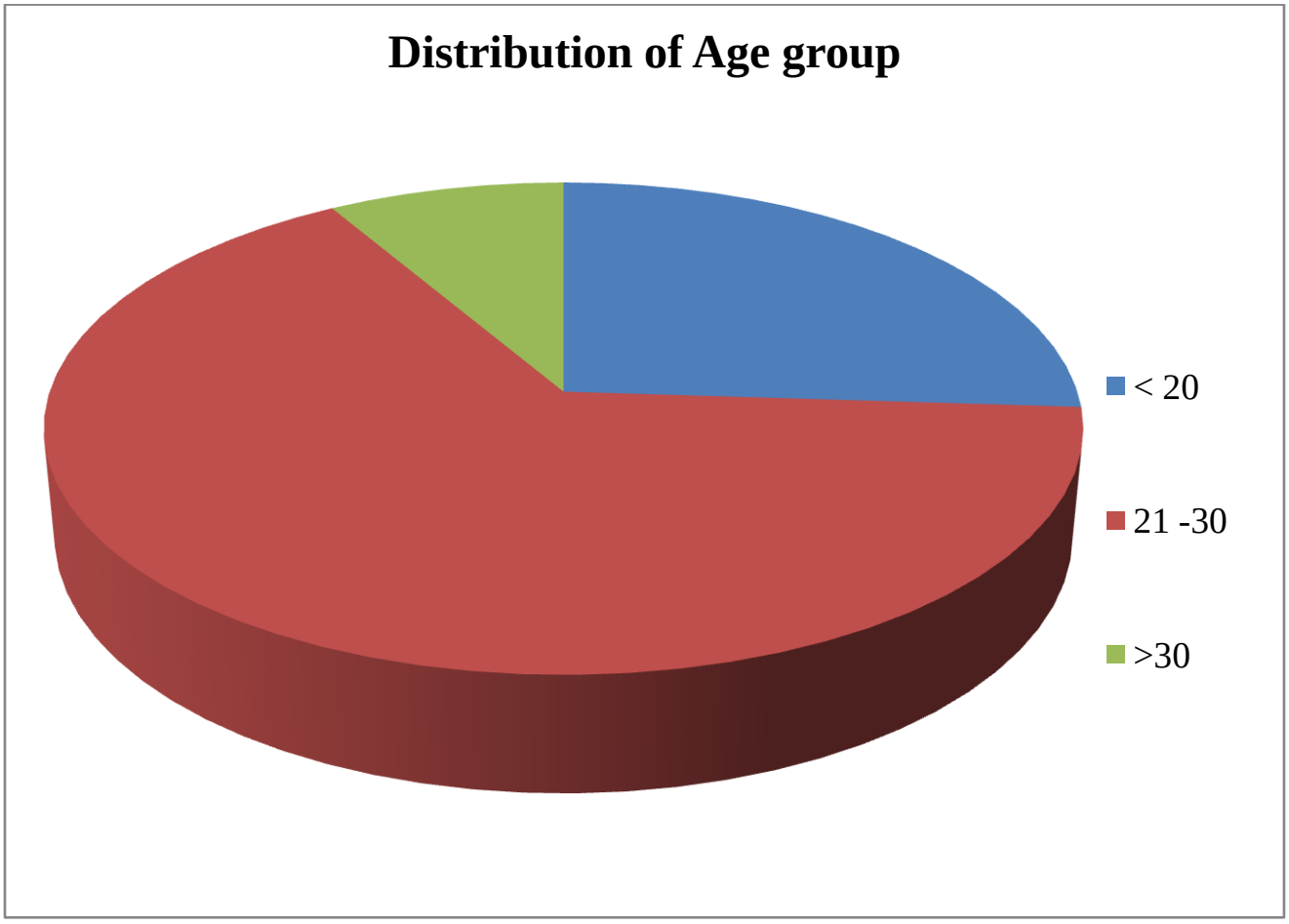


Figure-1

DISTRIBUTION OF PREECLAMPSIA IN STUDY GROUP ACCORDING TO AGE GROUP

Table-2

Age in years	**Developed preeclampsia**	**normotensives**	Total
<20	9(4.5%)	43(21.5%)	52(26%)
21-30	12(6%)	119(59.5%)	131(65.5%)
>30	5(2.5%)	12(6%)	17(8.5%)
Total	26(13%)	174(87%)	200(100%)

Among who developed preeclampsia, 12(46.2%) were in the age group of 21-30 years,9(34.6 %) were below the age group of 20 years and 5(19.2%) above 30 years of age.

DISTRIBUTION OF PRE-ECLAMPSIA IN STUDY GROUP ACCORDING TO AGE GROUP

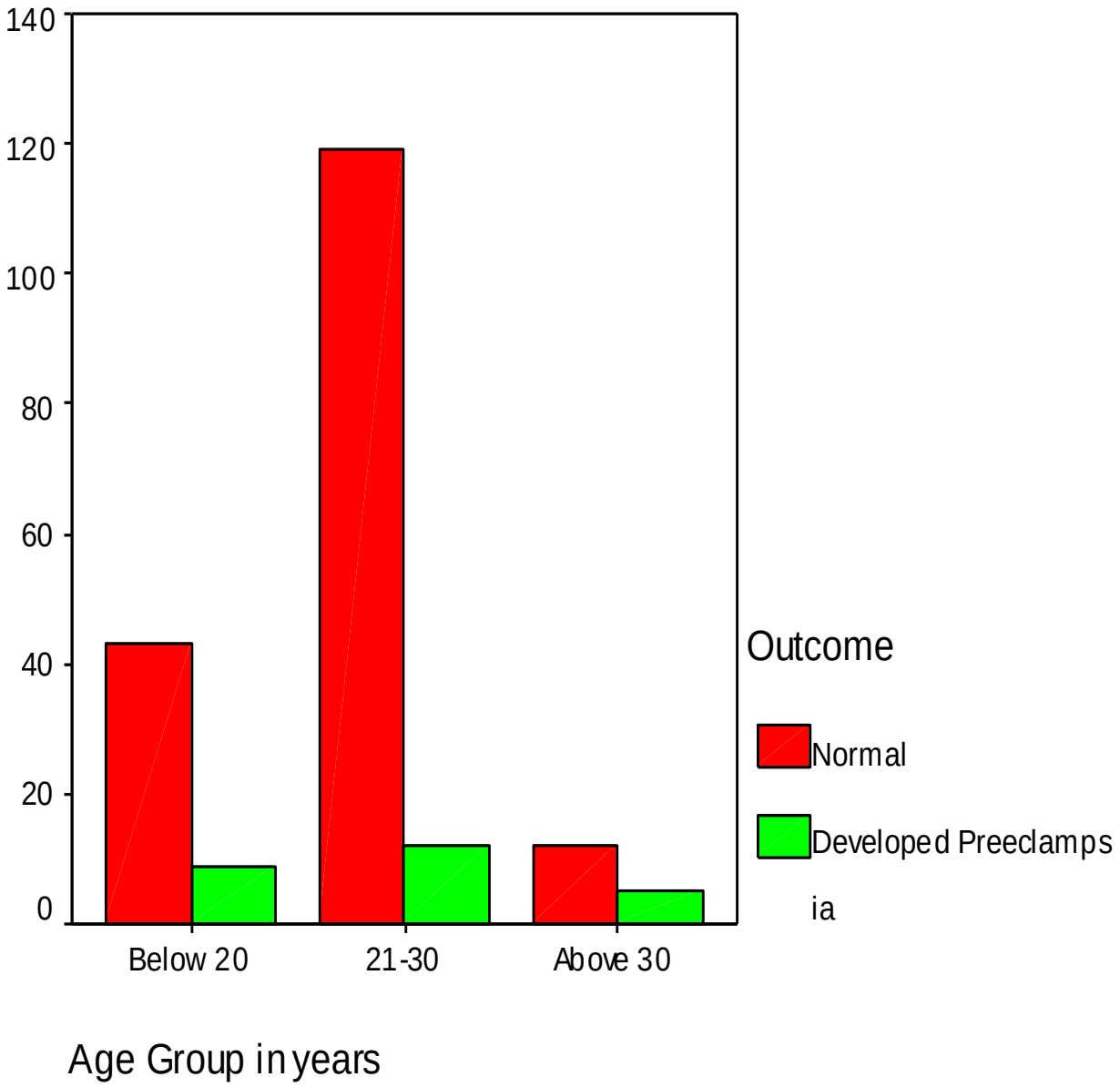


Figure-2

DISTRIBUTION OF STUDY GROUP ACCORDING TO PARITY

Table-3

Obstetric code	**number**	**Percentage**
Primi	124	62
multi	76	38
total	200	100

In this study, out of 200 women 124(62%) were primigravida and 76(38%) were multigravida.

DISTRIBUTION OF STUDY GROUP ACCORDING TO PARITY

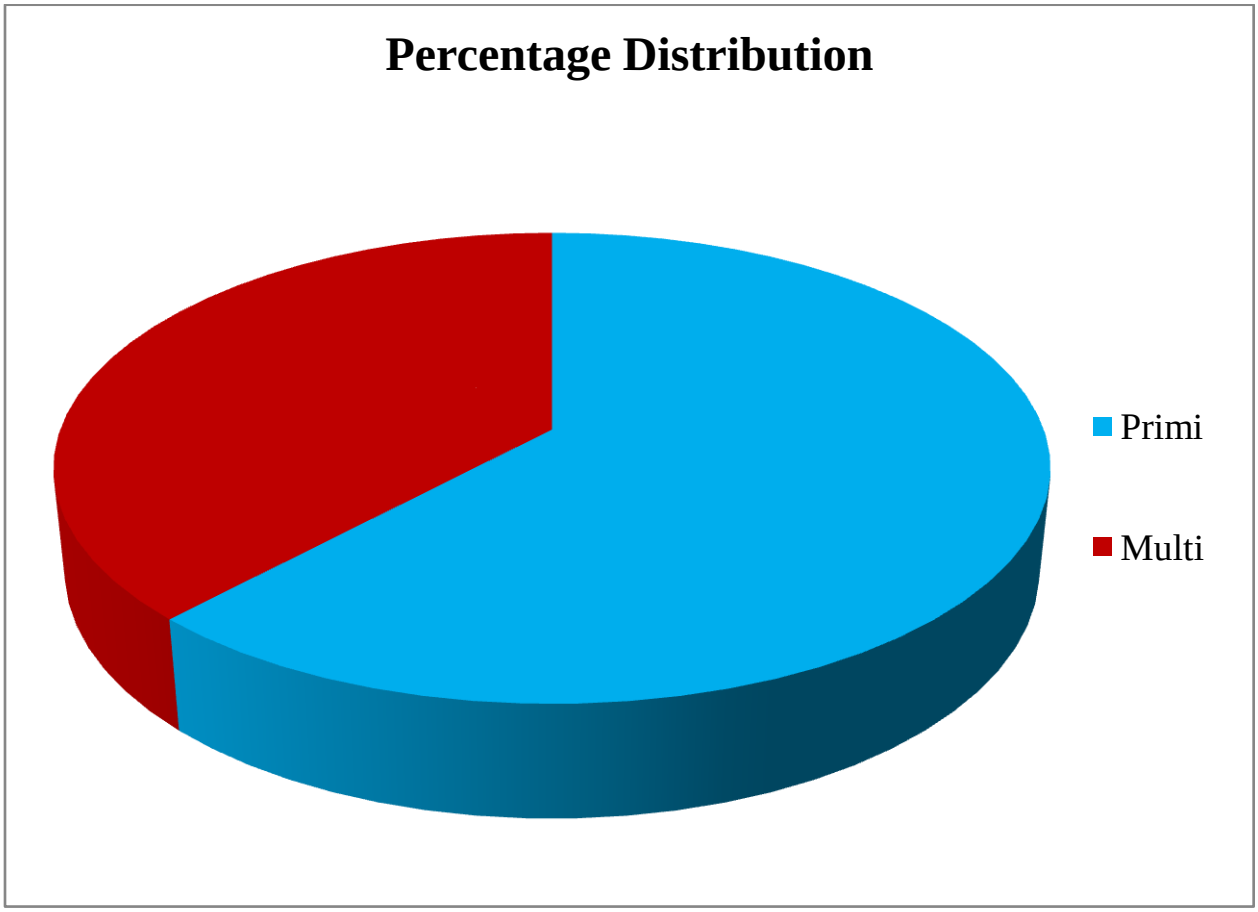


Figure-3

DISTRIBUTION OF PRE-ECLAMPSIA ACCORDING TO PARITY

Table-4

Obstetric code	**Developed preeclampsia**	**normotensive**	**Total**
Primi	17(8.5%)	107(53.5%)	124(62%)
Multi	9(4.5%)	67(33.5%)	76(38%)
total	26(13%)	174(87%)	200(100%)

- Among those who developed preeclampsia, 17(65.4%) were primigravida and 9 of them (34.6%) were multigravida.

- This shows that the incidence of preeclampsia in primigravida is higher than the multigravida.

DISTRIBUTION OF PRE-ECLAMPSIA ACCORDING TO PARITY

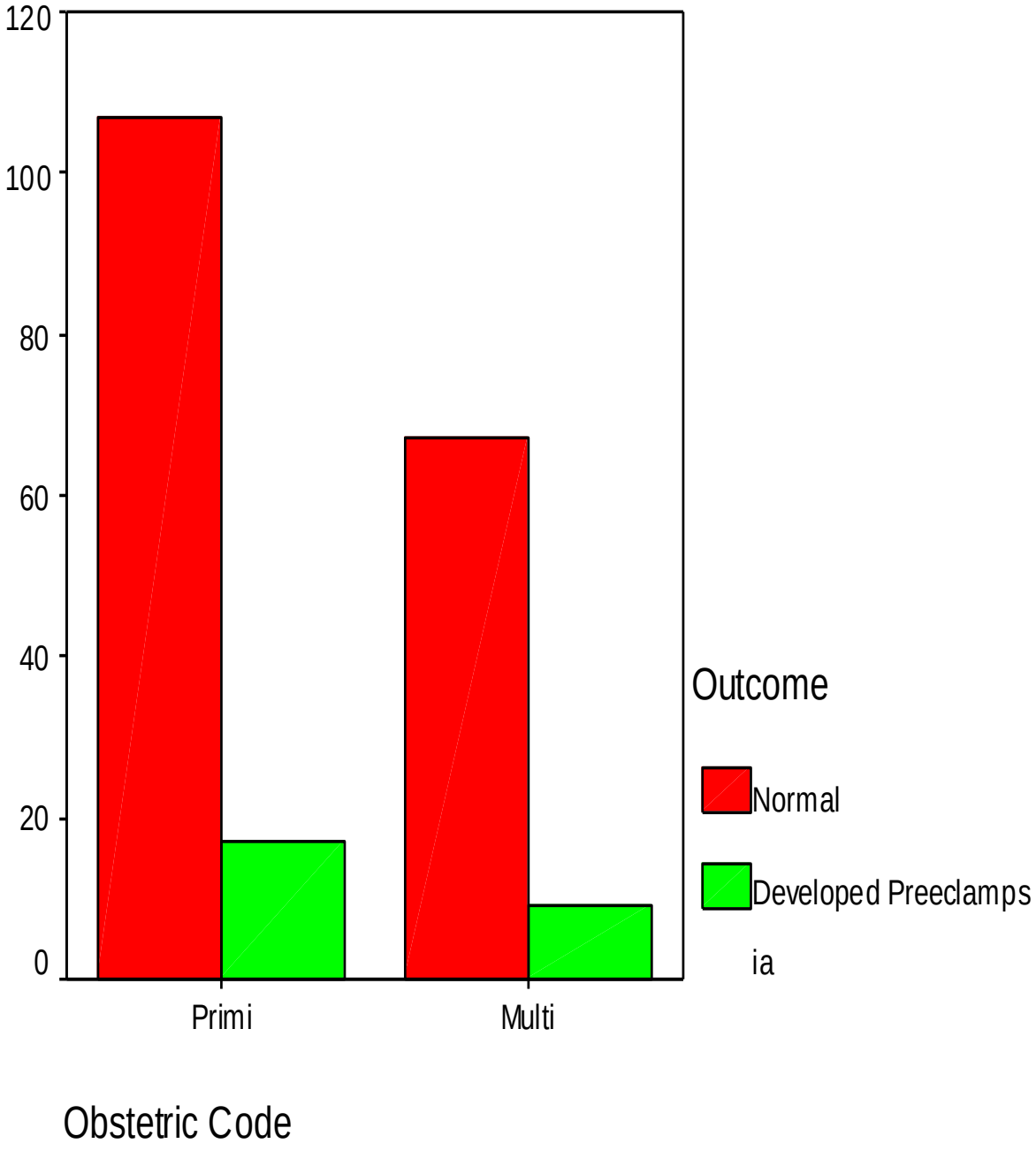


Figure-4

URINE CALCIUM –CREATININE RATIO(UCCR) AND DEVELOPMENT OF PRE-ECLAMPSIA

Table 5

UCCR	**Developed preeclampsia**	**normotensives**	**total**
Test positive	19(9.5%)	4(2%)	23(11.5%)
Test negative	7(3.5)	170(85%)	177(88.5%)
total	26(13%)	174(87%)	200(100%)

- Among the 200 women studied,23(11.5%) were test positive-UCCR of less than or equal to 0.04 and 177(88.5%) were test negative-UCCR >0.04.

- Among the women who were test positive for UCCR, 19(82.6%) developed preeclampsia and those with test negative for UCCR,7(4%) developed preeclampsia.

URINE CALCIUM –CREATININE RATIO (UCCR) AND DEVELOPMENT OF PRE-ECLAMPSIA

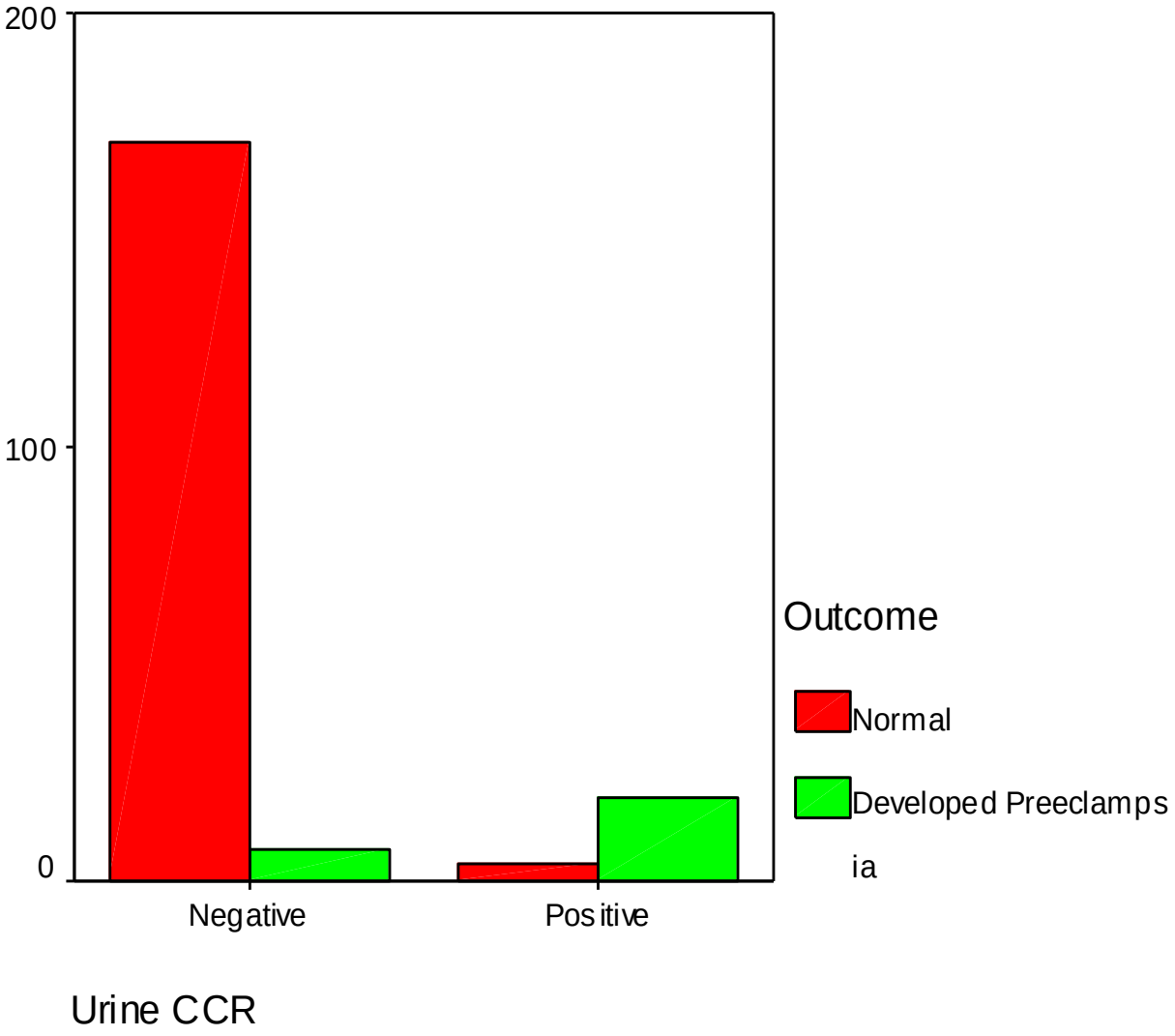


Figure-5

URINE MICROALBUMIN AND DEVELOPMENT OF PRE-ECLAMPSIA

Table-6

Urine microalbumin	**Developed preeclampsia**	**normotensive**	**Total**
Positive	16(8%)	26(13%)	42(21%)
Negative	10(5%)	148(74%)	158(79%)
total	26(13%)	174(87%)	200(100%)

- Among the 200 women studied,42(21%) were test positive for urine microalbumin-30 to 300mg/L and 158(79%) were test negative<30mg/L.

- Among the women with test positive for urine microalbumin,16(38.1%) developed preeclampsia and of those with test negative 10(6.3%)developed preeclampsia.

URINE MICROALBUMIN AND DEVELOPMENT OF PRE-ECLAMPSIA

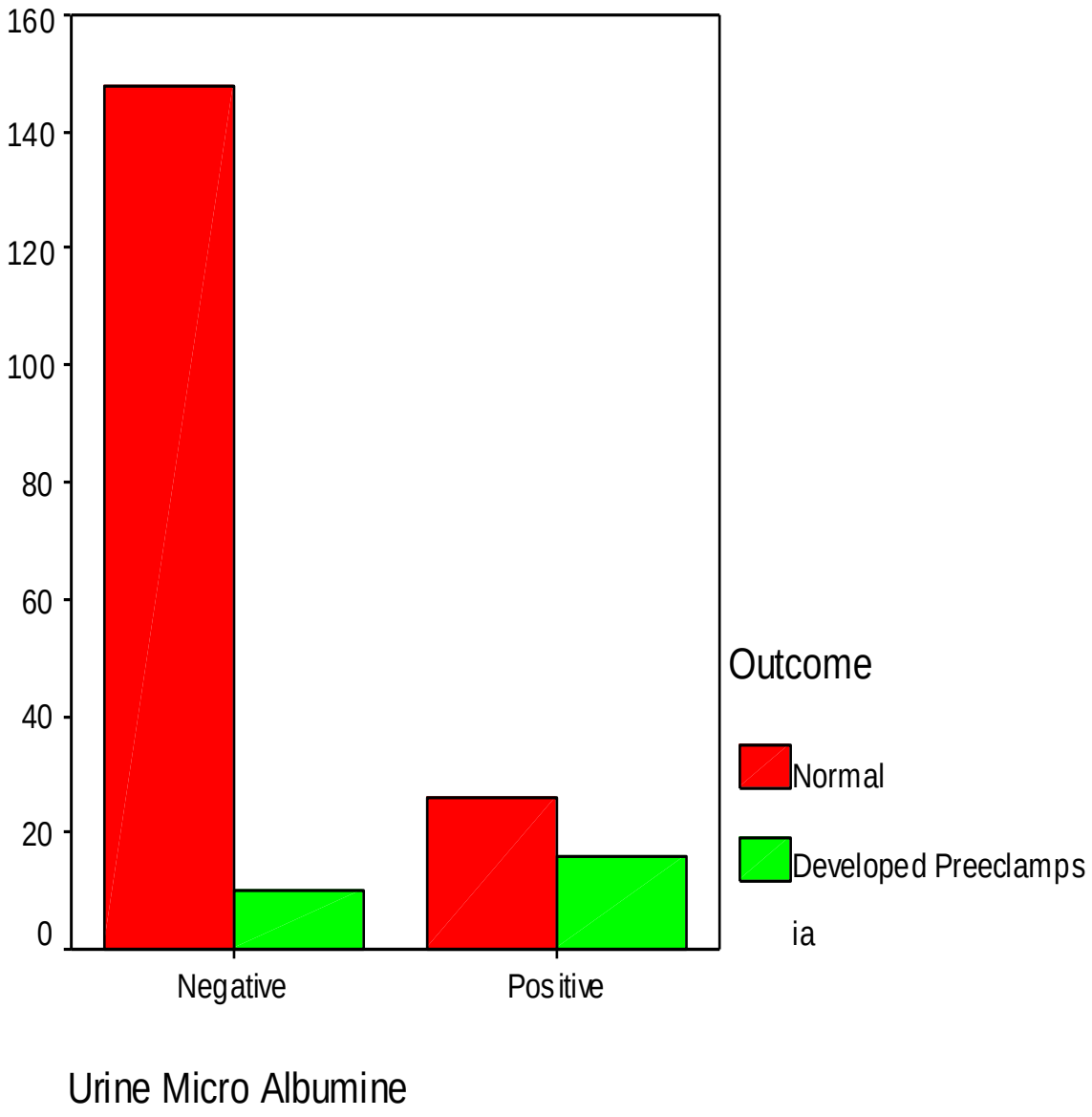


Figure-6

DISTRIBUTION OF PRE-ECLAMPSIA ACCORDING TO WEEKS OF GESTATION

Table-7

Gestation age (weeks)	number
<35	2
36-37	10
38- 40	14
total	26

- In this study, 14 patients developed preeclampsia at 38 to 40 weeks, 10 patients developed at 36 to 37 weeks and 2 of them developed at gestation age of less than 35 weeks.

DISTRIBUTION OF PRE-ECLAMPSIA ACCORDING TO

WEEKS OF GESTATION

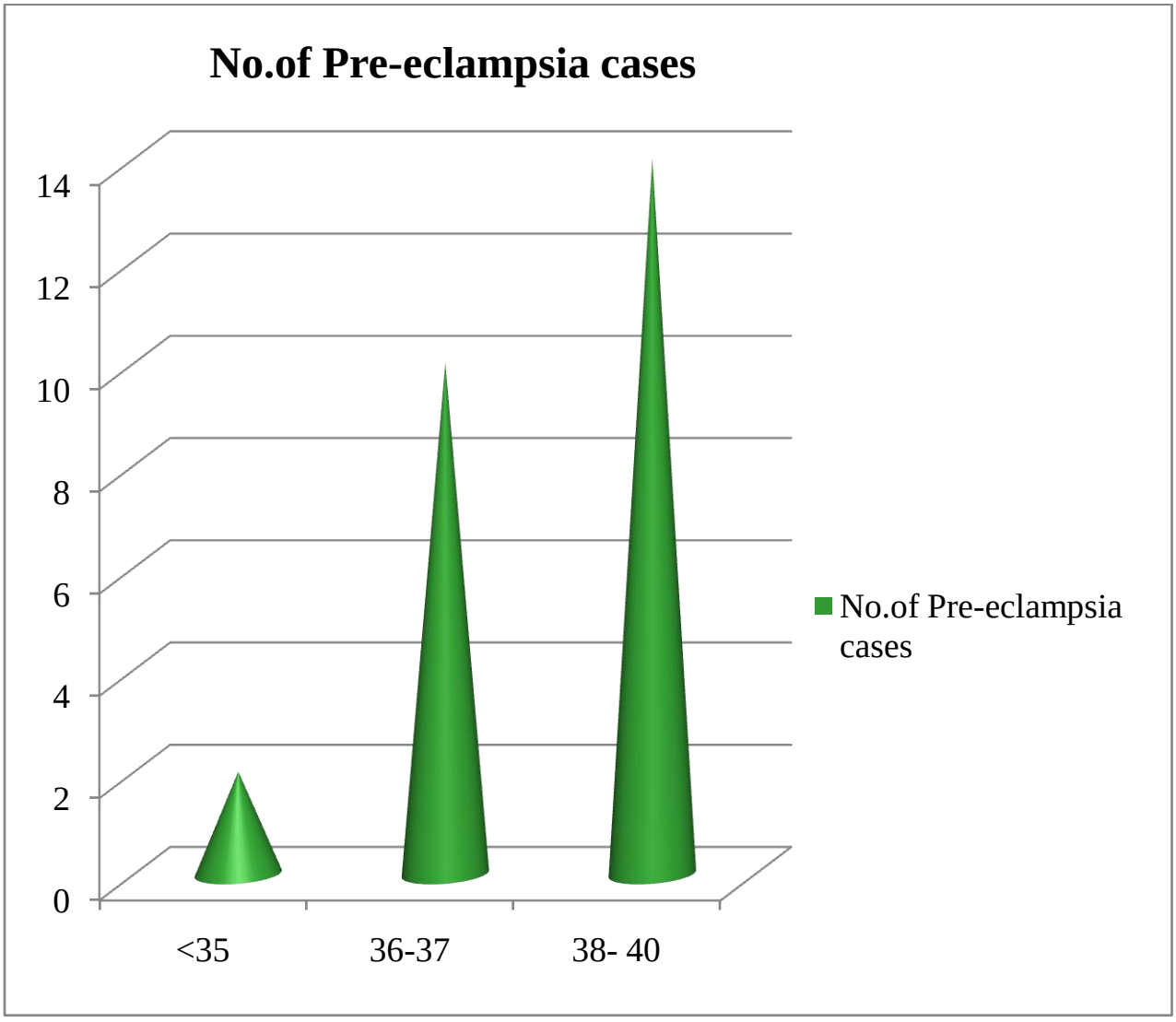


Figure-7

ASSOCIATION OF URINE CALCIUM – CREATININE RATIO AND PRE-ECLAMPSIA

Table-8

UCCR < 0.04	**Developed PRE-ECLAMPSIA**	**NORMOTENSIVE**
Positive (23)	19(9.5%)	4(2%)
Negative (177)	7(3.5%)	170(85%)
total	26(13%)	174(87%)

Using Chi square test/Fisher Exact test:

p value - <0.001

Statistical accuracy-94.5%

Sensitivity-73.1%

Specificity-97.7%

Positive predictive value-82.6%

Negative predictive value-96%

ASSOCIATION OF URINE CALCIUM – CREATININE RATIO

AND PRE-ECLAMPSIA

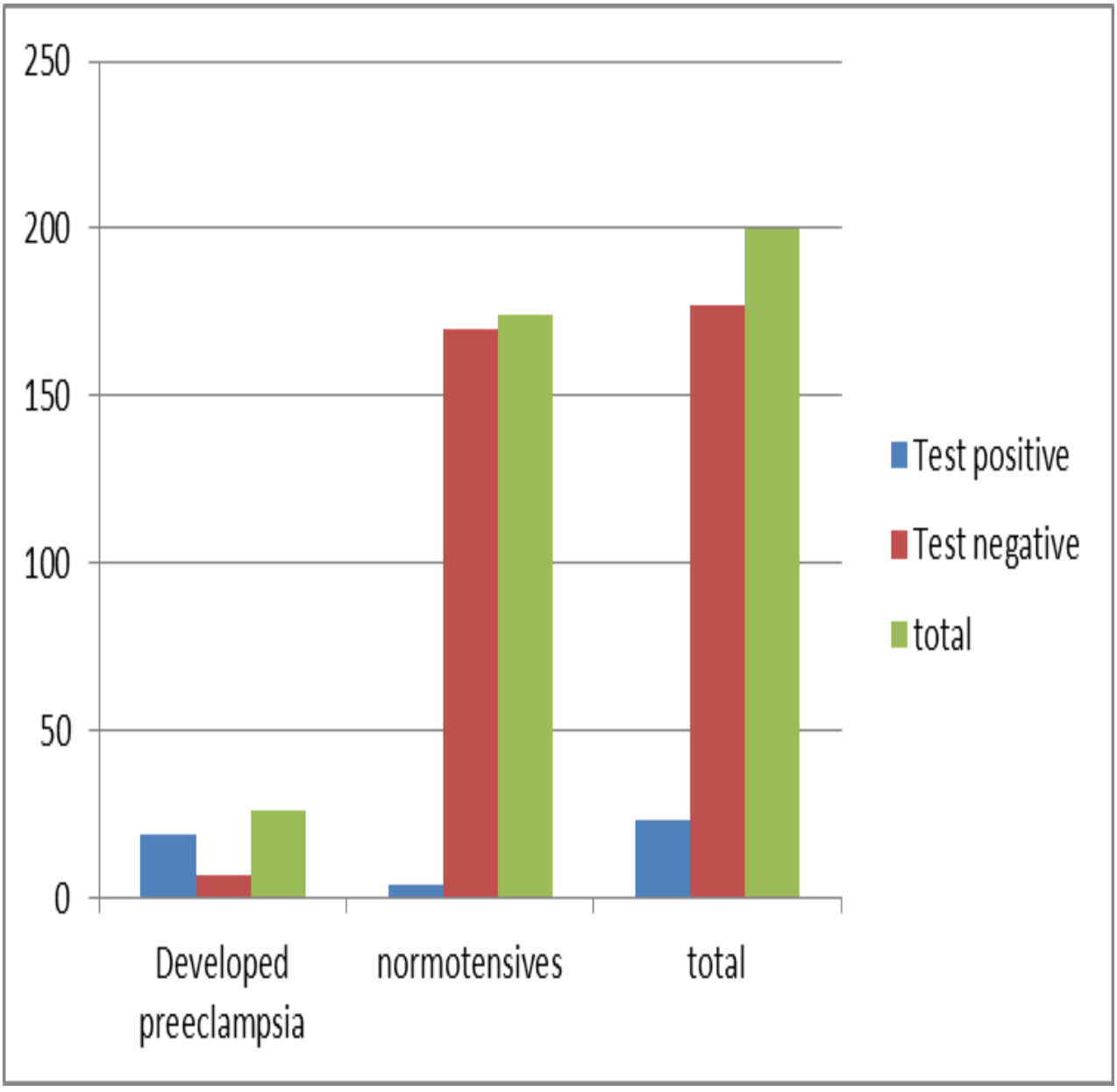


Figure-8

ASSOCIATION OF MICROALBUMINURIA AND PRE-ECLAMPSIA

Table-9

Urine microalbumin	**Developed preeclampsia**	**normotensive**
Positive(42)	16(8%)	26(13%)
Negative(148)	10(5%)	138(74%)

Using Chi square test/Fisher Exact test:

p value - <0.001

Statistical accuracy – 82%

Sensitivity-61.5%

Specificity- 85%

Positive predictive value-38.1%

Negative predictive value-93.7%

ASSOCIATION OF MICROALBUMINURIA AND PREECLAMPSIA

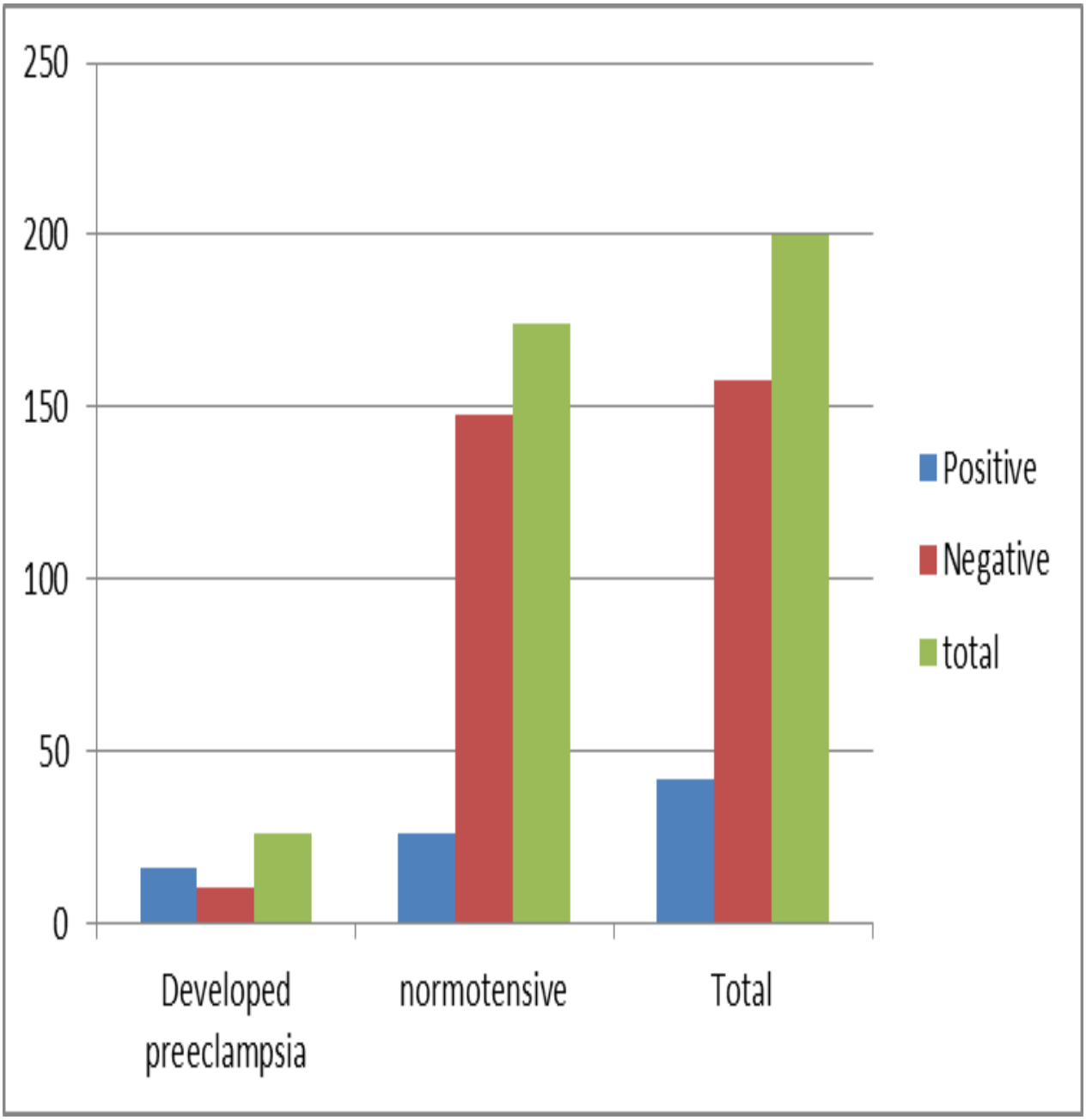


Figure-9

PREDICTIVE VALUES OF URINE CALCIUM –CREATININE RATIO AND MICROALBUMINURIA FOR PRE-ECLAMPSIA, USING AREA UNDER RECEIVER OPERATOR CURVE (ROC)

Table-10

	AUC	**SE**	**95% CI**	**REMARKS**
UCCR	0.901	0.39	0.825-0.997	Good test
Microalbuminuria	0.709	0.059	0.593-0.824	Fair test

AUC – Area Under the Curve

SE – Standard Error

CI – Confidence Interval

- When predictive value of urine calcium – creatinine ratio was calculated using area under curve of ROC it was found that UCCR at less than or equal to 0.04 was a good test.
- Predictive value of microalbuminuria for preeclampsia using area under curve of ROC showed that it was only a fair test for prediction of preeclampsia.

DISCUSSION

DISCUSSION

Our present study was a prospective study comprising 200 asymptomatic pregnant women between 20 -24 weeks of gestation. Urine calcium- creatinine ratio and microalbumin was estimated from a single spot urine test .Similar studies were done by Sheela CN, Beena S R between 20 to 24 weeks. Kazeroni T et al at 20 to 24 weeks, Rodriguez H M between 24 and 34 weeks, DayaSirohiwal et al between 20- 28 weeks.

Incidence of pre-eclampsia increases with extremes of age. 46.2% of women with pre-eclampsia were in the age group of 21-30years followed by 34.6% women were <20years and 19.2% were above 31years in our study.

Pre-eclampsia is more common in primigravida.

In our study, 65.4% of women with Preeclampsia were primigravida and 36.4% of women with preeclampsia were multigravida. Karith J et al showed that nulliparity with decreased calcium -creatinine ratio were at high risk for developing pre-eclampsiaHusselman (1924) showed that primigravida were at eight times higher risk to develop eclampsia than multigravida.

In this study, urinary calcium/ creatinine ratio was lower in women with preeclampsia when compared to Normotensive women. Statistical analysis showed significant correlation of urinary calcium – creatinine ratio between women who developed Preeclampsia and Normotensive women with p value of < 0.001. These findings were similar to the studies of Hellen Rodriguez M et al , Ozcan T et.al , Patricia A devine et.al , Das Gupta mandira et al, Kazerooni T et.al , Kar J et.al , Suzuki Y et.al.

In our study, 23(11.5%) out of 200 were CCR positive (<0.04) and 177(88.5%) were CCR negative (>0.04). Among women who developed pre-eclampsia, 19(82.6%) were tested positive and 7 (4%) were tested negative. Among Normotensive women 4 (17.4%) were test positive and 170 (96%) were test negative.

In our study ,urine calcium-creatinine ratio(CCR) at less than or equal to 0.04 in a spot urine sample had sensitivity of 73.1%, specificity of 97.7%, positive predictive value of 82.6%, negative predictive value of 96%, and diagnostic accuracy of 94.5% .Urine calcium – creatinine ratio was found to be a good test for predicting preeclampsia

These results were similar to studies done by Rodriguez H M and co-workers in 1988 also estimated the CCR at 0.04, they analyzed a sensitivity less of 70%, specificity of 95%, PPV of 64%, NPV of 96% for prediction of pre-eclampsia. Study conducted by Sheela CN, Beena SR, MhaskarArun et al in 2011, reported that calcium –creatinine ratio at less than or equal 0.04 in spot urine sample showed a sensitivity of 69%, specificity of 98 %, PPV of 85.6% and NPV of 95.5%.They found it to be a good test. Sudan et .al, reported sensitivity of 68% and sensitivity of 70%. Ozcan et al reported that CCR might be an effective marker of preeclampsia. In addition, studies done by Kazeroomiet .al. and Kar et evaluated predictive values of CCR at 0.04 was a satisfactory test for prediction of preeclampsis.

Thus, the above mentioned authors, in their studies gave results which showed that decreased urinary CCR in single spot sample has a significant association with development of pre-eclampsia and it can be used as screening test.

In our study, 42(21%) out of 200 were urine microalbumin test positive (30 – 300mg/L) and 158(79%) were test negative (<30mg/L). Among women who developed pre-eclampsia, 16(61.5%) were tested positive and 10(38.5%) were

tested negative. Among Normotensive women 26(14.9%) were tested positive and 148(85%) were test negative.

Statistical analysis for urine microalbumin showed significant p-value of < 0.001. The cut of value for urine microalbumin>30-300mg/L was found to have sensitivity 61.5%, specificity 85.1%, positive predictive value 38.1%, negative predictive value 93.7%, and diagnostic accuracy of 82% for prediction of pre-eclampsia. It was found to be a fair test.

Salako et al reported that a single estimation of microalbuminuria had a high sensitivity (88.9%) but a low PPV (22%). Shaarawy et.al.evaluated the clinical value of microtransfferrinuria and microalbuminuria in prediction of preeclampsia in asymptomatic women and concluded that microtransfferrinuria was a more sensitive marker than microalbuminuria. Chhabraet.al found that estimation of microalbuminuria around 18 weeks of gestation was useful in primigravida

Hence urine calcium-creatinine ratio was found to be a good test for prediction of pre-eclampsia and can be used as screening test Microalbuminuria was found to be a fair test and further studies are needed recommend it as a screening test.

SUMMARY

SUMMARY

- In our study , majority (65.5%) were in the age group of 21 to 30 years,26% were in the age group of below 20 years,8.5% were in the age group of above 30 years of age

- Preeclampsia developed in 46.2% of study group who were in the age group of 21-30 years,34.6% who were below the age group of 20 years and 19.2% who were above 30 years of age.

- 65.4% of primigravida developed preeclampsia and 34.6% of multigravida developed preeclampsia

- Among the women who were test positive for urine calcium – creatinine ratio, 19 (82.6%) developed preeclampsia. This was statistically highly significant.

- Among those with test positive for urine microalbumin, 16(38.1%) developed preeclampsia, which was statistically significant

- Urine calcium – creatinine ratio at less than or equal to 0.04 showed these statistical results- p value was <0.001, Sensitivity- was 73.1%,Specificity was 97.7% ,Positive predictive value was 82.6%, Negative predictive value-96% and Statistical accuracy of 94.5%

- Urine microalbumin at 30 – 300 mg showed these statistical results- p value was <0.001, Sensitivity was 61.5%,Specificity was 85% ,Positive predictive value was 38.1%, Negative predictive value-93.7% and Statistical accuracy of 82%

- Predictive value of urine calcium – creatinine ratio w using area under curve of ROC showed that UCCR at less than or equal to 0.04 was a good test.

- Predictive value of microalbuminuria using area under curve of ROC showed that it was a fair test

CONCLUSION

CONCLUSION

Screening test for preeclampsia is very essential to prevent complications of preeclampsia, which is a major cause for maternal and fetal mortality and morbidity. There has been a constant research to find an effective screening test for prediction and prevention of preeclampsia, which would give a idea to implement measures of primary prevention.

In past few decades number of clinical and biochemical methods for screening preeclampsia have been developed. However, they cannot be used as screening test because of their false positive results and subjective interpretation. Hence there is immense need for validated test for identifying pregnant women who are at risk for development of pre-eclampsia

In our present study of asymptomatic pregnant women between 20 – 24 weeks gestation ,estimation of calcium – creatinine ratio at less than or equal to 0.04 in a spot urine sample was found to be a good test for predicting preeclampsia .It is also cost effective and can be used as a screening test for pregnant women. Estimation of urine microalbumin in a spot sample was a fair test for predicting preeclampsia. It is also not cost effective .As of present situation; using urine microalbumin alone cannot be used as screening test. Many more trials are needed to recommend it as a screening test.

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ANNEXURES

PROFORMA

Name

Age OP No.

LMP:

Date of visit:

Obstetric Formula:

Complaints:

Menstrual History: R / IR

Obstetric History:

S.No.	**Sex**	**Age**	**GA at Birth**	**Mode of Delivery**	**Birth wt**	**Interval**

PAST HISTORY:

FAMILY HISTORY**:**

GENARAL EXAMINATION:

Pallor Temp Edema Breast

HT Pulse CVS Thyroid:

PER ABDOMINAL EXAMINATION:

INVESTIGATIONS:

HB

PCV

VDRL

BT , CT

BLOOD SUGAR

BLOOD GROUP

BLOOD UREA

SERUM CREATININE

URINE – ALBUMIN

SUGAR

MICROSCOPY

URINARY CALCIUM

URINARY CREATININE

URINE CALCIUM/CREATININE RATIO

USG

Follow up:

At TERM – BP

MODE OF DELIVERY

Date	Gestation age	BP	Urine albumin By dipstic	S/S of Imminent eclampsia	Urine calcium-creatinine ratio	Urine microalbumin

MASTER CHART

Sl no	Name	Age	O.P. No	Obstetric code	Urine Calcium (mg/dl)	Urine Creatinine (mg/dl)	Urine CCR	Urine Micro Albumin (mg/lit)	Outcome	Onset of Preelampsia at Gestation Age (weeks)
1	NANDHINI	18	7093	primi	5.1	54	0.0944	79		
2	LAKSHMI	24	10477	primi	6.3	107	0.0589	10		
3	GIRIJA	20	19220	primi	8.2	145	0.0566	85		
4	NAGARANI	22	19234	$G_3P_2L_2$	5.4	218	0.0248	243	Developed Preeclampsia	37
5	LAKSHMI	28	15261	$G_2P_1L_1$	2.8	96	0.0292	68	Developed Preeclampsia	38
6	VINODHINI	19	19248	primi	4	66	0.0606	5		
7	PAPITHA	19	19256	primi	3.6	30	0.1200	13	Developed Preeclampsia	38
8	PREMA	27	19257	$G_2P_1L_1$	2	92	0.0217	15	Developed Preeclampsia	37
9	HARITHA	20	14107	primi	8	14	0.5714	6		
10	SELVI	22	4505	primi	5	118	0.0424	28		
11	SUGANYA	21	15663	primi	12	110	0.1091	9.7		
12	LATHA	30	19935	$G_2P_1L_1$	30	260	0.1154	25		
13	MALLIGA	35	18384	$G_2P_1L_1$	16.8	78	0.2154	23.5		
14	LATHA	27	5982	$G_2P_1L_1$	17.5	220	0.0795	25		
15	NADHIYA	25	20079	primi	6.3	84	0.0750	2.5		
16	ANITHA	30	15143	$G_2P_1L_1$	3.9	112	0.0348	35	Developed Preeclampsia	38
17	MANJUMARANI	22	9966	G_2A_1	14.8	165	0.0897	11.7		
18	BHAGIYAM	28	17812	primi	13.3	197	0.0675	11.9		
19	SELVARANI	25	20139	G_2A_1	19	157	0.1210	11.9		
20	SHEELA	20	20164	primi	12.3	151	0.0815	40		
21	NOORJAHAN	20	22882	primi	3.5	38	0.0921	13.3	Developed Preeclampsia	37
22	GOMATHI	24	20299	primi	24	220	0.1091	55		
23	MANJULA	29	20318	primi	7	58	0.1207	24		
24	MEGALA	26	20305	$G_4P_1L_1A_2$	17	86	0.1977	3.5		
25	VASANTHA KUMARI	20	16293	primi	4.2	95	0.0442	33		
26	DIVYA	26	17070	primi	19.4	245	0.0792	22		
27	REENA	20	20495	primi	10.1	62	0.1629	17.1		
28	TAMILSELVI	22	6750	G_2A_1	12.9	110	0.1173	41		
29	PONNI	24	18210	$G_3P_2L_1$	3.9	170	0.0229	17	Developed Preeclampsia	38
30	SEETHA	22	16548	primi	4	95	0.0421	4		
31	SARALA	20	11038	primi	3.5	108	0.0324	53	Developed Preeclampsia	37
32	KAVITHA	30	12623	$G_2P_1L_1$	14.5	180	0.0806	27		
33	SUGANYA	21	24341	$G_2P_1L_1$	5.6	105	0.0533	65		
34	RAMYA	20	24234	primi	6.7	75	0.0893	23		
35	KOMALA	28	26527	$G_2P_1L_1$	8.6	140	0.0614	29		

36	NITHYAKALYANI	23	29310	primi	5	275	0.0182	56	Developed Preeclampsia	37
37	INDHUMATHI	19	29779	primi	14.3	140	0.1021	2.3		
38	GIRIJA	21	28857	primi	45	197	0.2284	6.5		
39	KAVITHA	25	27182	$G_2P_1L_1$	10.8	60	0.1800	107		
40	SUMATHI	24	30189	primi	6.9	45	0.1533	22		
41	LAVANYA	20	22731	primi	8.5	180	0.0472	28.6		
42	PRIYA	23	14752	primi	14.9	142	0.1049	24		
43	SRIDEVI	20	17210	primi	14	65	0.2154	28		
44	MENAKA	22	29210	$G_2P_1L_1$	12	95	0.1263	15.4		
45	SENDHAMARAI	27	19978	$G_2P_1L_1$	6.5	240	0.0271	36.8	Developed Preeclampsia	38
46	SIVAGAMI	19	22733	primi	12	216	0.0556	20		
47	THENMOZHI	20	15715	primi	15	153	0.0980	18		
48	VEDHAVALLI	20	11875	primi	6	188	0.0319	40	Developed Preeclampsia	36
49	PREMA	22	22397	primi	6.9	30	0.2300	26		
50	HARIPRIYA	20	15718	$G_2P_1L_1$	4	50	0.0800	23		
51	BANU	20	15675	primi	7.1	125	0.0568	10.3		
52	DHANALAKSHMI	23	15569	primi	5	75	0.0667	13.7	Developed Preeclampsia	36
53	JANAKI	28	22988	$G_3P_2L_2$	25	40	0.6250	13		
54	AMULU	26	24123	primi	38	65	0.5846	16.7		
55	SARITHA	21	20153	primi	2.4	90	0.0267	32	Developed Preeclampsia	37
56	LAKSHMI	27	21644	primi	8	150	0.0533	12.8		
57	SAIRABEGAM	23	22737	primi	11	135	0.0815	9.6		
58	NALINI	23	30567	primi	18	125	0.1440	62		
59	SANGEETHA	26	15601	$G_4P_1L_1A_2$	12.5	30	0.4167	47		
60	MAHALAKSHMI	30	15587	$G_2P_1L_1$	6	25	0.2400	8.7		
61	KAVITHA	25	15584	$G_2P_1L_1$	7.6	60	0.1267	2.8		
62	KASTHURI	22	15127	primi	10	40	0.2500	3.1		
63	THULASI	20	15697	primi	6.5	50	0.1300	17.8		
64	SHAKIRA BEGAM	21	15566	primi	7	45	0.1556	11.7		
65	MALATHI	30	22989	$G_2P_1L_1$	5.1	55	0.0927	110		
66	UMA	27	22663	$G_2P_1L_1$	5.6	60	0.0933	13.5		
67	NIRMALA	25	22994	primi	4.8	35	0.1371	91		
68	BRINDHA	26	23655	$G_2P_1L_1$	6.4	45	0.1422	79		
69	LALITHA	24	22971	primi	5.5	155	0.0355	85	Developed Preeclampsia	38
70	SHARMILA	29	23656	primi	10.5	162	0.0648	28		
71	DURGA	23	23670	$G_2P_1L_1$	15.2	185	0.0822	26		
72	YASMIN	21	25628	primi	14.5	190	0.0763	12		
73	PRIYA	20	25732	primi	10.9	172	0.0634	28		
74	SHUBASHINI	23	25623	primi	16	175	0.0914	23.4		

75	DIVYA	22	25607	primi	18.2	188	0.0968	12		
76	SUGANYA	20	19076	primi	20	187	0.1070	10.6		
77	UMA	20	23667	primi	17.6	200	0.0880	20		
78	THOOYARASI	36	23662	primi	13.1	215	0.0609	25.5		
79	JAYANTHI	39	22684	$G_2P_1L_1$	14.8	186	0.0796	18		
80	SOWMIYA	20	21652	primi	11.8	174	0.0678	13		
81	NIRMALA DEVI	32	14568	$G_2P_1L_1$	12	196	0.0612	10		
82	SEETHA	32	16548	primi	5.2	160	0.0325	32	Developed Preeclampsia	37
83	SHANTHA KUMARI	23	24302	primi	15.5	176	0.0881	34		
84	AMUDHA	25	13463	$G_2P_1L_1$	14.2	198	0.0717	29		
85	THASLIM BANU	20	24301	primi	7.6	78	0.0974	23		
86	SHANTHI	28	19923	$G_2P_1L_1$	8.4	96	0.0875	12		
87	NARMADHA	22	18622	$G_3P_1L_1A_1$	6.7	86	0.0779	15.5		
88	SUDHA	26	15138	primi	4.8	37	0.1297	22		
89	BHARATHI	21	17351	$G_2P_1L_1$	5.5	82	0.0671	14		
90	DURGA DEVI	22	14233	primi	8	40	0.2000	6		
91	RAJERMUNISHA	21	19761	$G_2P_1L_1$	6.2	80	0.0775	8.4	Developed Preeclampsia	37
92	DHANALAKSHMI	26	17984	primi	4.5	165	0.0273	9.2	Developed Preeclampsia	36
93	FAMIDHA	26	22326	primi	4.8	170	0.0282	25		
94	RAJESHWARI	28	14916	G_2A_1	7.6	82	0.0927	28		
95	MUTHAMMA	25	19804	$G_2P_1L_0$	14.2	182	0.0780	29		
96	SHALINI	24	12661	G_3A_2	12	186	0.0645	29.5		
97	TAMILSELVI	31	13190	$G_3P_1L_1A_1$	14.4	198	0.0727	9.1		
98	VIJAYA	20	13196	primi	6.5	165	0.0394	31	Developed Preeclampsia	38
99	UMA MAHESWARI	24	13761	primi	4.8	156	0.0308	75	Developed Preeclampsia	39
100	JEEVITHA	20	10741	$G_2P_1L_1$	7.2	96	0.0750	12		
101	KANNAGI	20	12024	primi	12	154	0.0779	8.6		
102	REVATHI	26	10701	$G_3P_2L_2$	6.9	126	0.0548	2		
103	GEETHA	33	13798	primi	10.5	115	0.0913	10		
104	JOYCE	25	13825	primi	5.6	120	0.0467	12.5	Developed Preeclampsia	37
105	RADHA	26	13867	primi	12	126	0.0952	14		
106	RAMYA	23	13852	primi	6.2	86	0.0721	22		
107	VANISHREE	20	13837	primi	19	150	0.1267	29.8		
108	PUSHPA	28	9887	primi	24	226	0.1062	11.7		
109	NOORJAHAN	18	10628	primi	10.5	65	0.1615	11.8		
110	JAYANTHI	21	11656	primi	13	110	0.1182	12.6		
111	THENMOZHI	26	15099	primi	14.1	105	0.1343	17.4		
112	RENUKA	27	15101	$G_2P_1L_1$	9.6	186	0.0516	18.9		
113	HEMAVATHI	21	13160	primi	6.4	108	0.0593	9.6		

114	PREMALATHA	23	15123	primi	8.8	40	0.2200	21		
115	ASHKASIBEGAM	28	13781	primi	6.2	174	0.0356	26		
116	GEETHA	33	13789	primi	10.5	210	0.0500	25		
117	SHUBASHINI	31	15131	primi	14.2	115	0.1235	26		
118	DURGA DEVI	22	14233	primi	6.5	90	0.0722	28		
119	GAYATHRI	20	21279	primi	8.2	66	0.1242	29		
120	SHYAMALA	23	15344	primi	15	181	0.0829	27.7		
121	SABEENA	22	15351	primi	14	196	0.0714	9.2		
122	VIJAYA LAKSHMI	23	16173	primi	14.3	152	0.0941	7.4		
123	RATHNA	23	20159	$G_2P_1L_0$	25.6	220	0.1164	6		
124	CHITRALEKA	21	15147	$G_3P_1L_1A_1$	15.9	250	0.0636	20		
125	UMA MAHESWARI	20	22974	G_2A_1	16.5	200	0.0825	11		
126	LALITHA	24	23019	$G_2P_1L_1$	12	196	0.0612	13.5		
127	SHENBAGAM	24	19817	$G_2P_1L_1$	10	160	0.0625	24		
128	ZAHIDA BEGUM	23	16869	primi	6.4	172	0.0372	126	Developed Preeclampsia	37
129	JAMILA	28	24145	$G_3P_1L_1A_1$	10	160	0.0625	4		
130	HELEN MARY	20	21039	G_3A_2	14.6	182	0.0802	18		
131	DEVI	27	24718	$G_2P_1L_1$	26	118	0.2203	23		
132	KALAIVANI	25	28235	primi	18	220	0.0818	25		
133	NANDHINI	18	23833	primi	16.4	235	0.0698	5		
134	VENMADHI	22	28290	primi	18.1	190	0.0953	4.5		
135	RENUKA	27	27724	$G_3P_2L_2$	12.2	172	0.0709	20		
136	SARASWATHI	20	16031	primi	14.5	162	0.0895	10.5		
137	BHARATHI	21	20632	$G_2P_1L_1$	15	186	0.0806	12.4		
138	SUGANYA	20	21782	primi	12	180	0.0667	17.6		
139	ESHA	23	14773	primi	14	165	0.0848	20		
140	MANONMANI	25	16846	$G_2P_1L_1$	5.2	180	0.0289	26.7		
141	DHANALAKSHMI	26	22510	primi	6.5	105	0.0619	26		
142	SALOMI	23	10241	$G_3P_2L_2$	8.6	150	0.0573	28		
143	MAHESWARI	30	18410	primi	13	110	0.1182	12		
144	VANITHA	20	15004	primi	16.8	80	0.2100	14.3		
145	PARVATHI	34	15954	$G_3P_1L_1A_1$	20	162	0.1235	11.7		
146	HEMALATHA	21	25466	primi	3.3	38	0.0868	11.7	Developed Preeclampsia	38
147	VIMALA	29	27050	primi	12	152	0.0789	21.8		
148	NANDHINI	19	18406	primi	18.8	152	0.1237	29		
149	RAMYA VANI	18	16849	primi	4.2	190	0.0221	189	Developed Preeclampsia	35
150	KUTTIYAMMAL	20	25127	primi	12	115	0.1043	28		
151	PAVITHRA	24	15123	primi	8.3	6.7	1.2388	11.9		
152	RADHIKA	23	20156	primi	11.5	210	0.0548	10.7		

153	LAKSHMI	28	24633	primi	6.2	90	0.0689	9		
154	RAJESHWARI	24	27301	primi	24	210	0.1143	3		
155	SYED ALI FATHIMA	26	18550	$G_2P_1L_1$	15.4	211	0.0730	3.3		
156	LAKSHMI	28	15201	$G_4P_2L_2A_1$	7.5	92	0.0815	2.5		
157	VENKATA LAKSHMI	28	26571	primi	8.2	94	0.0872	4.9		
158	VASANTHI	27	24688	$G_3P_2L_2$	7.2	84	0.0857	28		
159	JAYANTHI	20	24711	primi	6.7	96	0.0698	18		
160	NIRMALA	22	18331	primi	9.2	220	0.0418	19.2		
161	MUSTAN BEE	30	18243	$G_2P_1L_1$	13.7	125	0.1096	6.7		
162	VALARMATHI	20	23485	primi	3.8	45	0.0844	141		
163	SARASWATHI	30	19928	$G_2P_1L_1$	2.5	55	0.0455	25	Developed Preeclampsia	37
164	SANKARI	23	18370	$G_2P_1L_1$	1.9	50	0.0380	3		
165	SARITHA	27	10135	G_3A_2	17.5	55	0.3182	32		
166	RAJESWARI	20	23533	primi	13.5	105	0.1286	16.4		
167	SONI	22	23637	primi	10	190	0.0526	6.9		
168	SUBHALAKSHMI	21	10487	$G_2P_1L_1$	9.2	50	0.1840	6		
169	JAYANTHI	20	21069	primi	10.7	195	0.0549	171		
170	GUNASUNDARI	23	6793	$G_2P_1L_1$	9.5	29	0.3276	1		
171	SUSHEELA	35	21128	primi	11.8	215	0.0549	1.2		
172	JAYESHREE	25	13742	$G_2P_1L_1$	5.6	355	0.0158	75	Developed Preeclampsia	35
173	POORNIMA	24	21141	$G_2P_1L_1$	8.1	190	0.0426	26.3		
174	CHITHRA	22	23385	$G_2P_1L_1$	10.2	120	0.0850	3.8		
175	KANIMOZHI	29	12861	primi	11.7	330	0.0355	160	Developed Preeclampsia	36
176	SUGANYA	20	21612	primi	7.2	35	0.2057	124		
177	ABDUL BEEVI	22	15726	$G_2P_1L_1$	5.9	100	0.0590	79.1		
178	PRIYA	30	23661	primi	11.6	120	0.0967	70		
179	SOWMIYA	20	24354	primi	5.5	75	0.0733	14.3		
180	BENITHA JENIFER	21	19936	G_2A_1	17.1	105	0.1629	33		
181	LAKSHMI	24	19460	primi	8.2	30	0.2733	29		
182	PADMAVATHI	29	22776	primi	13.4	100	0.1340	38		
183	BARKATHBANU	19	14311	primi	12.2	236	0.0517	18		
184	SHANTHI	26	8845	primi	8.4	30	0.2800	14		
185	SHERIN BANU	19	23811	primi	9.5	30	0.3167	2.9		
186	SUJATHA	28	19917	primi	7.1	87	0.0816	14		
187	RAMYA	23	18466	primi	12.3	145	0.0848	10.3		
188	PRAVEENA	21	15029	primi	7.1	80	0.0888	72		
189	KOKILA	25	20960	G_3A_2	7.7	123	0.0626	51		
190	ESHWARI	27	16038	primi	14.1	138	0.1022	52		
191	ILAKKIYA	19	24223	primi	11.7	62	0.1887	49		

192	MAHALAKSHMI	25	6960	$G_2P_1L_1$	8.4	42	0.2000	24		
193	DEVIKA	23	11982	primi	14.9	112	0.1330	12.6		
194	AYESHYA	24	13931	$G_2P_1L_0$	11.2	196	0.0571	11.9		
195	JAYAMALA	23	11986	$G_2P_1L_1$	12.5	142	0.0880	25.6		
196	BHAVANI	23	11452	$G_2P_1L_1$	8.6	92	0.0935	28		
197	MALA	31	8850	$G_2P_1L_1$	7.8	45	0.1733	26.4		
198	VAISHNAVI	19	12655	primi	8.2	30	0.2733	29		
199	BANUPRIYA	22	20953	$G_2P_1L_1$	12.6	152	0.0829	22		
200	SRIVIDYA	22	22172	$G_2P_1L_1$	11.5	172	0.0669	10.5		

ABBREVIATIONS

ACOG	American College of Obstetrics and Gynaecology
BMI	Body Mass Index
BP	Blood Pressure
ET	Endothelin
NHBEP	National High Blood Pressure Education Program
NO	Nitric Oxide
OCPC	Ortho Cresolpthaleincomplexone reaction
PTH	Parathyroid Harmone
p value	Probability value
PlGF	Placental Growth Factor
SFlT	Soluble FMS like Tyrosine kinase
S eng	Soluble endoglin
VEGF	Vascular Endothelial Growth Factor
UCCR	Urine Calcium Creatinine Ratio

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Calcium creatinine ratio and microalbuminuria as Recommendation for screening test of pre-eclampsia

Principal Investigator : Dr.A.Poornima

Designation : P.G. in M.S (OG)

Department : Department of O & G
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 07.02.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

7/2/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI