THE ROLE OF SERUM CALCIUM, MAGNESIUM AND ZINC IN PREGNANCY INDUCED HYPERTENSION

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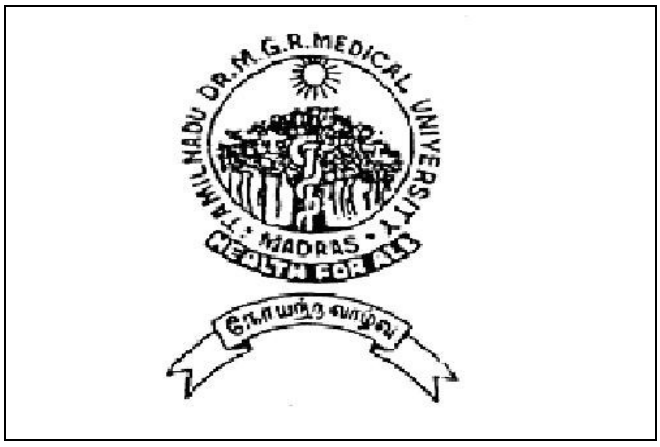

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"THE ROLE OF SERUM CALCIUM, MAGNESIUM AND ZINC IN PREGNANCY INDUCED HYPERTENSION",** is a bonafide record work done by **Dr.K.VIDHYA,** under my direct supervision and guidance, submitted to The Tamilnadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for M.D Branch -V (Physiology).

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DECLARATION

I **Dr. K. VIDHYA,** solemnly declare that the dissertation titled **"THE ROLE OF SERUM CALCIUM, MAGNESIUM AND ZINC IN PREGNANCY INDUCED HYPERTENSION"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.D degree Branch – V (Physiology) to be held in April 2012.

Place: Madurai **Dr.K.VIDHYA**

Date:

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CONTENTS

THE ROLE OF SERUM CALCIUM, MAGNESIUM AND ZINC IN PREGNANCY INDUCED HYPERTENSION

Abstract:

Aim and Objective:

Pregnancy induced hypertension or preeclampsia is triad of hypertension, proteinuria and edema occurring after 20 weeks of gestation in previously normotensive women. It is the most common medical complication of pregnancy with incidence of 5% to 10% with increased in maternal and infant mortality and morbidity. The exact etiology is not known although various elements might play a role in preeclampsia.
The aim of the study is to analyze and compare the concentration of serum calcium, magnesium and zinc level in women with preeclampsia and in normal pregnant women.

Materials and Methods:

This is a cross sectional case-control study involving 25 women with pre-eclampsia in case group and 25 normal pregnant women in control group. The inclusion criteria for case group were age group in between 20-40 yrs including both primi and second gravida in third trimester of pregnancy (>24 weeks of pregnancy). The blood pressure measured by sphygmomanometer in upper arm in sitting posture was ≥140/90mmHg in two different occasions taken 6 hours apart. The urine albumin was ≥1+ or in the mid stream random sample of urine. The controls group was formed by 25 age matched normal pregnant women either primi or second gravida in third trimester of pregnancy. The patients with medical complications such as Diabetes Mellitus, renal failure, chronic hypertension, heart failure or ischaemic heart disease, multiple pregnancies, pregnancy < 24 weeks of gestation, patients on magnesium sulphate and calcium lactate therapy were excluded from the study.
The Body Mass Index (BMI), serum calcium, magnesium and zinc levels were compared between the case and control groups.

Results:

The BMI was significantly higher in preeclamptic women when compared to normal pregnant women 28.71±4.70 versus 22.46±3.42 P<0.001. The serum calcium, magnesium and zinc levels in preeclamptic women were significantly lower when compared to normal pregnant women 8.07±0.43 versus 8.96±0.59 P<0.001, 1.62±0.16 versus 1.92±0.16 p<0.001, 80.7±9.78 versus 93.28±9.44 for cases and controls respectively.

Conclusion:

Although the calcium, magnesium and zinc deficiency cannot be pinpointed as the sole factors for the etiology of preeclampsia, they have a definite role in the development of preeclampsia.

Key words: Preeclampsia, serum calcium, serum magnesium and serum Zinc.

INTRODUCTION

Nutritional deficiencies are common during pregnancy. Pregnant women in the developing countries have been reported to consume diets that are low in minerals and vitamins **Begum *et al.,* 2000**. An inadequate dietary intake before and during pregnancy might be a risk not only for the mother but also for the fetus. Deficiency of the elements such as magnesium, zinc have been implicated in the pregnancy wastage, congenital anomalies, pregnancy induced hypertension, placental abruption of membrane, low birth weight and still births **Hofmeyr *et al.,* 2007**.

On the physiological basis, calcium plays an important role in muscle contraction and the modification of plasma calcium concentration leads to an alteration in the blood pressure. Magnesium has been known as an essential cofactor for many enzyme systems. It also plays an important role in the neurochemical transmission and peripheral vasodilatation. Zinc is required for the DNA replication, transcription and cellular replication as it is the metallic component of various related enzymes (i.e) DNA polymerase, RNA polymerase and thymidine

kinase. Essentiality of the zinc during pregnancy is evident. In the zinc deficient animals and women poor outcome of pregnancy is observed **Carey *et al.*, 2000**.

Pregnancy induced hypertension or preeclampsia is a transient but potentially dangerous complication of pregnancy, with worldwide significance to the mother and the infants. It affects approximately 5-10% of the pregnancies world wide **Skjaervan *et al.*, 2002** and results in 15% of preterm deliveries and 14% of maternal deaths per year **Belizan *et al.*, 1983.** In the developing countries, preeclampsia accounts for 20-80% of the strikingly increased maternal mortality **Sarsam *et al.*, 2008**. In India the incidence of preeclampsia is reported to be 8-10% of pregnancies.

Preeclampsia has been dubbed as the 'Disease of theories' because of the multiple hypothesis that have been proposed to explain its occurrence. Although many pathophysiologic factors such as inflammation, cytokine production, dyslipidaemia **Hube, 1998**, elevated homocysteine Laivuori ***et al.*, 1999**, oxidative stress **Roberts and Hubel, 2004**, reduced calcium intake and

excretion and an imbalance between the thromboxane and prostacyclin **Paknahad *et al.,* 2008** have been implicated in the etiology of preeclampsia, the complete etiologies have not been fully elucidated **Golmohammad *et al.,* 2008**.

Although the high rate of preeclampsia in developing countries has forced some authors to propose the involvement of the nutrition, especially the trace elements in the etiology of the disorder **Caughey *et al.,* 2005** studies on the relationship between the maternal serum trace elements concentrations and the preeclampsia have produced inconsistent results **Harma *et al.,* 2005**.

Hence this study is taken up to analyze and to compare the concentrations of calcium, magnesium and zinc in the serum of women with preeclampsia and in the normal pregnant women and to evaluate their role in the pregnancy induced hypertension.

It is hoped that this study will contribute to the knowledge of the role of serum calcium, magnesium and zinc in pregnancy induced hypertension.

AIM AND OBJECTIVES

This study involves

1) The estimation of serum calcium, magnesium and zinc levels in preeclamptic women in their third trimester of pregnancy as patients group.
2) The estimation of the serum calcium, magnesium and zinc levels in age matched healthy normotensive pregnant women in third trimester as control group.
3) Comparison of concentration of calcium, magnesium and zinc in the serum between the patient and the control group.
4) To evaluate the role of calcium, magnesium and zinc in pregnancy induced hypertension.

REVIEW OF LITERATURE

PREGNANCY INDUCED HYPERTENSION

Pregnancy induced hypertension or preeclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after 20 weeks of pregnancy in previously normal and non-proteinuric patient.

Historical aspects:

The fact that some pregnant women had epileptiform fits was known to Hippocrates, who lived in the fourth century BC. The condition was called eclampsia, although the word does not refer to fits. The original Greek word meant **flash out**, in the sense of sudden event. Little more was known about eclampsia, until **John Lever** in **1843** found that many of the women who had fits also had albumin in their urine. However, it was not until early in this century, when the sphygmomanometer was introduced, it was recognized that eclampsia was associated with hypertension, which could precede the onset of fits, give rise to the concept of preeclampsia as a clinical condition.

For many years it was postulated that toxins was liberated from the pregnant uterus and the disorder became known as **toxemia of pregnancy**. All efforts have so far failed to demonstrate any such toxin and the word toxemia is now avoided.

The Placenta:

Historical aspects:

The placenta was already recognized and venerated by early Egyptians, while it was the Greek physician **Diogenes of Apollonica** (Ca.480 BC) who first ascribed the function of fetal nutrition of the organ. **Arsitolle** (384-322 BC) described that the fetus is fully enclosed within the membranes and it was only during the **Renaisance** that the term placenta, the word derived from the Latin root meaning a **"flat cake"** was introduced by **Realdus Colombus in 1559**.

Placental organization:

The term **hemochorial** is used to describe human placentation. It derives from hemo referring to the maternal blood, which directly baths the syncytiotrophoblast and the chorio for chorion (Placenta).

Chorionic villi:

Approximately on the 12th day after fertilization chorionic villi can first be distinguished. Mesenchymal cords derived from the extraembryonic mesoderm invade the solid trophoblast and this forms secondary villi. After angiogenesis begins in the mesenchymal cords, the resulting villi are termed as tertiary villi.

Villi are covered by the outer layer of syncytium and inner layer of cytotrophoblast, which are known as **Langhans cells**. Cytotrophoblast proliferation at the villi tips produces the trophoblastic cell columns that form anchoring villi.

Placental development:

Development of chorion and decidua:

In early pregnancy, the villi are distributed over the entire periphery of chorionic membrane. As the blastocyst with its surrounding trophoblasts grows and expands into the decidua, one pole extends outwards towards the endometrial cavity. The opposite pole will form the placenta from villous trophoblasts and anchoring cytotrophoblast. Chorionic villi in contact with the

decidua basalis proliferate to form the **chorionic frondosum**, which is the fetal component of the placenta.

Maternal regulation of trophoblast invasion and the vascular growth:

Decidual natural killer cells accumulate in the decidua during the first half of the pregnancy and are found in direct contact with the trophoblast. These cells lack the cytotoxic functions as well as other unique properties that distinguish them from circulating natural killer cells**.** This is important because it prevents them from recognizing and destroying the fetal cells as "foreign". The decidual natural killer cells attract and promote th**e** invasion of trophoblast into decidua and promote the vascular growth **Hana and associate 2006**. The Decidual natural killer cells express both **interleukin-8** and **interferon inducible protein-10**, which binds to receptors on invasive trophoblast, cells to promote their invasion into decidua towards spiral arteries. Decidual natural killer cells also produce proangiogenic factors including the vascular endothelial growth factor (VEGF) and the

placental growth factor (PGF), which promote vascular growth in decidua.

Trophoblast invasion of endometrium:

The extravillious trophoblasts are highly invasive. They form columns of cells that extend from the endometrium to the inner third of myometrium. The invasive ability of trophoblasts results from their ability to secrete numerous proteolytic enzymes capable of digesting the extracellullar matrix as well as activating proteinases already present in the endometrium. Trophoblasts produce urokinase type plasminogen activator, which converts the plasminogen into the broadly acting serine protease plasmin. This in turn both degrades mature proteins and activates matrix metalloproteinases (MMPs), which are a family of structurally similar enzymes. One member of the family, Matrix metalloproteinase-9 (MMP-9), appears to be critical for the human trophoblast invasion. MMP-9 production is increased by the trophoblast factors such as IL-1 and hCG as well as paracrine uterine factors such as leukemia inhibiting factor and colony-stimulating factor-1 **Bischof, 2009**.

Invasion of spiral arteries:

One of the most remarkable features of human placental development is the extensive modification of maternal vasculature by trophoblasts. Modifications of spiral arteries are carried out by two populations of extravillous trophoblast (i) interstitial trophoblast that surrounds the arteries and (ii) endovascular trophoblast, which penetrate the spiral arterial lumen. Although earlier work has focused on the role of endovascular trophoblast, function of interstial trophoblast has more recently been investigated **Pijnenborg and colleague, 1983.**

Endovascular trophoblast enters the lumen of spiral arteries and initially forms the cellular plugs. It then destroys vascular endothelium via an apoptosis mechanism, which invades and modifies the vascular media. Thus the fibrinoid material replaces smooth muscle and connective tissue of the vascular media. The spiral artery later regenerates the endothelium.

The development of the uteroplacental vessels proceeds in two waves of stages. The first occurs before 12^{th} weeks post fertilization and consists of invasion and modification of the spiral

arteries upto the border between decidua and the myometrium. The second wave is between 12th and 16th weeks and involves some invasion of intra myometrial segments of the spiral arteries. The remodelling by this two-phase invasion converts the narrow lumen muscular spiral arteries into dilated, low resistance uteroplacental vessels.

Placental growth:

In the first trimester, placental growth is more rapid than that of the fetus. By approximately 17th postmenstrual weeks, placenta and fetal weight are almost equal. By term, the placental weight is about one sixth of the fetal weight. The average placenta at term is 185mm in diameter and 23mm in thickness, with a volume of 497 ml and weight of 508 gm. Viewed from the maternal surface, the number of slightly elevated convex areas, called **lobes** varies from 10 to 38 **William Obstetrics 23rd edition**. The total number of placental lobes remains the same throughout gestation and individual lobes continue to grow although less actively at term **Crawford, 1959**.

Terminology and Classification:

The working group of National High Blood Pressure Education Program **NHBPEP (2000)** classification of hypertensive disorder complicating pregnancy is

1) Gestational hypertension
2) Preeclampsia and eclampsia syndrome
3) Preeclampsia syndrome superimposed on chronic hypertension and
4) Chronic hypertension.

1) Gestational hypertension:

- Systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg for the first time during pregnancy.
- No proteinuria.
- BP returns to normal before 12 weeks post partum.

2) Preeclampsia and eclampsia syndrome:

Preeclampsia:

Minimum Criteria:

- BP ≥ 140/90 mmHg after 20 weeks of gestation.
- Proteinuria ≥ 300mg/24 hrs or ≥ 1+ dipstick.

Increased certainty of preeclampsia:

- BP ≥ 160/100 mmHg.
- Proteinuria 2.0gm/24 hrs or ≥ 2+ dipstick.
- Serum creatinine > 1.2mg/dl unless known to be previously elevated.
- Platelets < 100000/µl of blood.
- Microangiopathic hemolysis – increased lactate dehydrogenase (LDH).
- Elevated serum transaminase level – alanine aminotransferase (ALT) or aspartate aminotransferase (AST).
- Persistent headache or other cerebral or visual disturbance.
- Persistent epigastric pain.

Eclampsia:

- Seizure that cannot be attributed to other causes in women with preeclampsia.

3) Superimposed preeclampsia on chronic hypertension:

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

- A sudden increase in proteinuria or blood pressure or platelet count < 100000/μl in women with hypertension and proteinuria before 20 weeks gestation.

4) Chronic hypertension:

- BP ≥ 140/90 mmHg before pregnancy or diagnosed before 20 weeks gestation not attributable to gestational trophoblastic disease.

(Or)

- Hypertension first diagnosed after 20 weeks gestation and persistent after 12 weeks post partum.

Etiology:

Preeclamsia as a two-stage disorder:

Observations that the abnormal interfaces between maternal, paternal and fetal tissues may cause preeclampsia have led to hypotheses that the syndrome is a two stage disorders. In this scenario, there is a spectrum to include "Maternal and Placental preeclampsia" **Ness and Roberts, 1996**.

Stage 1 is caused by the faulty endovascular trophoblastic remodelling that downstream causes the stage 2 clinical

syndrome. Importantly, stage 2 is susceptible to modification by the preexisting maternal condition that includes cardiac or renal diseases, diabetes, obesity or hereditary influences.

Abnormal trophoblastic invasion:

In the normal implantation, the uterine spiral arterioles undergo extensive remodelling as they are invaded by endovascular trophoblast. These cells replace the vascular endothelial and muscular linings to enlarge the vessel diameter. The veins are invaded only superficially in preeclampsia, which may be due to an incomplete trophoblastic invasion. The deeper myometrial arterioles do not lose their endothelial lining and muscular elastic tissue, their mean external diameter is only half that of vessels in normal placenta. The magnitude of defective trophoblastic invasion of the spiral arteries correlates with severity of the hypertension disorder **Madazli and associates, 2000**. **De wolf and co-workers**, **1980** examined arteries taken from implantation site and reported that early preeclamptic changes included endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells and medial

necrosis. Lipid accumulated first in myointimal cells and then within macrophages. Lipid laden cells and associated findings referred as **atherosis** by **Hertig, 1945**.

Immunological factors

Loss of maternal immune tolerance to the paternally derived placenta and fetal antigen and its dysregulation is another theory cited to account for preeclampsia syndrome. It has been proposed that endothelial cell dysfunction is due to an extreme activated state of leucocyte in maternal circulation **Faas, 2000.**

Nutritional factors:

In general population, a diet high in fruits and vegetables that have antioxidant activity is associated with decrease in blood pressure **John and co-workers 2002**. The incidence of preeclampsia was doubled in women whose daily intake of ascorbic acid was less than 85 mg **Zhang and associates 2002**.

Genetic factors:

Preeclampsia is a multifactorial, polygenic disorder. Incident risk of preeclampsia is 20-40% of daughter of

preeclamptic mothers, 11-37% for sisters of preeclamptic women and 20-47% in twin studies **Wang et al**., **2002.**

Pathophysiology:

Vasospasm:

In preeclampsia the blood vessels throughout the body undergo vasoconstriction. The constricted segments contribute to the heightened peripheral resistance and hence hypertension. At the same time, the endothelial cell damage cause interstitial leakage through which blood constituents including platelets and fibrinogen are deposited subendothelially. With diminished blood flow because of maldistribution, ischaemia of the surrounding tissue would lead to necrosis, hemorrhage and other end-organ disturbances characteristic of the syndrome **Suzuki and co-workers 2003**.

Endothelial cell activation:

The clinical syndrome of preeclampsia is thought to result from these widespread endothelial cell changes. Circulating endothelial cell CEC levels are significantly elevated fourfold in the peripheral blood of preeclamptic women **Grundmann and**

associates 2008. Damaged or activated endothelial cell may produce less nitric oxide and secrete substances that promote coagulation and increased sensitivity to vasopressors.

Increased pressor response:

The pregnant women normally develop refractoriness to infused vasopressors. Women with early preeclampsia, however have increased vascular reactivity to infused norepinephrine and angiotensin II. Normotensive nulliparas remain refractory to infused angiotensin II but those who subsequently become hypertensive lost this refractoriness several weeks before the onset of hypertension.

Prostaglandins:

A number of prostanoids are thought to be central to the pathophysiology of the preeclampsia syndrome. Specifically, the blunted pressor response seen in normal pregnancy is atleast partially due to the decreased vascular responsiveness mediated by the endothelial prostaglandin synthesis. The endothelial prostacyclin (PGI_2) production is decreased in preeclampsia. This action is mediated by phospholipase A_2. At the same time

thromboxane A_2 secretion by platelet is increased and prostocyclin : thromboxane A_2 ratio decreases. The net result favour increased sensitivity to infused angiotensin II and ultimately vasoconstriction **Spitz and colleagues, 1988**.

Nitric oxide:

The potent vasodilator is synthesized from L-arginine by the endothelial cells. Withdrawal of nitric oxide results in a clinical picture similar to preeclampsia in a pregnant animal model. In human, nitric oxide is the compound that maintains the normal low pressure, vasodilated state characteristic of fetoplacental perfusion.

Endothelins:

These 21 amino acid peptides are potent vasoconstrictors, and endothelin-1 (ET-1) is the primary isoform produced by the human endothelium. Plasma ET-1 levels are increased in normotensive pregnant women but women with preeclampsia have higher levels **Ajne, 2003.** The placenta is not the source of increased ET-1 concentration and they likely arise from systemic endothelial activation. The treatment of preeclamptic women with

magnesium sulphate lowers ET-1 concentration **Sagsoz and Kucukozkan 2003**.

Angiogenic and antiangiogenic proteins:

Placental vasculogensis is evident by 21 days after conception. There are many pro and anti angiogenic substance involved in placental vascular development. In preeclampsia there exists an angiogenic imbalance with excessive amounts of antiangiogenic factors are hypothesized to be stimulated by worsening of hypoxia at the uteroplacental interface. Trophoblastic tissue of women destined to develop preeclampsia overproduces atleast two antiangiogenic peptides that enter maternal circulation.

1. Soluable Fms-like tyrosine kinase 1 (sFlt-1) is a variant of the Flt-1 receptor decreases the circulating free placental growth factor (PGF) and vascular endothelial growth factor (VEGF) concentration leading to the endothelial dysfunction.
2. Soluble endoglin (sEng) is a placenta derived 65-kDa molecule is a co-receptor for the TGF-β family. This soluble form of endoglin inhibits various TGF-β isotopes from binding to

endothelial receptors and results in decreased endothelial nitric oxide dependant vasodilatation **Levine and co-workers 2006.**

Although the cause of preeclampsia still remains unknown, evidence for its manifestation begins early in pregnancy with covert pathophysiological changes that gain momentum across gestation and eventually become clinically apparent. Unless delivery supervenes, these changes ultimately results in the multi-organ involvement that can be life threatening for both mother and fetus.

Changes in Maternal system:

The cardiovascular system:

Severe disturbance of normal cardiovascular functions in preeclampsia are related to

1) Increased cardiac afterload caused by hypertension.

2) Cardiac preload, which is substantively affected by pathologically diminished hypervolemia of pregnancy.

3) Endothelial activation with extravasation of intravascular fluid into extracellular space and importantly into the lungs.

Apart from left ventricular mass increase in normal pregnancy there is no convincing evidence that additional structural changes are induced by preeclampsia.

The Blood volume:

In preeclamptic women the normally expected hypervolemia is severely curtailed and in some women, even absent **Zeeman and colleague, 2009.** The women of average size should have blood volume nearly 5000ml during last several weeks of normal pregnancy compared with approximately 3500ml of when not pregnant. With preeclampsia however much or all of the anticipated normal excess 1500ml is lost. Such hemoconcentration results from generalized vasoconstriction that follows endothelial activation and leakage of plasma into interstitial space because of increased permeability. Women with gestational hypertension but without preeclampsia, usually have a normal blood volume **Silver and colleagues, 1998.**

The blood and coagulation:

Thrombocytopenia:

Thrombocytopenia with preeclampsia has been described atleast since 1922 by **Stancke**. The frequency and the intensity of thrombocytopenia vary and are dependent on the severity and duration of preeclampsia syndrome. The overt thrombocytopenia defined by platelet count < 1,00,000/µl – indicates severe disease. In general, the lower the platelets count, higher the rates of maternal and fetal morbidity and mortality **Leduc and co-workers, 1992**. In addition to thrombocytopenia the other platelet alteration include platelet activation with increased degranulation, thromboxane A_2 release and decreased life span.

Hemolysis:

Severe preeclampsia is frequently accompanied by evidence of hemolysis. It is evidenced by elevated serum lactate dehydrogenase levels and the other evidences are schizocytes, spherocytosis and reticulocytosis in peripheral blood.

Coagulation:

There is increased factor VIII consumption, increased levels of fibrinopeptides A and B and of fibrin degradation products and decreased levels of regulatory proteins antithrombin III and protein C and S.

The Endocrine changes:

Plasma levels of renin, angiotensin II and aldosterone are substantively increased during normal pregnancy. With preeclampsia, despite decreased blood volume, these values decreased substantively, but still remain above the non-pregnant values.

The Kidneys:

During normal pregnancy, the renal blood flow and glomerular filtration rate are increased appreciably. With development of preeclampsia, renal perfusion and filtration are reduced. Mildly diminished glomerular filtration may result from reduced plasma volume. Most of the decrement is probably from increased renal afferent arteriolar resistance that may be elevated upto five fold. The morphological changes include glomerular

endotheliosis, blocking the filtration barrier. Diminished filtration cause serum creatinine values to rise than the values seen in non pregnant individuals. Plasma uric acid concentration is typically elevated in preeclampsia. This elevation is likely due to enhanced tubular reabsorption **Chesley and Williams, 1945**. Another possibility is from increased placental urate production compensatory to increased oxidative stress.

Proteinuria:

At least some degree of proteinuria will establish the diagnosis of preeclampsia. Proteinuria may develop late and some women may be delivered or have an eclamptic convulsion before it appears. 10-15 percent of women with HELLP syndrome did not have proteinuria at presentation. 17 percent of eclamptic women did not have proteinuria by the time of seizures **Sibai, 2004.**

Another problem is that the optimal method of establishing either abnormal levels of urine protein or albumin remains to be defined. The clean catch and catheterized urine specimen correlate well. The dipstick qualitative determinations depend on the

urinary concentration and notorious for the false-positive and negative results. There are several methods used to measure proteinuria, and none detect all of the various proteins normally excreted. A more accurate method involves measurement of albumin excretion. Albumin filtration exceeds that of larger globulins, and with glomerular disease such as preeclampsia, much of the protein in the urine is albumin.

Finally, although the worsening proteinuria has been considered by most to be sign of severe disease the quality of protein alone as an indicator of preeclampsia severity is currently being investigated **Airoldi and Weinstein, 2007.**

Anatomical changes:

Glomeruli are enlarged by approximately 20 percent; they are "bloodless" and capillary loops variably dilated and contracted. Endothelial cells are swollen, and this was termed glomerular capillary endotheliosis by **Spargo and associates, 1959**. Endothelial cells are often so swollen that they block or partially block the capillary lumens. Homogenous subendothelial deposits of proteins and fibrin-like material are seen. Rarely acute

tubular necrosis and acute renal failure develops in women with preeclampsia.

The Liver:

The characteristic lesions commonly found were regions of periportal hemorrhage in liver periphery. The microhemorrhages may then coalesce to give rise to a subcapsular hematoma. In rare instances, the hemorrhage may further increase to cause liver rupture and hemoperitoneum.

HELLP Syndrome:

HELLP is an acronym, which was coined by **Louis Weinstein 1892** denoting Hemolysis, Elevated liver enzymes and Low platelets. It is a recognized complication of severe preeclampsia although at times, it can occur in the absence of hypertension and proteinuria. It occurs in 0.2-0.6% of all pregnancies and 4-12% pregnancies complicated by preeclampsia **Ian Donald, 6th edition**.

The Nervous System:

The cerebral pathology comprises thrombosis, fibrinoid necrosis of cerebral arterioles, diffuse microinfarcts and petechial

hemorrhages. Reversible foci of cerebral ischemia or oedema have also been identified on magnetic resonance imaging usually in the posterior cerebral circulation. The cause for the cerebral dysfunction of preeclampsia is not known. The autopsy evidence that the problem is of ischemia secondary to intense vasoconstriction.

The visual changes:

Scotoma, blurred vision or diplopias are common with severe preeclampsia. Blindness is less common, usually reversible and may arise from three potential areas. These are visual cortex of occipital lobe, lateral geniculate nuclei and retina. In retina, lesions may include ischemia, infarction and detachment.

The Uteroplacental circulation:

Impairment of the uteroplacental circulation affects the placental functions that sustain the fetus. Preeclampsia is considered to be a maternal disorder in which the fetus is an incidental participant, but from the fetus's point of view, it could be a fetal disorder in which the mother is an incidental participant **Turnbull's Obstetrics 2nd edition**. It is a placental disorder,

which causes both maternal and fetal syndromes. Preeclampsia is an important cause of intrauterine growth retardation in congenitally normal singletons. Fetal growth failure is more a feature of early onset disease. Perinatal mortality increases once proteinuria is established. About three quarters of the excess mortality can be explained by overt placental pathology consistent with the view that preeclampsia is a primary placental disease **Naeye & Friedman, 1979**.

THE CALCIUM

Introduction:

The calcium is the fifth most common elements in our body. Physiologically calcium is classified as either intracellular or extra cellular. The Intracellular calcium has many important functions including muscle contraction, hormone secretion, glycogen metabolism and cell division. The extracellular calcium provides calcium ion for maintenance of the intracellular calcium, bone mineralisation, blood coagulation and plasma membrane potential.

The total body calcium in adult human is 1-2 Kg. The skeleton contains 99% of body calcium, 0.1% of total body calcium is in the extracellular fluid. 1% of calcium is present inside the cells. In blood the total calcium concentration is normally 8.5 – 10.5 mg/dl (2.2 – 2.6 mmol/l) **Harrison Principle of internal medicine 17th edition.**

The calcium in plasma present in three forms (1) About 41% of calcium is combined with plasma proteins and in this form is non-diffusible through capillary membrane. (2) About 9% is diffusible through the capillary membrane but is combined with

anionic substance of plasma and interstitial fluids (Citrate & phosphate) in such manner that is is not ionized. (3) Remaining 50% of calcium is diffusible through capillary membrane and is ionized **Guyton and Hall 11th edition.**

The concentration of ionized calcium in extracellular fluid must be maintained within a narrow range because of the critical role it plays in wide array of cellular functions, especially those involved in neuromuscular activity, secretion and signal transduction. Control of the ionized calcium concentration in extracellular fluid is accomplished by adjusting the rates of calcium movement across intestinal and renal epithelia.

These adjustments are mediated mainly via changes in the blood levels of hormones parathyroid hormone and 1,25-dihydroxycholecalciferol. Blood ionized calcium directly suppresses the PTH secretion by activating parathyroid calcium sensing receptors (CaSRs). Also ionized calcium indirectly affects PTH secretion via effects on 1,25-dihydroxycholecalciferol production. This active vitamin D metabolite inhibits PTH

production by an incomplete understood mechanism of negative feedback.

Even slightest decrease in the calcium ion concentration in extracellular fluid caused the parathyroid glands to increase their rate of secretion within minutes. The PTH stimulates enough calcium absorption from the bones to maintain a normal plasma ion concentration. Conversely the conditions that increase the serum ionized calcium lead to decrease in PTH secretion.

Calcium in vascular tone regulation:

The vascular smooth muscle cells contract when stimulated by rise in intracellular calcium concentration by calcium influx through the plasma membrane and calcium release from intracellular stores. In vascular smooth muscle cells, voltage – dependent L-type calcium channels open with membrane depolarization, which is regulated by energy – dependent ion pumps such as $Na^{+}K^{+}$-ATPase and ion channels such as the Ca^{2+} sensitive K^{+} channels. Local changes in the intracellular calcium concentration, termed as calcium sparks, results from the influx of calcium through the voltage- dependent calcium channel and are

caused by the co-ordinated activation of a cluster of ryanodine-sensitive calcium release channels in the sarcoplasmic reticulum. The calcium sparks lead to a further direct increase in intracellular calcium concentration.

Vascular smooth muscle cell contraction is principally controlled by the phosphorylation of myosin light chain kinase and myosin light chain phosphatase. Myosin light chain kinase is activated by calcium through the formation of calcium-calmodulin complex; with the phosphorylation of myosin light chain by this kinase, the myosin ATPase activity increased and contraction sustained. Myosin light chain phosphatase dephosphorylates myosin light chain, reducing myosin ATPase activity and contractile force.

The role of calcium in pregnancy induced hypertension:

Abnormalities in Calcium homeostasis may contribute to the increased vascular sensitivity in preeclampsia. Calcium metabolism is under strain during pregnancy. The daily requirement of calcium during pregnancy is 1200mg. The expectant mothers need to store about 30-50gm of calcium during

the course of pregnancy, of which 25gms are needed by fetus. Eighty percent of total fetal calcium is deposited during third trimester. The transport of ionized calcium from the mother to fetus increases from about 50mg/day at 20 weeks of gestation to maximum of about 350mg/day at 35 weeks of gestation **Forkes GB 1976**. Maternal total serum calcium levels decrease during pregnancy, with a nadir at 28 to 32 weeks related to decrease in albumin levels that accompany the increase in vascular volume.

Decreased serum calcium levels lead to an increase in parathyroid hormone levels, thereby increasing the intracellular calcium levels, which leads to an increase in the vascular smooth muscle contraction and thus an increase in the blood pressure. Despite low circulating calcium levels, the intracellular calcium ions are high which leads to hypertension **Belizan et al. 1988.**

THE MAGNESIUM

Introduction:

Magnesium is the fourth most abundant and the second most prevalent intracellular divalent cation. Magnesium is a cofactor for more than 300 enzymes in the body. It is required for enzyme substrate formation ($Mg^{++}ATP$). In addition magnesium is an allosteric activator of many enzyme systems. Magnesium plays an important role in oxidative phosphorylation, glycolysis, cell replication, nucleotide metabolism and protein biosynthesis.

Intracellular magnesium forms a key complex with ATP and is important cofactor for a wide range of enzymes, transporters and nucleic acid required for normal cellular function, replication and energy metabolism. Extracellular magnesium provides for maintenance of intracellular magnesium. Reduction in serum magnesium concentration results in increased neuromuscular excitability because magnesium competitively inhibits the entry of calcium into neurons.

The total body magnesium is 25mg**.** The concentration of serum magnesium is 1.7- 2.4 mg/dl (1.5 – 2 mEq/L, 0.7-1.0 mmol/ L) **Harrison Principles of Internal Medicine 17th edition.**

Approximately 55% of total body magnesium is in the skeleton. The extra cellular magnesium accounts for 1% of the total magnesium content. The remainder is intracellular. Within the cell, magnesium is bound primarily to proteins and negatively charged molecules. 80% of cytosolic magnesium is bound to ATP. Approximately 0.5- 5% is free, which is the fraction that alters enzyme activity.

In serum about 55% of magnesium is free 30% is associated with proteins primarily albumin and 15% forms complex with phosphate, citrate and other anions.

The role of magnesium in pregnancy induced hypertension:

The daily requirement of magnesium during pregnancy is 310mg. The hypomagnesemia in most pregnant women is associated with hemodilution, renal clearance during pregnancy

and consumption of minerals by the growing fetus **Chanvitya et al, 2008**.

Magnesium deficiency causes hemodynamic abnormalities such as arterial wall thickening, abnormal vascular tone and endothelial dysfunction which are due to alteration in the biology of cellular and noncellular components of arterial wall **Shalini Maksane et al, 2011.**

The role of Magnesium appears to be associated with its function as an activator of enzymes involved in membrane transport and integrity and with its relationship to prostaglandins-specifically, the ratio of prostacyclins (vasodilators) and thromboxane (some of which are vasoconstrictors), which is dramatically altered in the case of low serum magnesium. Both the prostacyclins and thromboxane substances are increased during a normal pregnancy. However, women who develop preeclampsia have a much smaller increase in prostacycline production than other pregnant women, while thromboxane continue to rise at the same rate, thus increasing vasoconstriction and rising blood pressure **M Zakir H Howlader et al, 2009**. In

addition magnesium depletion increases the vasoconstrictor effect of angiotensin II and adrenaline **Indumati et al, 2011.**

Magnesium works as a natural calcium channel blocker. Magnesium is the physiological antagonist of calcium **Fawett et al, 1999**. It has been postulated that if the concentration of extracellular magnesium is lowered, calcium influx is enhanced. Magnesium acts by opposing calcium dependent arterial constriction and may also antagonize the increase in intracellular calcium concentration **Kumuru et al, 2003.**

THE ZINC

Introduction:

The zinc is second to Iron as the most abundant trace element in the body. It is an integral component of nearly 300 enzymes in different species of all phyla. The important zinc containing metalloenzymes in human include carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, thymidine kinase, carboxypeptidases and alcohol dehydrogenase. The zinc atoms firmly bound to the active site of the metalloprotein molecule to contribute to the conformational and structural stability of metalloenzymes.

The zinc plays a major role in protein synthesis and has an important function in gene expression, the involvement in gene expression is both a structural and an enzymatic role. Metal binding by DNA and RNA affects the chemical and physical properties of the macromolecules in ways that may be related to replication and protein synthesis. Thymidine kinase and various DNA and RNA polymerase require Zinc for their activity **Magri et al, Kumru et al, 2003**. Zinc finger proteins bind to the specific

domain of DNA molecule. These proteins require zinc for their conformation and DNA binding abilities.

In addition to its roles in catalysis and gene expression, zinc stabilizes the structures of proteins and nucleic acid, preserves the integrity of subcellular organelles, participates in transport processes, and has important role in viral and immune phenomenon.

The zinc is an important element in wound healing. Several studies have implicated zinc as a necessary factor in the biosynthesis and integrity of connective tissue. Zinc is absolutely required for normal spermatogenesis, fetal growth and embryonic development.

The normal serum Zinc concentration ranges from 75-120 μg/dl (11.5-18.4 μmol/L). Zinc is transported in blood mainly by albumin 60-70%, α_2 macroglobulin 30-40% and a small amount through transferrin and free amino acids. The diagnosis of zinc deficiency is usually made when serum zinc level of < 70 μg/dl.

Physiological basis of zinc in pregnancy induced hypertension:

During pregnancy there is a decline in circulating zinc and this increase as the pregnancy progresses possibly due to increase in blood volume and decrease in zinc binding and an increase in transfer of zinc from mother to fetus **Tamura et al, 2000.** Zinc is shifted from the plasma to Red corpuscles. The normal requirement of Zinc during pregnancy is 12mg/day.

Zinc has been reported to play a role in hypertension by exerting an inhibitory effect on ATP- dependent calcium pump that catalyzes the movement of calcium ions. Low extracellular zinc concentration favours the inflow and accumulation of calcium ion in the cells, leading to increased vasoconstriction **Tubek S, 2007**.

In vascular cells reactive oxygen species (ROS) are produced by NADPH oxidases, uncoupled nitric oxide synthase, xanthine oxidase and by mitochondrial sources. The reactive oxygen species might cause hypertension because the increased $O_2^{\cdot -}$ radical oxidize NO to peroxynitrite and subsequently to nitrite

and nitrate. This results in a loss of bioactive NO-mediated vasodilatation, an increase in vasoconstriction and subsequently an increase in systemic vascular resistance, raising the blood pressure.

Zinc has antioxidant property by the following ways

(1) A zinc containing enzyme, superoxide dismutase causes dismutation of $O_2^{\cdot-}$ by conversion to hydrogen peroxide **Aggett PJ, 1985**.

(2) Zinc can induce the production of metallothionein which is very rich in cysteine and is an excellent scavenger of free radical $OH^{\cdot}$.

(3) The enzyme NADPH oxidases which catalyze the production of free radicals from oxygen is inhibited by zinc **Prasad AS, 2008.**

Zinc deficiency impairs taste leading to an unwilling increase in salt consumption that is a known predisposing factor for hypertension **Chiplonkar et al, 2004**.

MATERIALS AND METHODS

This is a cross sectional case - control study conducted in the Department of Obstetrics & Gynecology, Government Rajaji Hospital, Madurai during the period from 20/6/2011 to 20/8/2011.

The Ethical and Research committee of Madurai Medical College and Hospital approved the study protocol.

Participants:

The study was conducted in 50 pregnant women of age group between 20 – 40 years. Of them, case group comprised of 25 pregnant women either primi or second gravida in third trimester (> 24 weeks of pregnancy) with preeclampsia admitted as in patients in Department of Obstetrics and Gynecology.

The diagnosis of preeclampsia was based on clinical criteria with blood pressure ≥ 140/90mmHg measured on two occasions 6 hours apart with proteinuria ≥1+ dipstick along with edema (NHBPEP Classification).

The control group was formed by 25 normal pregnant women either primi or second gravida in third trimester > 24 weeks of pregnancy receiving antenatal care as out patients.

Exclusion criteria used for selecting participants:

Medical complicating pregnancy such as Diabetes Mellitus, Renal failure, Chronic hypertension, Heart failure, Multiple pregnancies and Pregnancy ≤ 24 weeks of gestation. Patients on magnesium sulphate and calcium lactate therapy were excluded from study.

Permission for conducting the study was obtained from The Dean, Madurai Medical College, The superintendent, Government Rajaji Hospital and from the Head of the Department, Obstetrics and Gynecology, Rajaji Hospital, Madurai.

Written consent was obtained from the participants after explaining the aim and methods of the project. The proforma was prepared and filled during the visit.

After filling the proforma the participants underwent a general examination and obstetrical examination, which consisted of fundal height, presenting part and fetal heart rate.

Examination of pedal edema:

A firm pressure was applied over the medial malleolus on both legs for 15 seconds in all participants and looked for pitting in that region to confirm the presence of pedal edema.

Anthropometry:

The heights of the participants were measured using standard methodology with the help of non-stretchable inch tape. The weights of the participants were measured using a weighing machine and BMI was calculated using Quetlet Index using the formula Wt (kg)/ht $(mt)^2$.

Measurement of Blood pressure:

With a standard sphygmomanometer and stethoscope the systolic and diastolic blood pressure of all participants were measured in the right upper arm in sitting posture by Auscultatory method. The first and fifth Korotkoff's phase were recorded as systolic and diastolic blood pressure respectively. The blood pressure for cases group was recorded at two occasions one at 9.00 Am and another at 5.00 Pm using the same procedure.

Estimation of urine albumin:

Clean catch midstream random urine sample was obtained from all participants. The urine protein was measured by dipstick method using Dip N Read reagent strip. The results was graded on the scale of 0 to 4+ (0, none; 1+, 30 mg/dl; 2+, 100 mg/dl; 3+, 300 – 1,999 mg/dl; 4+ ≥ 2000 mg/dl).

Blood sample collection:

Three ml of blood was drawn in all the participants from the cubital vein by using dispovan. The blood drawn was collected in a vaccum tube.

Estimation of Hemoglobin:

From the collected blood 0.02ml of the whole blood was used for hemoglobin estimation by Sahli's acid hematin method using hemoglobinometer.

Serum separation:

The blood samples were allowed to clot spontaneously at the room temperature. Then the clotted blood was centrifuged at 3,000rpm for 10 minutes. The serum separated was stored at 2 - 8 degrees Celsius until analysis.

Estimation of Calcium:

A part of serum was used for estimation of calcium.

Method:

Spectrophotometric method using O-cresolpthalein-complexone as colour indicator.

Principle:

In alkaline solution, calcium binds with metal complex O-Cresopthalein complexone (OCPC) to form a bluish- purple Complex, which is measured at 578nm. The intensity of colour is proportional to the calcium concentration in the sample. Hydroxyquinoline acts as a masking agent and eliminates the interference of magnesium.

Calcium + OCPC ⟶ Bluish + purple complex.

Reagents:

R 1	OCPC Reagent	O-Cresolpthalein complexone Hydrochloric Acid 8-Hydroxyquinoline	0.16 mM/ L 50 mM/L 17 mM/L
R 2	AMP Buffer	2 Amino 3 methyl propanol	500 mM/L
R 3	Calcium Standard	Calcium	10 mg/dl

Working reagent preparation:

Reagent 1 was diluted with Reagent 2 in equal proportion (1 ml of Reagent 1 + 1 ml of Reagent 2) and mixed properly by gentle swirling.

Stability: Working reagent is stable for 15 days at 2 - 8^0 C.

Procedure:

Pipette into vials	**Blank**	**Standard**	**Test**
Serum	-	-	20µl
Calcium Standard	-	20µl	-
Working reagent	1000µl	1000µl	1000µl

Reagents were mixed well and incubated at 37°C for 5 minutes. The analyzer was blanked with reagent blank. The absorbance was measured at 578nm first for the standard sample followed by test sample. The result was calculated using the formula.

Calculation:

$$\text{Serum Calcium (mg/dl)} = \frac{\text{Absorbance of Test}}{\text{Absorbance of standard}} \times 10$$

Estimation of Serum Magnesium:

A part of serum was used for serum magnesium estimation.

Method: Calmagite method.

Principle:

Magnesium combines with calmagite in an alkaline medium to form a red colour complex. Interference of calcium and proteins are eliminated by adding specific chelating agents and detergents. Intensity of the colour formed is directly proportional to the amount of magnesium present in the sample.

Magnesium + calmagite ⟶ Red coloured complex

Reagents:

R 1	Calmagite Potasium Chloride Polyvinylpyrrolidine	0.14 mM/L 77 mM/L 0.03 mM/L
R 2	Potasium cyanide Potassium Hydroxide	1.5 mM/L 14.3 mM/L
S	Magnesium standard	2.0 mEq/L

Working reagent:

Working reagent was prepared by mixing the equal volume of R 1 and R 2.

Stability: The working reagent is stable at 2 - 8^0 C for one month.

Procedure:

Pipette into vials	**Blank (B) ml**	**Standard (S) ml**	**Test (T) ml**
Serum			0.01
Magnesium standard		0.01 ml	
Working Reagent	1 ml		
Distilled water	0.01 ml		

The reagents were pipetted into clean dry test tube. Mixed well and incubated at room temperature (25^0 C) for 5 minutes. The absorbance was measured in analyzer at 510 nm first with standard against blank sample and then for the test sample against blank sample.

Calculation:

$$\text{Magnesium in mmol/L} = \frac{\text{Absorbance of test}}{\text{Absorbance of standard}} \times 2$$

Conversion factor:

Magnesium concentration mg/dl = Mg concentration mmol/L X 2.43

Estimation of serum Zinc:

A part of serum was used for serum magnesium estimation.

Method: Calorimetric method

Principle:

Zinc in an alkaline medium reacts with 5 – Br – Paps to form a purple coloured complex. Intensity of the complex formed is directly proportional to the amount of zinc present in the sample.

Zinc + 5 – Br- Paps ⟶ Purple coloured complex

Reagents:

R 1	5 – Br- Paps Sodium citrate Dimethylglyoxime Bicarbonate buffer	0.07mM/L 170 mM/L 4 mM/L 0.2 Mol/L
R 2	Salicyaldoxime	29 mM/L
S	Zinc Standard	200 µg/dl

Working Reagent:

Working reagents were prepared from mixing together four parts of R 1 and one part of R2.

Stability: The working reagent is stable upto 2 days at room temperature (below 35^0 C) or for one week at 2 - 10^0 C.

Procedure:

Pipette into vials	Blank (B) ml	Standard (S) Ml	Test (T) ml
Serum			0.05
Zinc Standard		0.05	
Working reagent	1.0	1.0	1.0
Distilled water	0.05		

The reagents were pipetted into clean dry test tubes. Mixed well and incubated at room temperature for 5 minutes. The absorbance was measured in an analyzer at 578 nm first with standard sample against the blank and then with test sample against the blank.

Calculation:

$$\text{Zinc in } \mu\text{gm/dl} = \frac{\text{Absorbance of Test}}{\text{Absorbance of standard}} \times 200$$

RESULTS AND OBSERVATIONS

Summary of the Study

Contents	Cases (n=25) (mean±SD)	Controls (n=25) (mean±SD)	p-value
Age (yrs)	23.80±3.48	23.52±2.52	0.746
BMI (kg/m^2)	28.71±4.70	22.46±3.42	<0.001
Gravida	1.480 ±0.51	1.52± 0.510	0.783
Parity	0.48 ±0.510	0.520 ±0.510	0.783
Weeks of gestation (Wks)	32.56±4.34	32.56±3.48	1.000
Pulse (/min)	97.36±8.56	94.16±10.59	0.246
Systolic BP (mmHg)	157.2±14.29	101.04±9.47	<0.001
Diastolic BP (mmHg)	100.8±7.59	68.0±6.45	<0.001
Hb (gm %)	10.32±1.45	10.36±1.08	0.912
Serum Calcium (mg/dl)	8.07±0.43	8.96±0.59	<0.001
Serum Magnesium (mg/dl)	1.62±0.16	1.92±0.16	<0.001
Serum Zinc (µg/dl)	80.6±9.78	93.28±9.44	<0.001

p-value < 0.05 is significant.

Table -1

Comparison of BMI between the preeclamptic women and normal pregnant women

Contents	Cases		Controls	
	Mean	**S.D**	**Mean**	**S.D**
BMI	28.71	4.70	22.46	3.42

$P < 0.001$

From the above result it is evident that p value is significant and the BMI of preeclamptic women is significantly higher than that of the normal pregnant women.

Table – 2

Comparison of pulse rate between the cases and the controls

Content	Cases		Controls	
	Mean	**S.D**	**Mean**	**S.D**
Pulse	97.36	8.58	94.16	10.59

P value = 0.246

From the above result it is evident that the p value is not significant and there is no significant difference in the pulse rate between the cases and the controls.

Table-3

Comparison of Systolic Blood Pressure between the preeclamptic women and the normal pregnant women

Content	Cases		Controls	
	Mean	**SD**	Mean	SD
Systolic Blood Pressure (mmHg)	157.2	14.2 9	101.04	9.47

P Value < 0.001

From the above results it is clear that the p value is significant and there is a significant increase in systolic pressure in the preeclamptic women compared to the normal pregnant women.

Table- 4

Comparison of Diastolic Blood pressure between the cases and the controls

Contents	Cases		Control	
	Mean	**SD**	Mean	SD
Diastolic Blood pressure (mmHg)	100.8	7.59	68.0	6.45

P value < 0.001

From the above results it is clear that there is a significant increase in diastolic blood pressure in the cases when compared to the controls.

Table – 5

Comparison of Hemoglobin between the preeclamptic and the normal pregnant women

Content	Cases		Controls	
	Mean	**S.D**	**Mean**	**S.D**
Hemoglobin	10.32	1.45	10.36	1.08

P value = 0.912

From the above results it is evident that there is no significant difference in the hemoglobin levels between the cases and the controls.

Table - 6

Comparison of serum calcium levels between the preeclamptic women and normal pregnant women

Content	Cases		Controls	
	Mean	**S.D**	**Mean**	**SD**
Serum Calcium (mg/dl)	8.07	0.43	8.96	0.59

P value < 0.001

The normal serum calcium concentration is 8.5 – 10.5 mg/dl. From the above results it is evident that there is a significant decrease in the level of serum calcium in the preeclamptic women when compared with the normal pregnant women.

Table – 7

Comparison of the serum Magnesium levels between the preeclamptic women and the normal pregnant women

Content	Cases		Controls	
	Mean	**SD**	**Mean**	**SD**
Serum Magnesium (mg/dl)	1.62	0.16	1.92	0.16

P value < 0.001

The normal serum magnesium concentration is 1.7–2.4mg/dl. From the above results it is clear that there is a significant decrease in the level of serum magnesium in the women with preeclampsia compared with the normal pregnant women.

Table – 8

Comparison of the serum zinc levels between the preeclamptic and the normal pregnant women

Contents	Cases		Controls	
	Mean	**SD**	Mean	SD
Serum zinc (µg/ dl)	80.7	9.78	93.28	9.44

P value < 0.001

The normal serum zinc concentration ranges from 75-120mg/ dl. From the above results it is evident that there is a significant decrease in the level of serum zinc in the women with preeclampsia compared with the normal pregnant women.

Statistical Analysis:

The comparison between the cases and controls was done by using one - way ANOVA test using SPSS (Statistical Package for Social Science) software, Sigma stat version 3.5. The significance was drawn at p value (probability) of < 0.05.

DISCUSSION

The changes in the levels of serum calcium, magnesium and zinc in preeclamptic women compared to the normal pregnant women were studied by several other investigators.

In the present study the Body Mass Index of preeclamptic women is significantly higher than that of the normal pregnant women. These findings are in agreement with the studies of **Chanvitya punthumapol et al, 2008. Akinloye et al, 2010** in their study showed that there was no significant difference in the BMI between the preeclamptic and the normal pregnant women. In **2001, Pipkin** in his study showed that the women with higher BMI become hypertensive than those with lower BMI.

In this study there is a significant decrease in the serum calcium levels in the preeclamptic women when compared to the normal pregnant women.

The data supported that the lowered calcium levels might be a cause in the development of preeclampsia. The effect of the serum calcium on the changes in the blood pressure could be explained by the level of intracellular concentration of calcium.

The increase in the intracellular calcium concentration when the serum calcium level went lower lead to constriction of the smooth muscles in blood vessels and an increase in vascular resistance.

Abdelmarouf H. Mohielden et al, 2007 showed in their studies that the mean calcium concentration in the preeclampsia group is significantly lower than the normal pregnant women.

Several studies had examined the effects of the calcium supplementation on blood pressure during pregnancy thus investigating the role of calcium supplementation and its effects on blood pressure. In **1996, Bucher HC et al** conducted a meta-analysis of randomized controlled trials on the effect of calcium supplementation on preeclampsia. They concluded that the supplementation during pregnancy leads to a reduction in both systolic and diastolic blood pressure and preeclampsia.

In the present study there is a significant decrease in the mean serum magnesium concentration in preeclamtic women compared to the normal pregnant women.

Serum magnesium levels have significant effects on the cardiac excitability and reactivity. Magnesium, as a calcium

antagonist promotes vascular smooth muscle relaxation. Thus the low levels of magnesium predispose to increase in the arterial pressure.

The studies of **Idogun et al, 2007** and **Indumati et al, 2010** showed that the serum calcium level and magnesium levels in preeclamptic pregnant women is significantly lower than that of the normal pregnant women.

In **2008, Chanvitya et al,** in his study revealed that the serum calcium level was lower in preeclamptic women when compared with the normal pregnant women but there was no difference in the serum magnesium levels.

In this study there is a decrease in the mean serum Zinc levels in preeclampsia when compared to the controls. This result is contradictory with the studies conducted by **Harma et al, 2005** in turkey **and Diez et al, 2002** who showed that the serum zinc levels in preeclamptics was higher than that in the normal pregnant women.

The result of this current study is in agreement with the studies of **Muhammed ashraf et al, 2007 and Parbin**

Bahadoran et al, 2010 who showed that there was a significant decrease in serum zinc levels in preeclampsia group compared to normal pregnancy. In **2010, Emmanuel I. Ugwuja *et al,*** in their study showed that there was no significant decrease in the serum zinc levels in preeclamsia.

Zinc insufficiency has been recognized by a number of experts as an important public health issue especially in developing countries. During pregnancy the decrease in the circulating zinc is possibly due to increased transfer of zinc from mother to the fetus and due to plasma expansion. Zinc is a metallic component of enzyme superoxide dismutase, which causes protection from damage by free radical. The hypozinemia suppressing the activity of superoxide dismutase may be a precipitating factor for preeclampsia.

There was no significant decrease in the mean serum calcium, magnesium and zinc levels between the preeclamptic and the normal pregnant women in the studies conducted by **Golmohammed et al, 2008.**

Studies by **Jain S et al, 2010** showed that there was a significant reduction in the levels of serum calcium, magnesium and zinc in the patient with preeclampsia compared with the normal pregnant women.

Further in the present study no significant correlation could be made between levels of serum calcium, magnesium and zinc and the severity of preeclampsia.

CONCLUSION

In this study the serum levels of calcium, magnesium and zinc is compared between 25 women with preeclampsia with 25 normal pregnant women in third trimester of the pregnancy.

This study has shown that the serum calcium, magnesium and zinc levels in preeclampsia are significantly lower than the normal pregnant women with p value < 0.001.

From the above study, though the calcium, magnesium and zinc deficiencies cannot be pinpointed as the sole factors for the aetiology of preeclampsia, they have a definite role in the development of preeclampsia.

Decrease in the extracellular calcium level causes increased intracellular calcium through parathyroid hormone. This leads to an increase in vascular smooth muscle contraction and thus increases the blood pressure. Magnesium as a physiological antagonist of calcium, antagonizes the increase in intracellular calcium concentration and decreases the vascular smooth muscle contraction. Zinc by its antioxidant property and inhibitory effect on ATP dependent calcium pump decrease the vascular smooth

muscle contraction there by decreasing the blood pressure. Hence decrease in these elements is a predisposing factor for pregnancy induced hypertension.

Therefore the calcium, magnesium and zinc consumption should be encouraged during the second and third trimesters of pregnancy. The dietary supplements of calcium, magnesium and zinc in the form of milk, cheese, soya bean products, leafy vegetables etc., during pregnancy could result in the reduction of incidence of preeclampsia. The direct supplementation therapy of these elements can be considered for the women with preeclampsia to ensure the child survival and the safe motherhood.

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PROFORMA

Serial No.: Date:

Name : Age : Sex:

Address :

Height : Weight: BMI:

Medical H/o : Diabetic / Heart Disease / Asthmatic / Renal failure / Under any medication

Family H/o : Hypertension /Diabetes Mellitus / Pre-eclampsia

Marital H/o :

Menstrual H/o :

Previous Obstetric H/O :

Gravida :
LMP : EDD: Weeks of Gestation:

On Examination:
Odema: Present/ Absent
Pulse :
BP : Systolic: Diastolic:

Obstetrical Examination:
Fundal Height: Presentation: Fetal heart rate**:**

Investigations:
Blood:
Hb% :
Serum Calcium :
Serum Magnesium :
Serum Zinc :

Urine :
Urine Al :

Figure-1

Comparison of BMI between the preeclamptic women and normal pregnant women

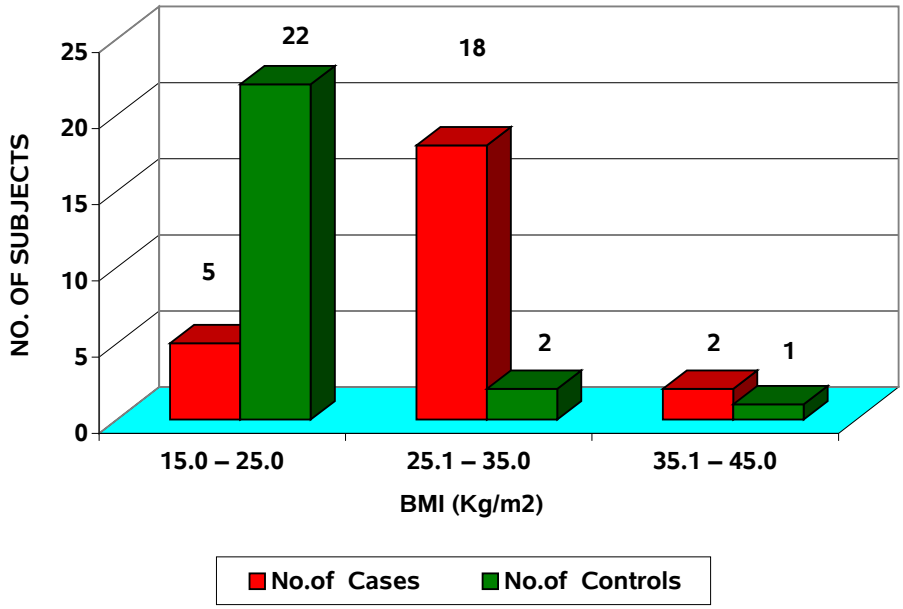


Figure-2

Comparison of pulse rate between the cases and the controls

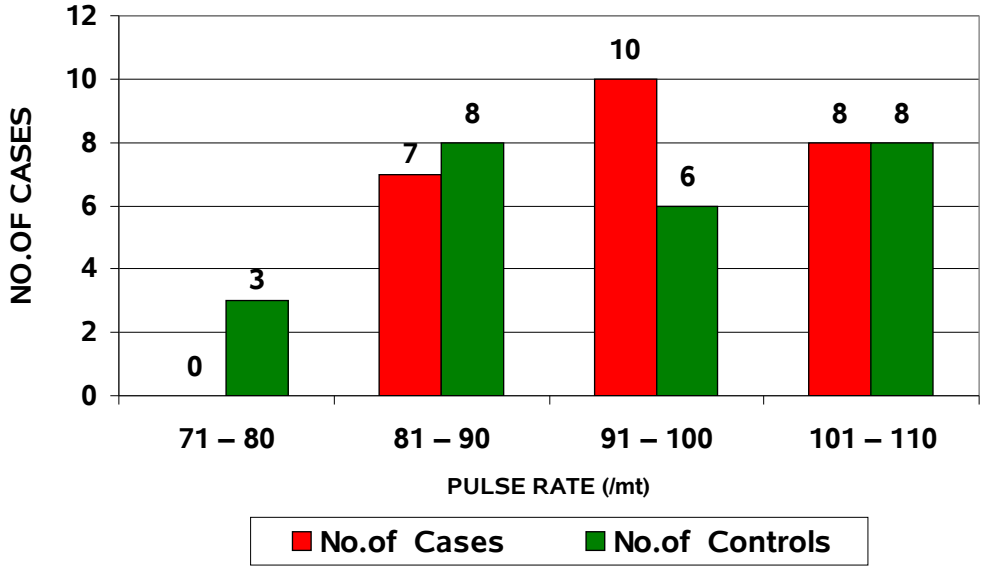


Figure-3
Comparison of Systolic Blood Pressure between the preeclamptic women and the normal pregnant women

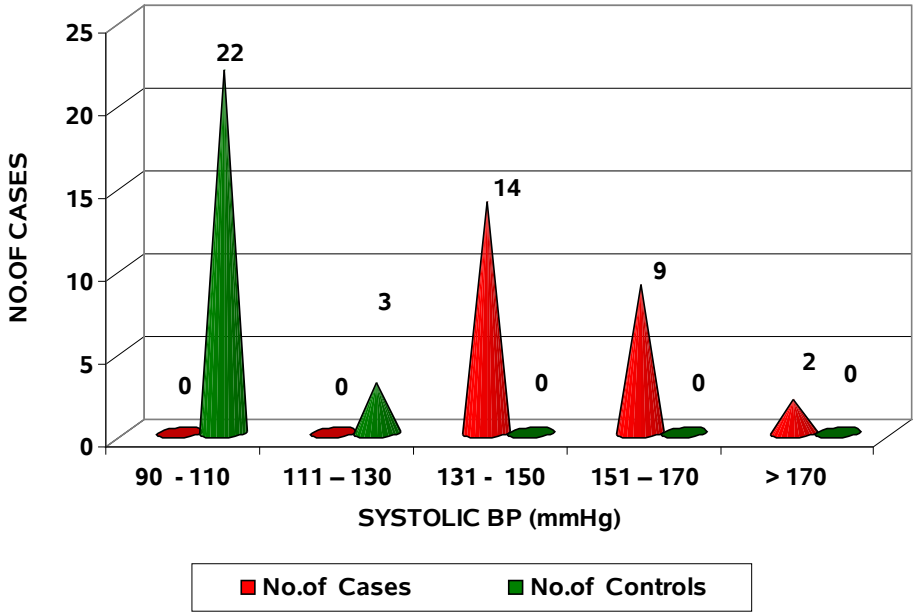


Figure-4
Comparison of Diastolic Blood pressure between the Cases and the controls

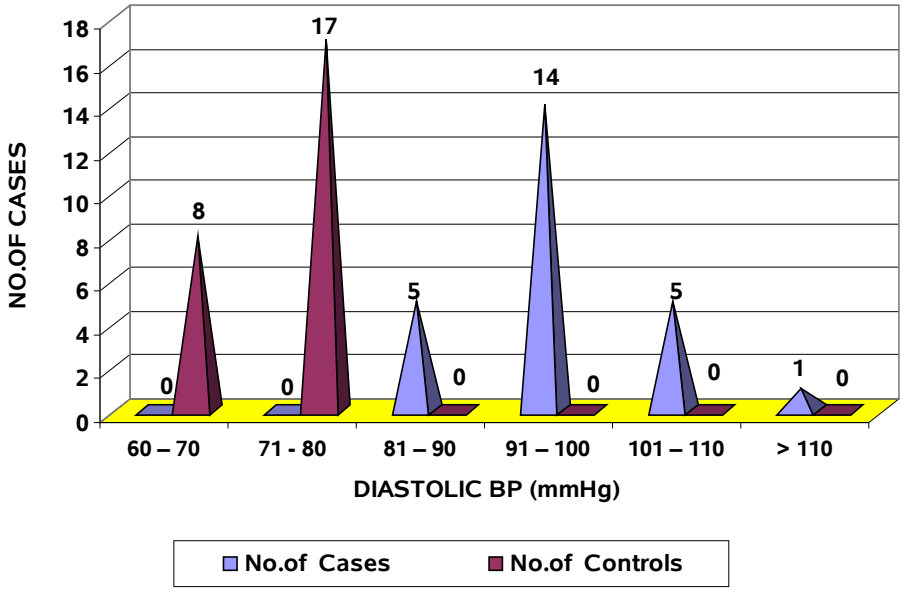


Figure-5
Comparison of Hemoglobin between the preeclamptic and the normal pregnant women

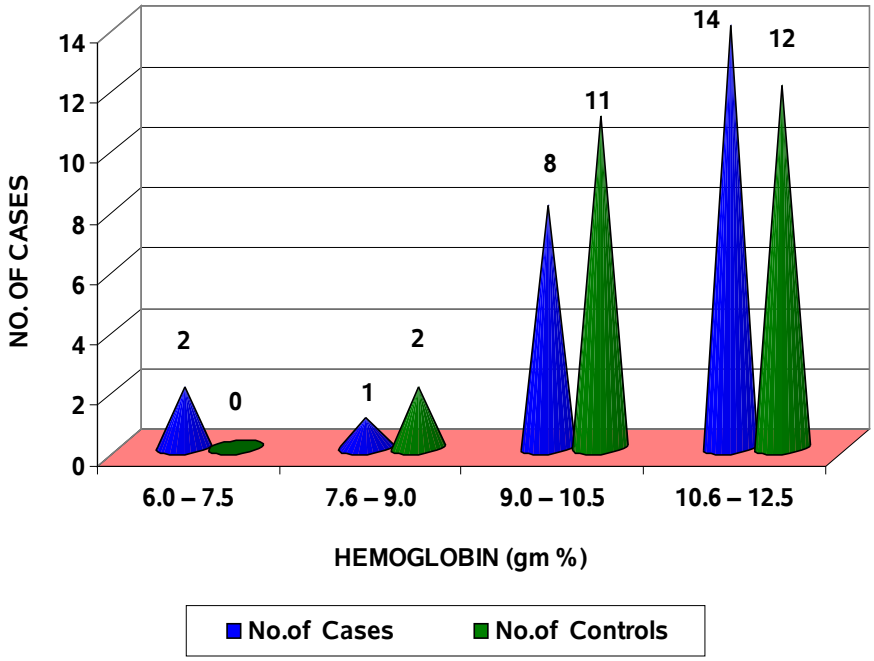


Figure-6
Comparison of serum calcium levels between the preeclamptic women and normal pregnant women

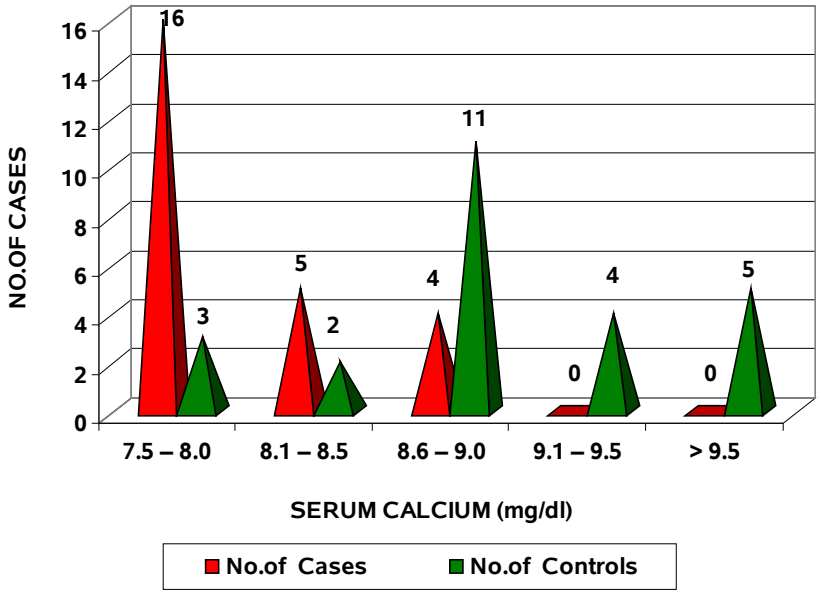


Figure-7
Comparison of the serum Magnesium levels between the preeclamptic women and the normal pregnant women

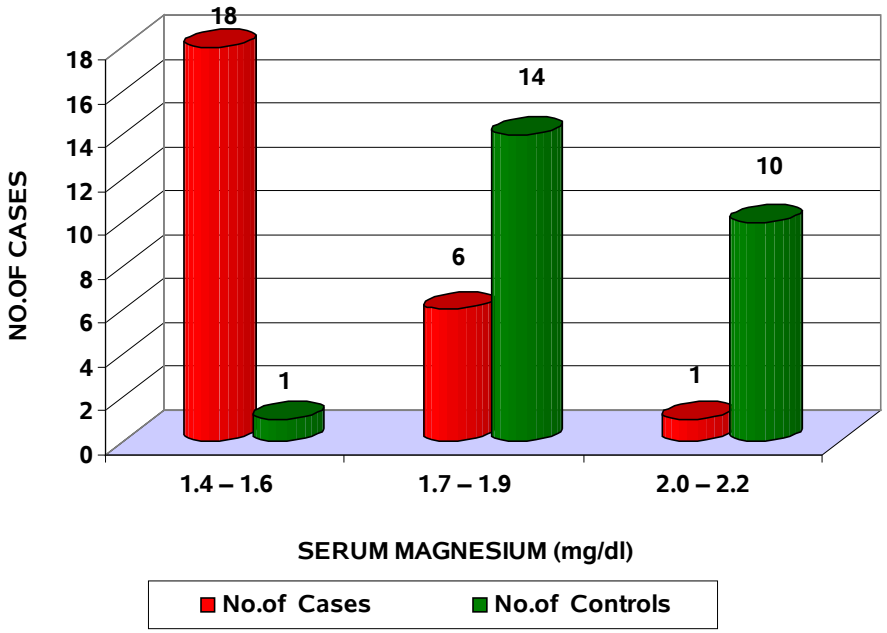
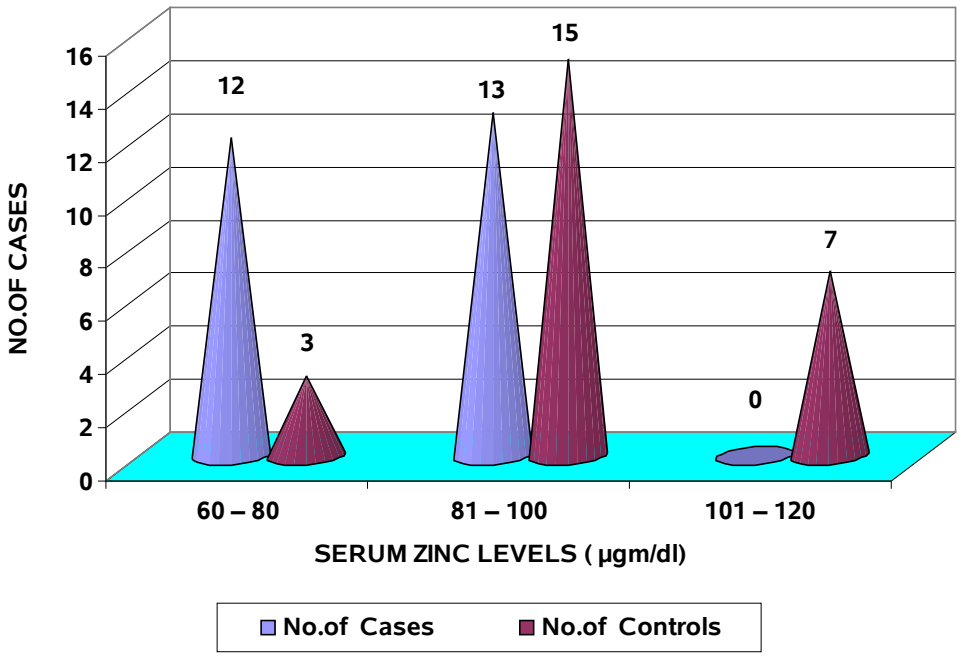
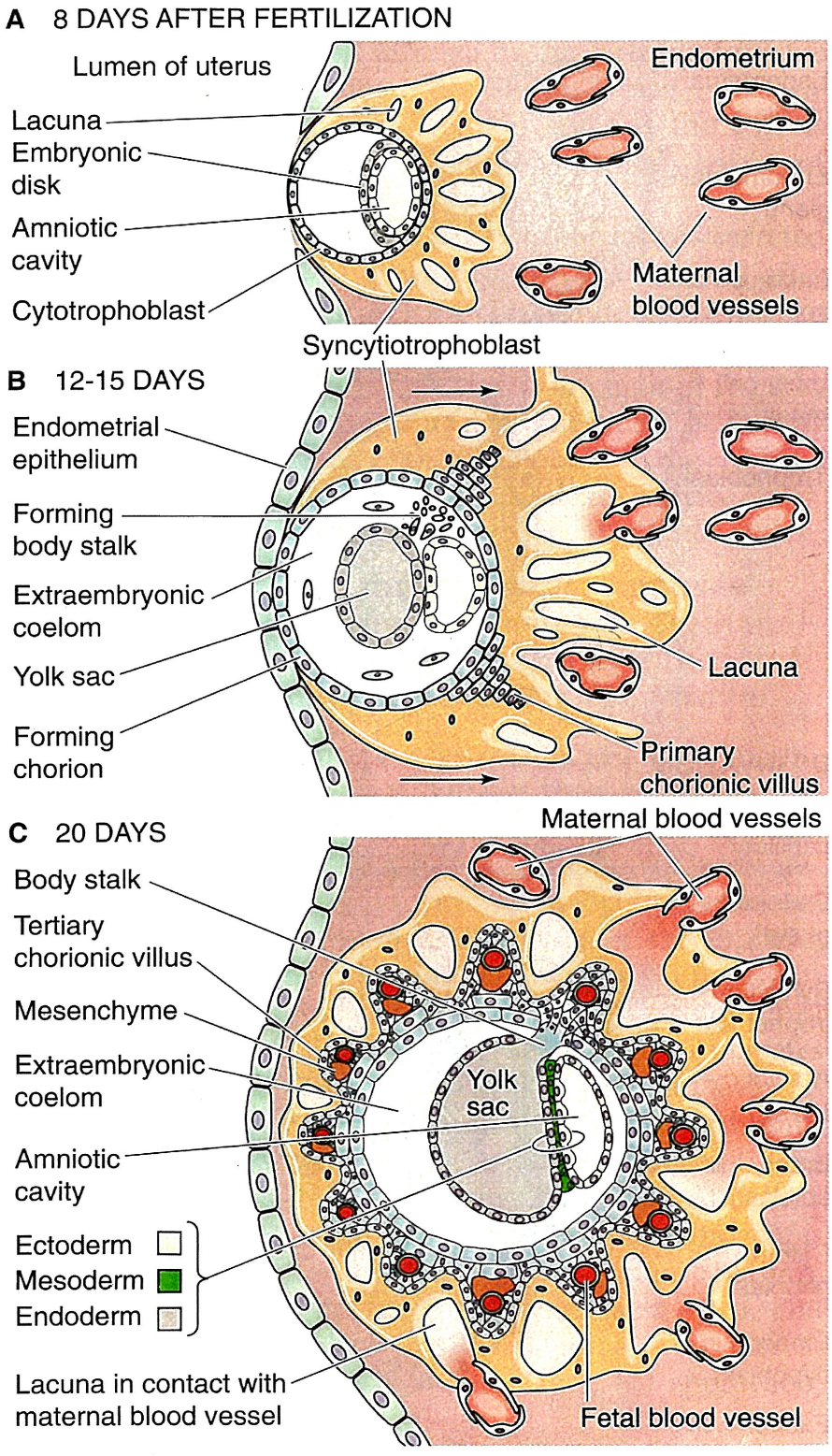


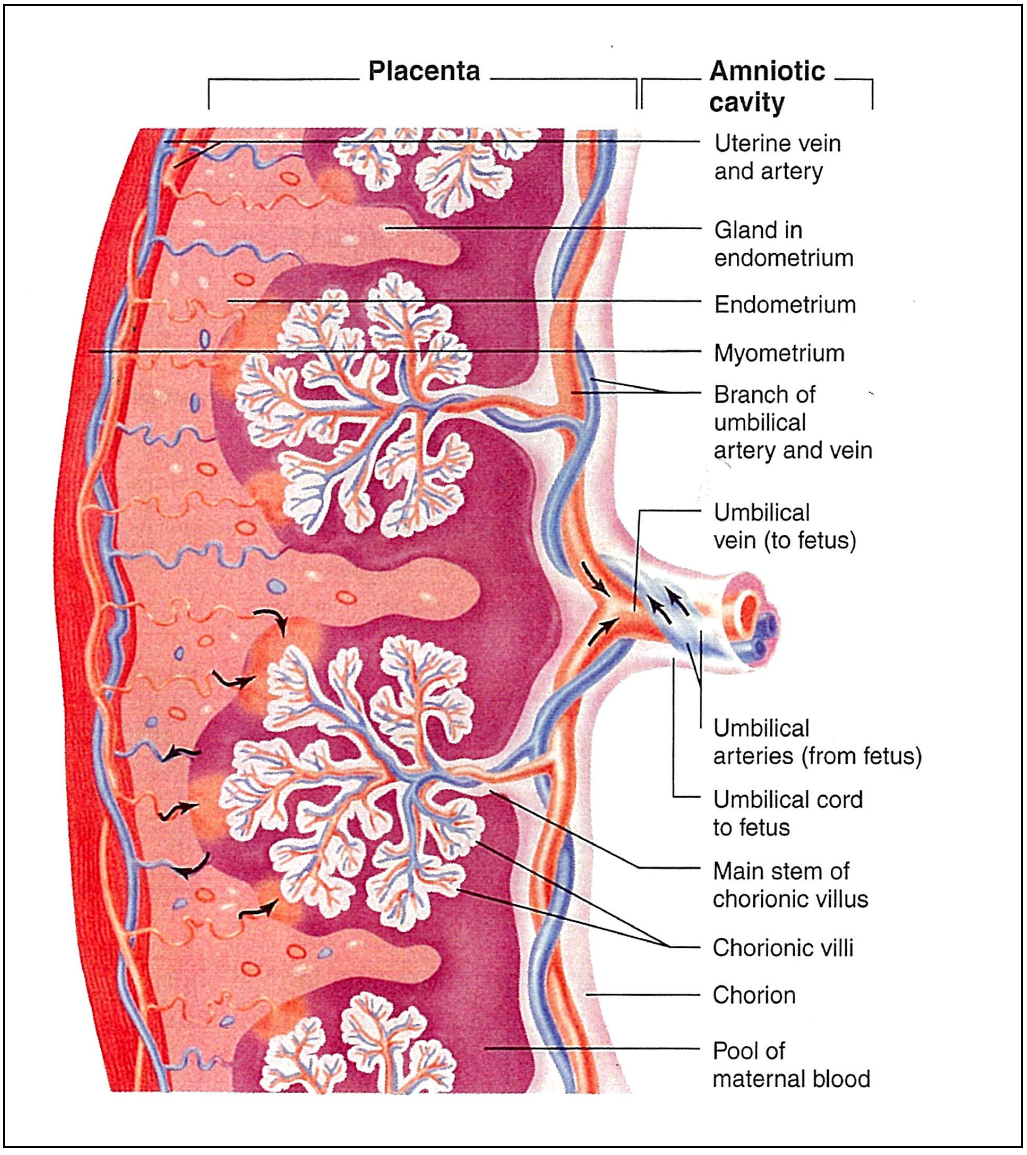
Figure-8
Comparison of the serum zinc levels between the preeclamptic and the normal pregnant women



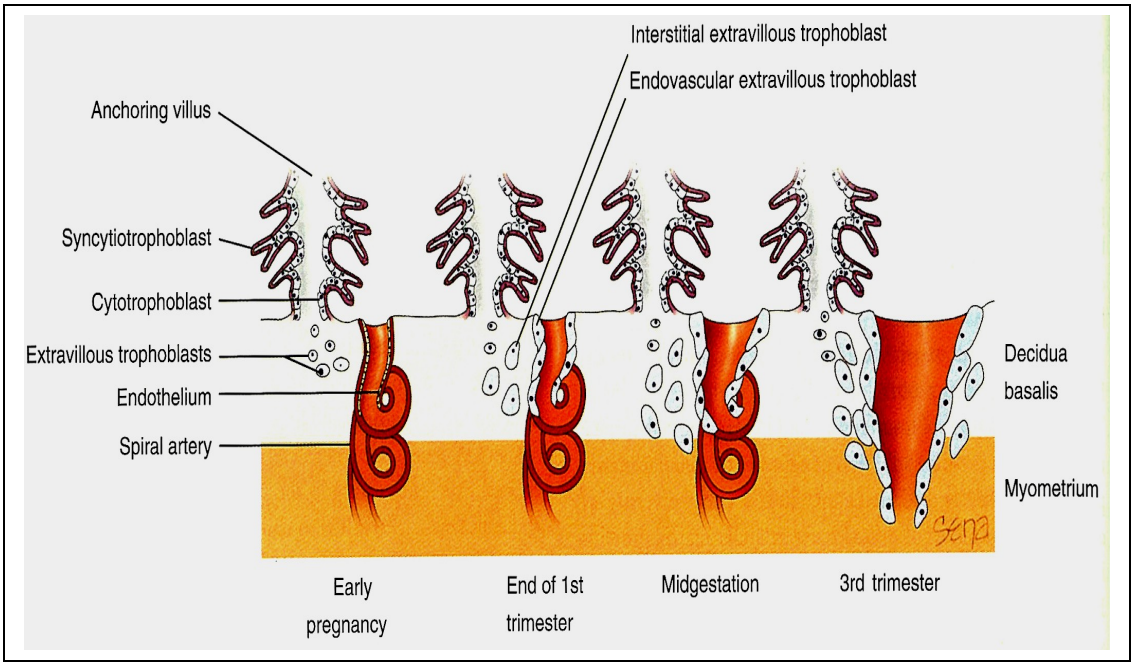
EARLY DEVELOPMENT OF PLACENTA



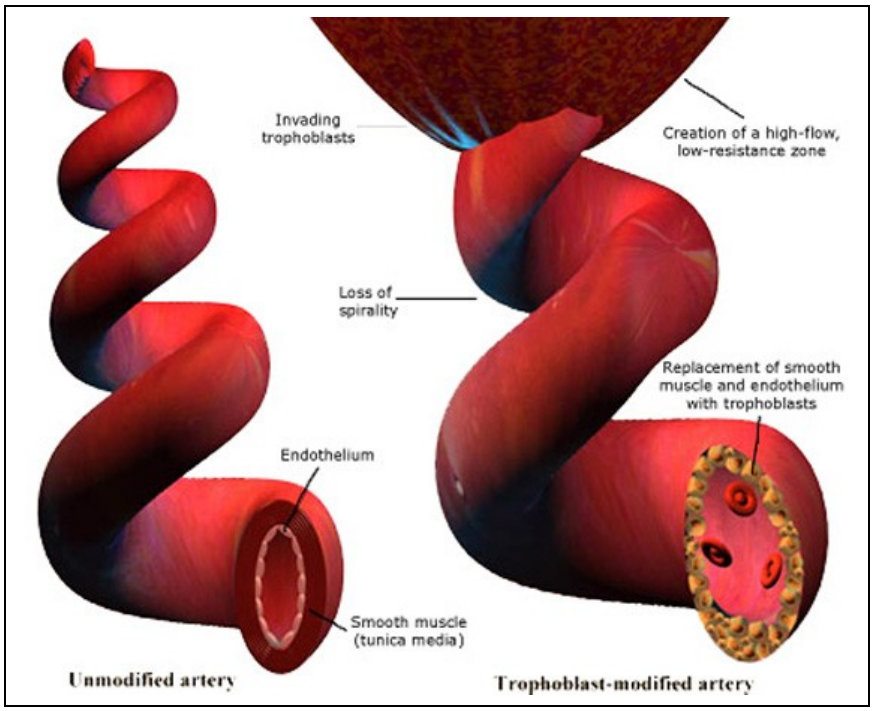
A SECTION THROUGH A FULL-TERM PLACENTA



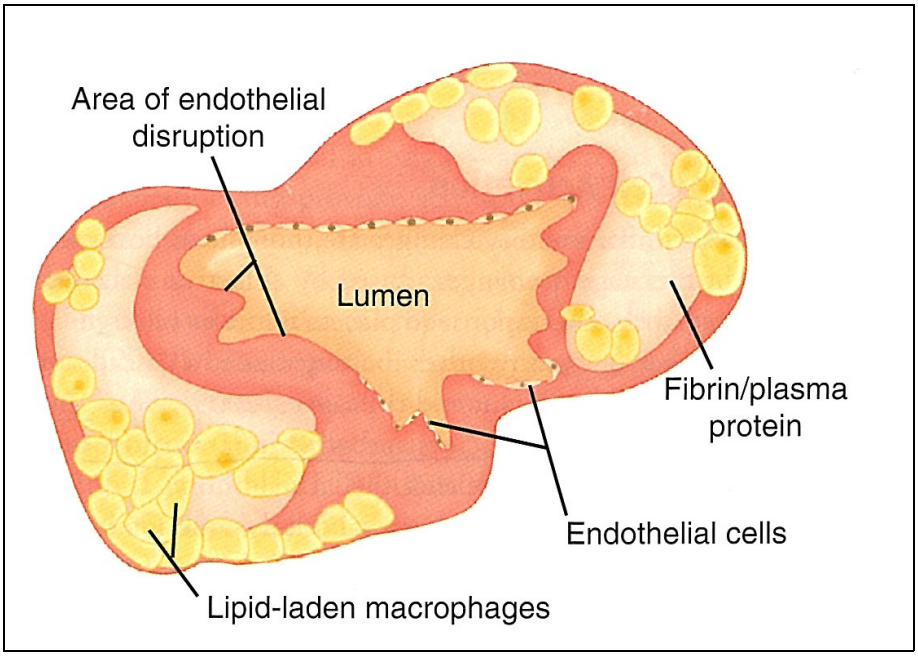
TROPHOBLAST INVASION OF SPIRAL ARTERIES



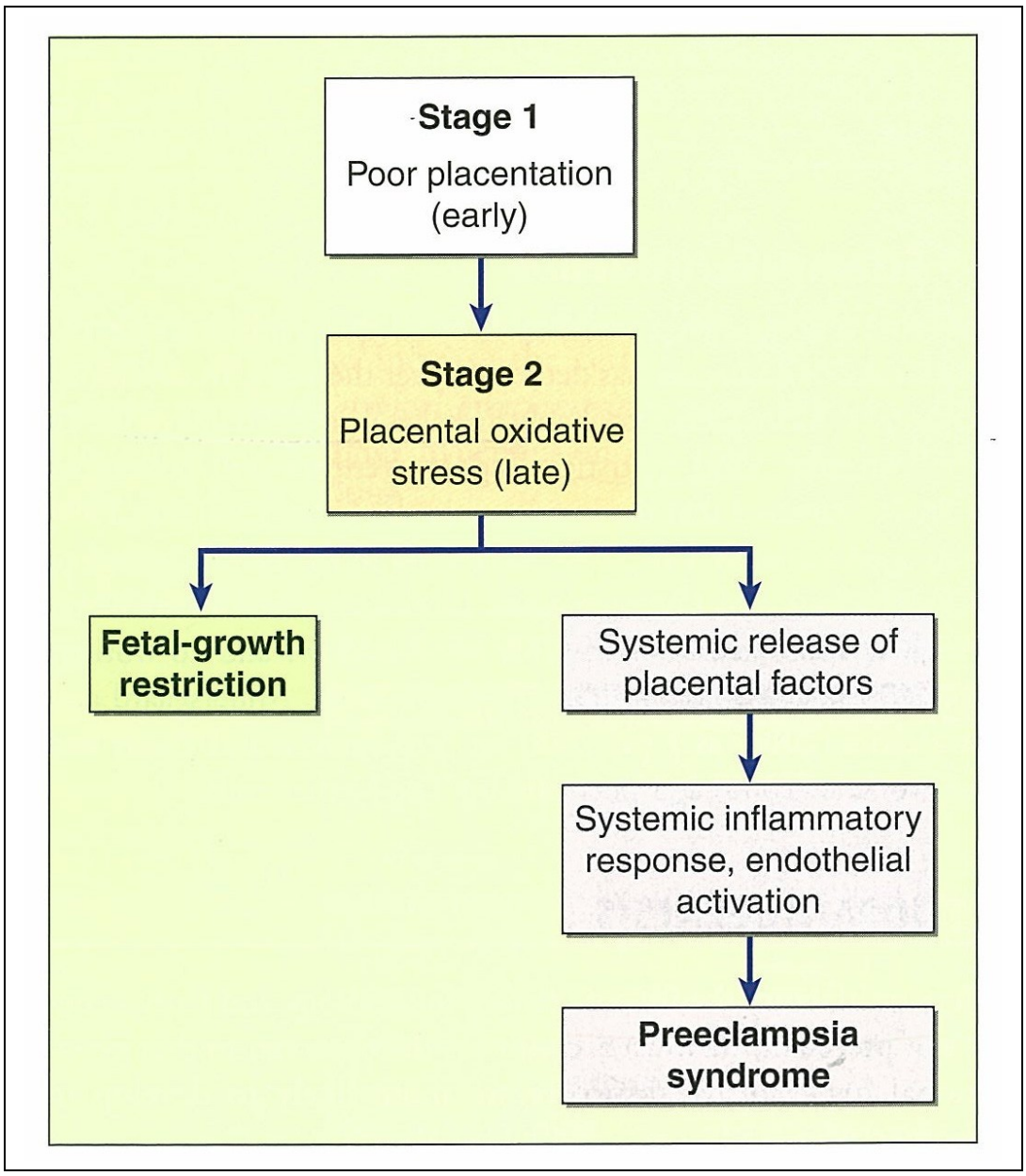
MODIFICATION OF SPIRAL ARTERIES



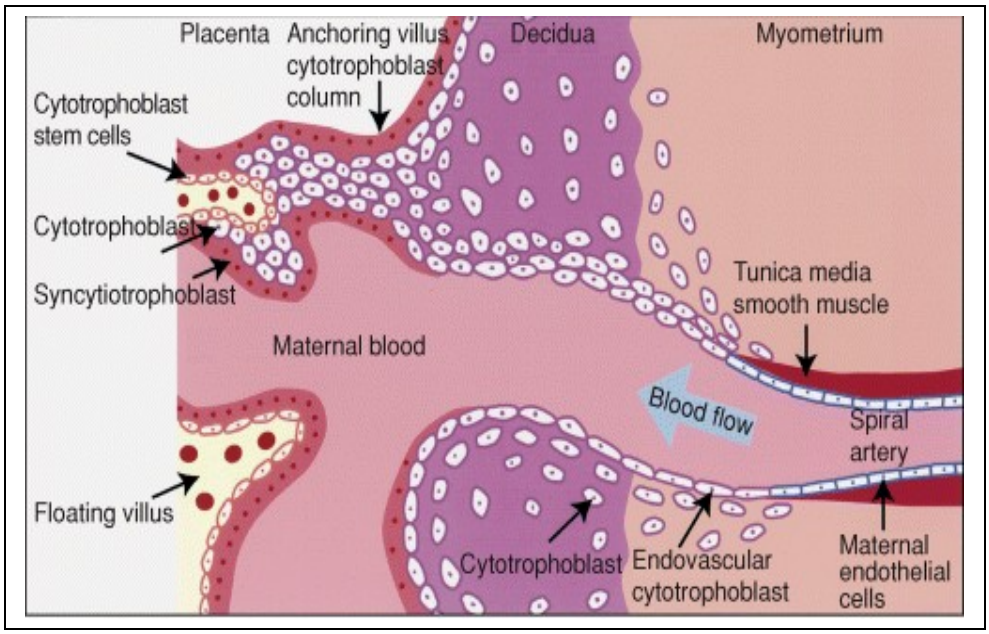
ATHEROSIS


Area of endothelial disruption
Lumen
Fibrin/plasma protein
Endothelial cells
Lipid-laden macrophages

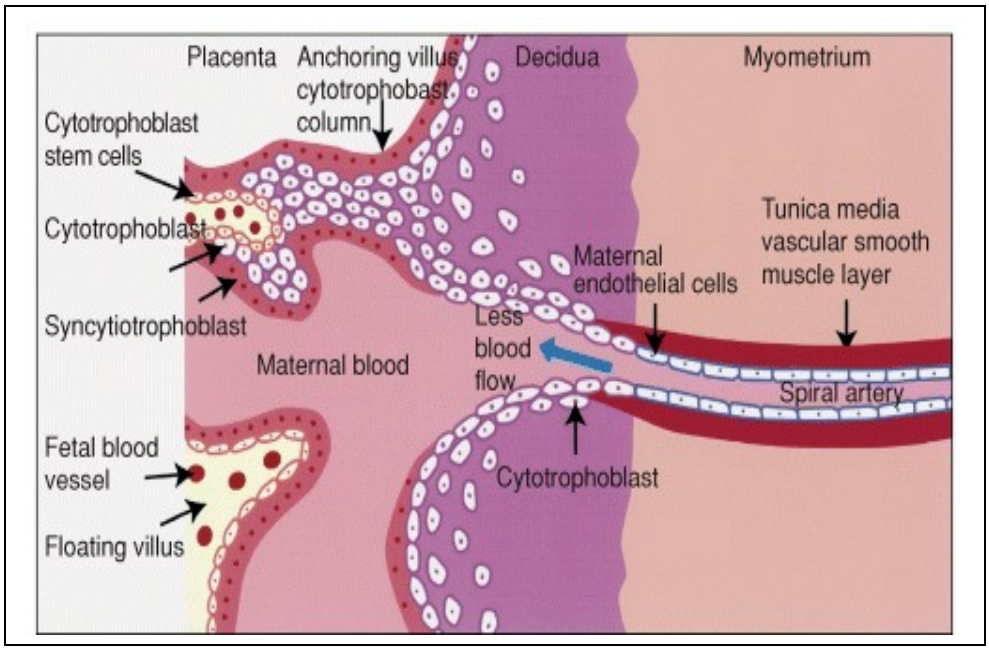
PREECLAMPSIA A "TWO STAGE DISORDER"



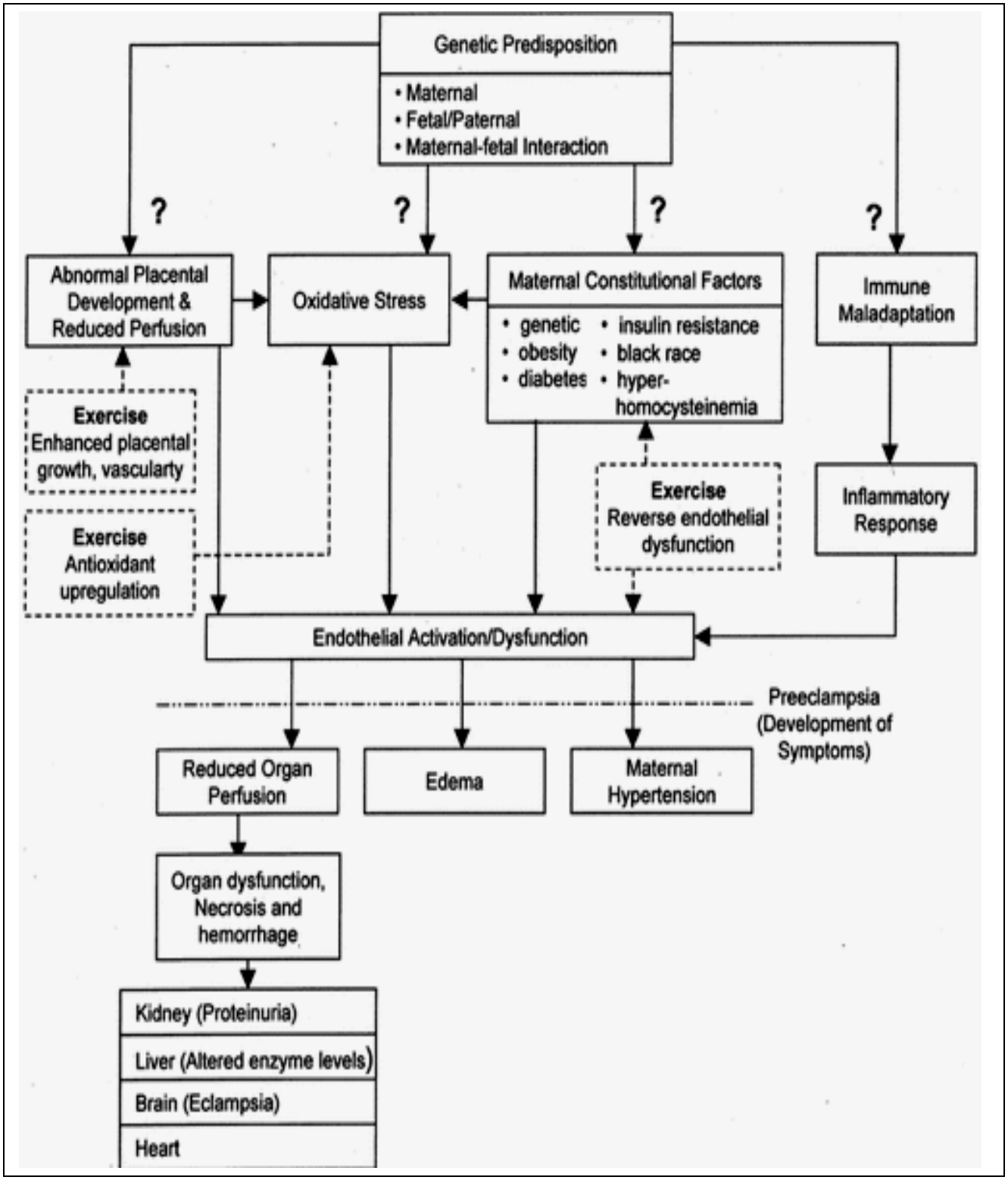
TROPHOBLASTIC INVASION IN NORMAL PREGNANCY



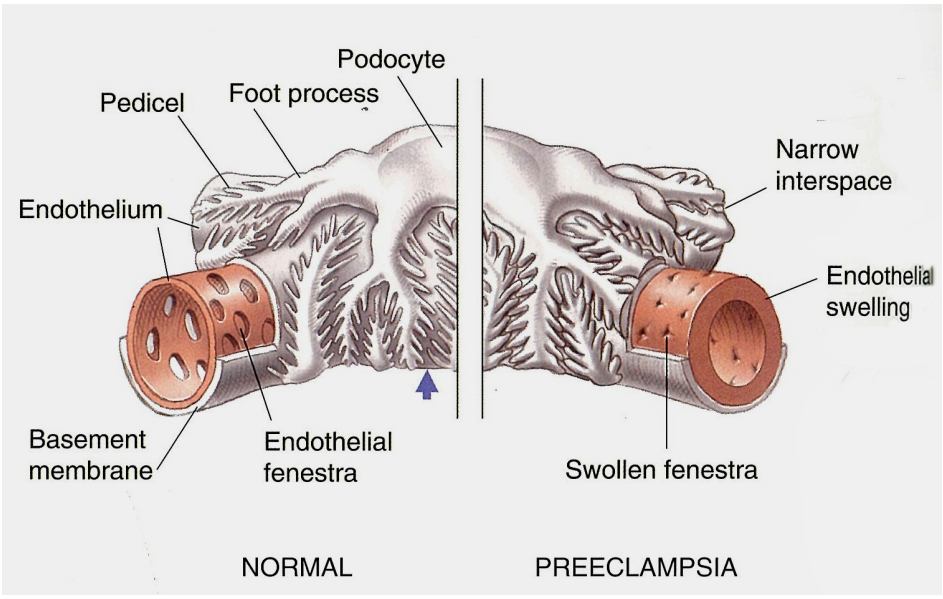
TROPHOBLASTIC INVASION IN PREECLAMPSIA



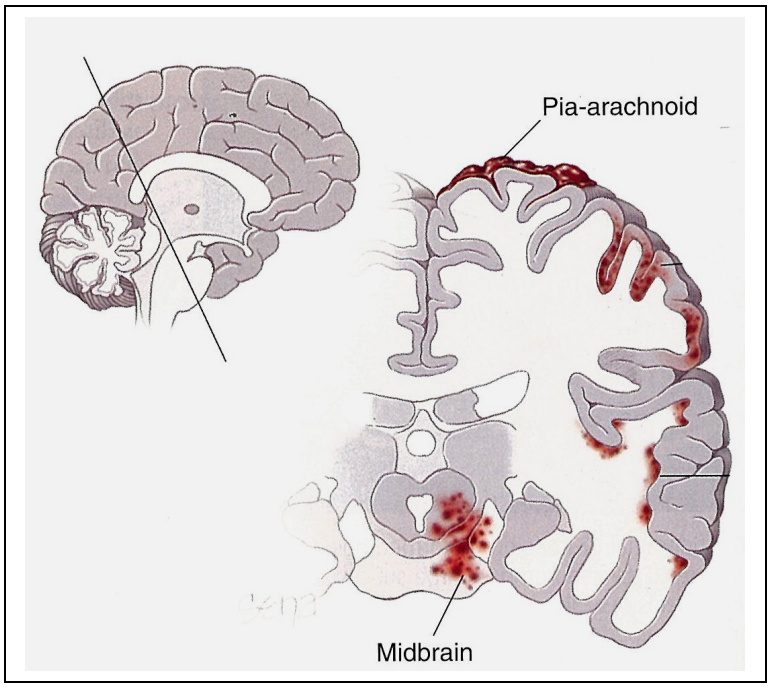
PATHOPHYSIOLOGY OF PREECLAMPSIA

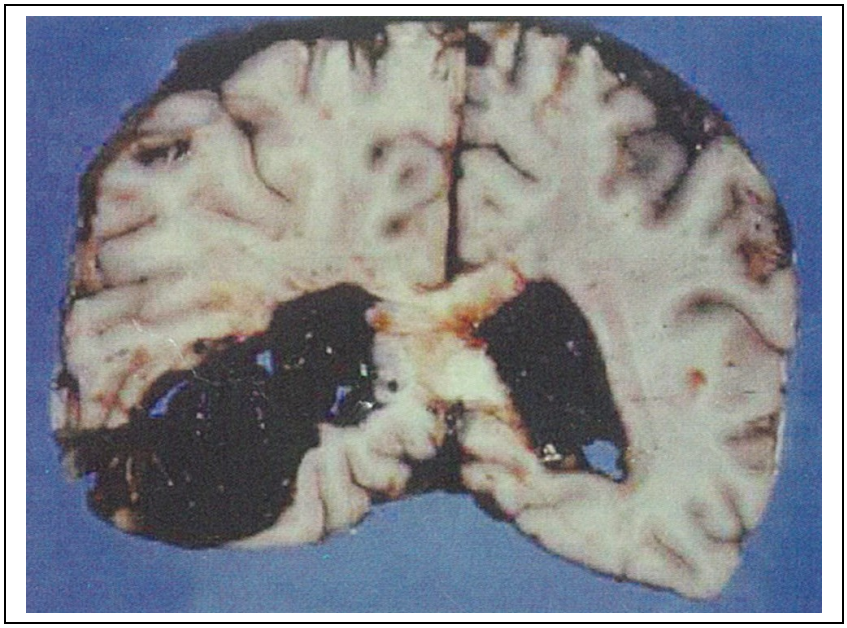


GLOMERULAR CAPILLARY ENDOTHELIOSIS

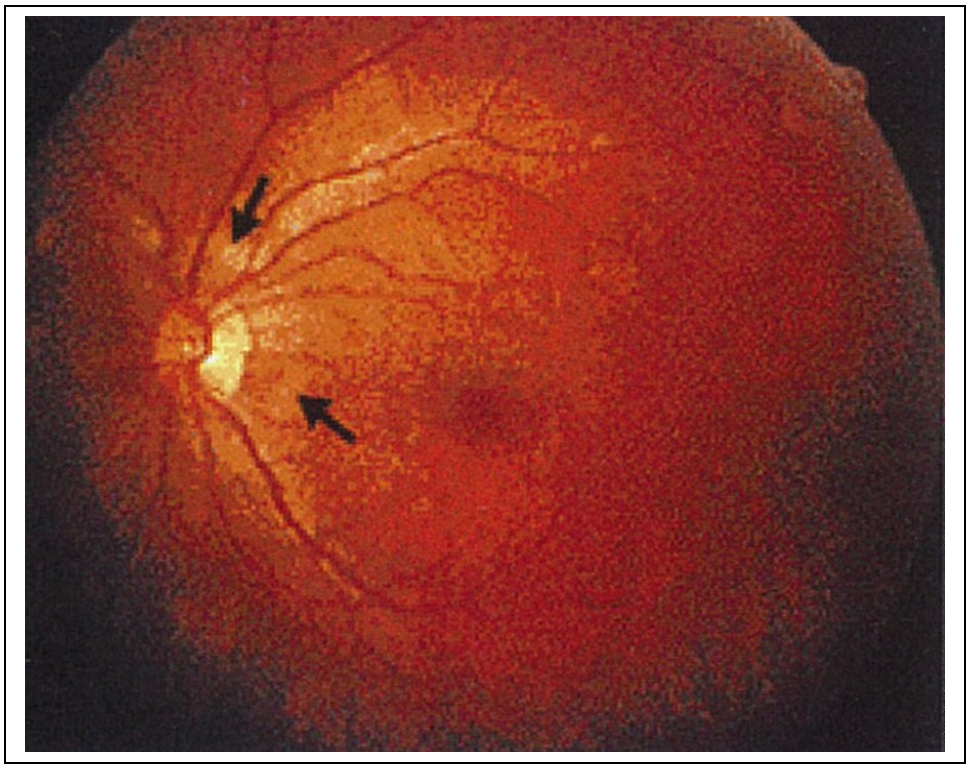


CEREBRAL HAEMORRHAGE

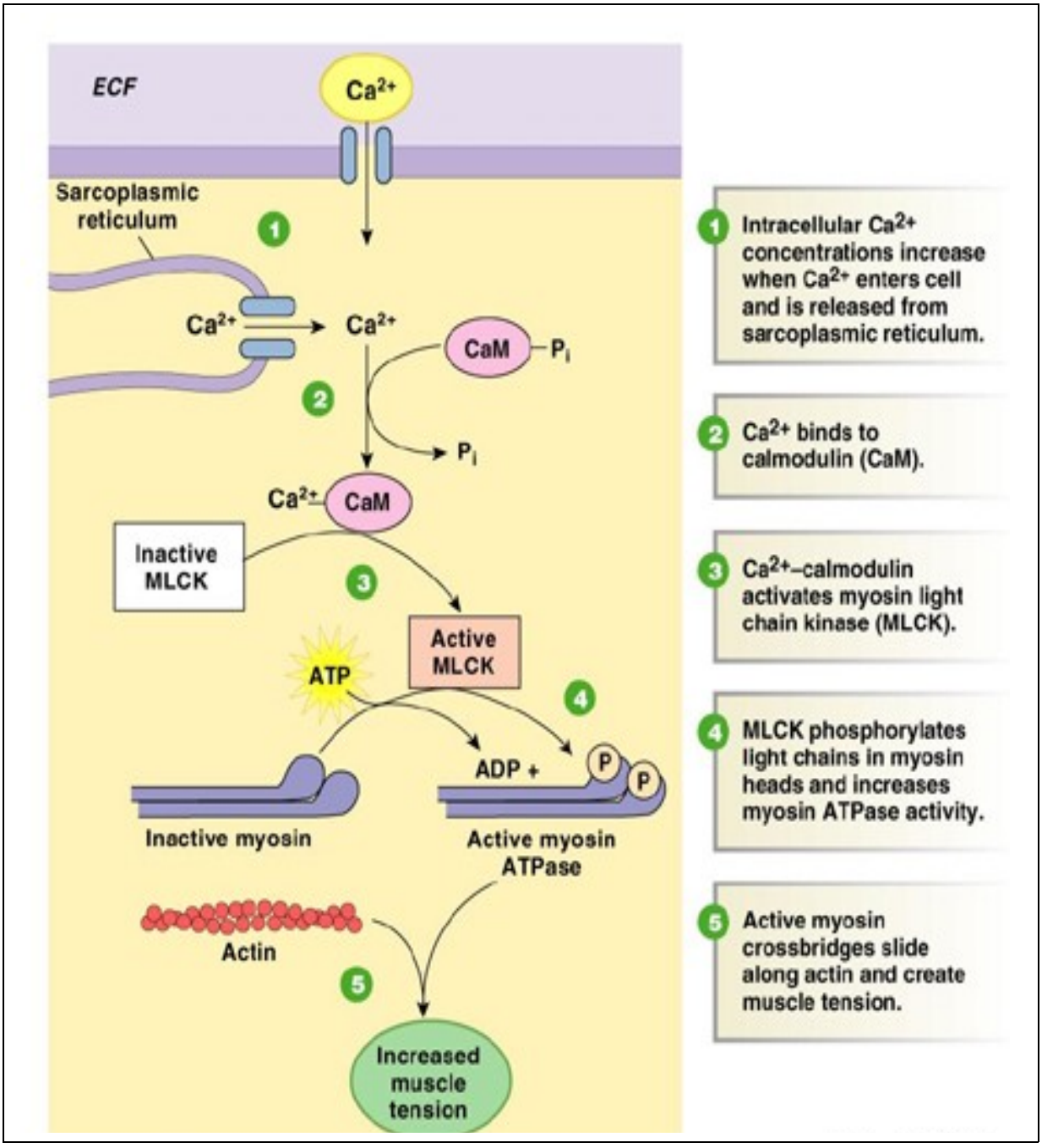




FUNDUS IN RETINAL ISCHEMIA



CALCIUM IN VASCULAR ENDOTHELIUM



MASTER CHART - CONTROL GROUP

S.No.	NAME	AGE (Yrs)	BMI (Kg/m2)	GRAVIDA	PARITY	WEEKS OF GESTAION	PULSE (/min)	SYSTOLIC BP(mmHg)	DIASTOLIC BP (mmHg)	URINE ALBUMIN	HEMOGLOBIN (gm%)	SERUM CALCIUM (mg/dl)	SERUM MAGNESIUM (mg/dl)	SERUM ZINC (mcg/dl)
1	V.Jothi	26	23.37	2	1	32	90	100	70	Nil	10.8	7.9	2.1	96
2	M.Panchavarnam	20	26.88	1	0	36	100	100	70	Nil	10.2	8	1.9	98
3	P.Saranya	25	22.22	1	0	29	76	90	70	Nil	9.4	8.5	1.9	88
4	S.Karpagasundari	20	20.73	2	1	32	74	110	70	Nil	10.6	8.8	1.9	94
5	S.Thamarai Selvi	23	23.81	2	1	38	96	100	80	Nil	11.4	9.7	1.9	93
6	T.Revathy	27	22.04	2	1	31	90	90	60	Nil	12.2	10.1	1.8	89
7	S.Ranjani	27	23.31	1	0	35	110	100	70	Nil	11.8	9.9	2.1	97
8	A.Shanthi	25	19.1	1	0	35	82	100	60	Nil	9.8	8.6	2	101
9	A.Sivapriya	22	23.6	1	0	38	84	90	70	Nil	11.6	9.2	2.2	74
10	S.Maharasi	20	17.48	1	0	27	102	90	60	Nil	9.2	9	2.1	104
11	V.Karupayee	25	23.01	1	0	33	106	100	70	Nil	9.8	9.6	1.5	93
12	P.Easwari	21	25.44	1	0	36	100	110	70	Nil	11.6	8.8	2	111
13	K.Selvi	26	21.5	2	1	37	90	90	60	Nil	11.8	8.8	1.8	90
14	U.Sudha	21	19.82	1	0	33	102	120	70	Nil	8.2	8.8	1.9	96
15	K.Vidhya	25	24.14	2	1	34	90	100	60	Nil	11.2	9	2	101
16	H.Geetha	29	21.93	2	1	29	98	90	70	Nil	8.8	8	1.8	103
17	M.Saradha	21	23.44	2	1	29	106	110	60	Nil	9.6	9	1.9	86
18	M.Muthulakshmi	24	18.59	2	1	35	84	100	70	Nil	10.8	8.7	2.1	106
19	V.Sangarammal	22	19.53	1	0	34	102	110	70	Nil	11.6	9.5	1.9	91
20	P.Poongani	22	22	2	1	34	96	112	80	Nil	9.2	9.6	1.7	74
21	G.Saradha	25	35.17	2	1	31	100	120	80	Nil	10.6	9.2	1.8	88
22	K.Sangeetha	25	19.34	1	0	34	104	100	60	Nil	9.8	8.1	2	102
23	G.Vidhya	22	21.85	1	0	27	80	90	70	Nil	10.2	9	1.7	92
24	S.Rani	21	21.64	2	1	29	110	110	70	Nil	9.4	8.8	2.1	76
25	N.Mallathi	24	21.64	2	1	26	82	94	60	Nil	9.8	9.4	1.9	89

MASTER CHART - CASES

S.No.	NAME	AGE (Yrs)	BMI (Kg/m²)	GRAVIDA	PARITY	WEEKS OF GESTAION	PULSE (/min)	SYSTOLIC BP(mmHg)	DIASTOLIC BP (mmHg)	URINE ALBUMIN	HEMOGLOBIN (gm%)	SERUM CALCIUM (mg/dl)	SERUM MAGNESIUM (mg/dl)	SERUM ZINC (mcg/dl)
1	S.Irulayee	30	31.58	1	0	33	98	160	90	++	10.8	7.9	1.9	88
2	P.Thangaratinam	20	29.73	1	0	34	90	150	90	++	12	8.1	1.4	95
3	M.Chitra	25	29.28	1	0	28	100	200	100	+++	10.2	8.4	1.6	68
4	S.Muthulakshmi	25	31.96	2	1	36	100	140	90	++	10.8	8.9	1.6	86
5	C.Kirthika	22	28.68	1	0	36	100	140	90	++	8.4	7.9	1.6	96
6	K.Panchavarnam	22	22.31	1	0	39	96	140	110	++	11.4	7.4	1.8	97
7	A.Muthujothi	26	43.9	2	1	35	98	150	90	++	9.4	8.4	1.6	88
8	P.Dharmambal	28	21.7	2	1	29	82	150	110	++	9.2	7.6	1.8	96
9	P.Roja	24	27.7	1	0	34	92	150	100	++	9.8	8	1.6	77
10	L.Backialakshmi	23	29.9	2	1	35	82	170	100	++	10.8	7.9	1.8	81
11	A.Chellathai	20	33.2	1	0	36	88	150	110	++	11	8.9	1.5	87
12	K.Murugeswari	22	28.01	2	1	30	110	150	100	++	11	8.9	1.6	81
13	S.Jeyalakshmi	28	30.73	1	0	36	90	170	120	++	10.8	8.4	2.1	79
14	R.Mallika	20	27.76	1	0	31	92	150	100	++	11.2	8.2	1.4	71
15	P.Selvi	34	26.66	2	1	27	90	160	100	++	6.8	7.7	1.5	72
16	R.Rani	24	31.07	2	1	37	108	140	100	++	12.2	7.9	1.6	74
17	K.Velammmal	20	29.43	1	0	39	98	150	100	+++	6.4	7.7	1.7	81
18	P.Nagarathinam	27	28.51	2	1	39	88	150	100	++	10	7.8	1.4	63
19	M.Pandiammal	22	26.88	1	0	28	92	170	110	++	11.8	7.8	1.5	70
20	M.Selvavelammma	21	28.68	1	0	27	110	160	100	+++	9.8	7.6	1.6	79
21	R.Thangam	23	35.17	1	0	26	102	180	110	++	9.6	8	1.7	64
22	T.Chitra	24	21.93	2	1	24	106	170	100	++	10.4	7.7	1.5	76
23	P.Meena	22	25.44	2	1	31	108	160	100	++	10.8	8.8	1.6	82
24	P.Surya	22	23.44	2	1	32	110	150	100	++	11.6	8.1	1.6	90
25	R.Jeyasundari	21	24.14	2	1	32	104	170	100	++	11.8	7.8	1.5	74