A STUDY OF ASSOCIATION OF SERUM CALCIUM LEVEL IN PREGNANT FEMALES WITH YPERTENSIVE DISORDERS IN GOVERNMENT VELLORE MEDICAL COLLEGE AND HOSPITAL, VELLORE

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GOVERNMENT VELLORE MEDICAL COLLEGE

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TAMILNADU, INDIA.

APRIL 2021

CERTIFICATE

This is to certify that the dissertation titled **"A STUDY OF ASSOCIATION OF SERUM CALCIUM LEVEL IN PREGNANT FEMALES WITH HYPERTENSIVE DISORDERS"** is a genuine work done by **DR.SREELAKSHMI M,** Post Graduate student (2018 – 2021) in the Department of General Medicine, Government Vellore Medical College, Vellore under the guidance of **PROF. DR. M. RANGASWAMI M.D.,DMRD.,**

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The request for an approval from the Institutional Ethical and Scientific Committee (IEC) was considered on the IEC meeting held on 24.04.2019 at the Conference Hall, Govt. Vellore Medical College, Vellore-11.

The Convenor, Chairperson, Member Secretary and committee members decided to approve the proposed work mentioned above submitted by the Principal Investigator.

The Principal Investigator is instructed to submit the status of this project periodically to this College Office.

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DECLARATION

I, **DR. SREELAKSHMI M** solemnly declare that this dissertation titled **"A STUDY OF ASSOCIATION OF SERUM CALCIUM LEVEL IN PREGNANT FEMALES WITH HYPERTENSIVE DISORDERS"** is a bonafide work done by me in Department of General Medicine, Government Vellore Medical College and Hospital, Vellore under the guidance and supervision of **Prof. Dr. RANGASWAMI. M ., M.D., DMRD.,**

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the university regulations for the award of M.D., Degree in General Medicine (Branch – I).

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CONTENTS

ABBREVIATIONS

ACOG : American College of Obstetricians and Gynecologists

AKI : Acute Kidney Injury

ABPM : Ambulatory Blood Pressure Monitoring

AST: Aspartate Aminotransferase

ALT: Alanine Aminotransferase

BMD: Bone Mineral Density

BMI: Body Mass Index

DIC : Disseminated Intravascular Coagulation

ECF: Extracellular Fluid

FGR : Fetal Growth Restriction

HELLP : The Hemolysis, Elevated Liver Enzymes, And Low Platelet Count

ISSHP: International Society for Study of Hypertension in Pregnancy

LDH: Lactate Dehydrogenase

LMIC : Low and/or Middle Income Countries

MRI : Magnetic Resonance Imaging

NICE: National Institute for Health and Care Excellence

PCWP : Pulmonary Capillary Wedge Pressure

PlGF: Placental Growth Factor

PRES: Posterior reversible encephalopathy syndrome

PTH: Parathyroid Hormone

PPH: Postpartum Hemorrhage

PIERS: Preeclampsia Integrated Estimate of Risk

CPEP : Calcium in Preeclampsia Prevention

RCVS: Reversible cerebral vasoconstriction syndrome

SGA: Small For Gestational Age

UA : Umbilical Artery

ABSTRACT

INTRODUCTION

Preeclampsia is a frequent disease with an incidence of 5 to 7% among the general population. . Preeclampsia is associated with a five-fold increase in perinatal mortality. In general, there is disagreement about many aspects of hypertensive disorders of pregnancy, including the diagnosis, classification, and management. Pregnancy is a period of high calcium demand because of fetal requirement. Many compensatory mechanisms comes into action to prevent calcium depletion from maternal skeletal reserves, like increased absorption, reduced renal losses, etc. But in pre-eclampsia, all these compensatory mechanisms tend to function abnormally. The studies have shown a strong correlation of calcium with preeclampsia. It has been proven that inverse association exists between calcium intake and development of hypertension during pregnancy. This study intends to find the serum calcium level and its association with hypertensive disorders in pregnancy.

AIM

1) Identify the prevalence of hypocalcemia in pregnant females with hypertensive disorders of pregnancy

2) Assess the compliance of calcium intake in the study group.

METHODOLOGY

100 patients who were diagnosed, or highly suspected to have hypertensive disorders of pregnancy, were selected randomly from the out-patient/ in-patient wards of the obstetrics and gynecology department. Informed consent was obtained, and data collected based on the preformed questionnaire. Required investigations were done, after general and systemic examination. Of importance, blood pressure, corrected calcium, urine protein(by dipstick) were checked in all the patients. Compliance of drug intake was assessed from the questionnaire.

Analysis was done, to find the average calcium level among the study population, and its correlation between severity of the disease.

RESULTS

Statistical analysis was carried out to find any association between serum calcium and severity of the disease. The mean calcium level varied significantly (reduction in the level) across the disease spectrum, namely, gestational hypertension, pre-eclampsia, and pre-eclampsia with severe features. Analysis also revealed significant association between serum calcium and other parameters, like bloop pressure, proteinuria. Compliance of drug intake was assessed, and there was significant association between compliance and the severity of the disease.

CONCLUSION

The findings of this study show that, there was significant association between serum calcium and hypertensive disorders of pregnancy, and its severity. Drug intake in the community was an important contributing factor, towards reducing the risk of developing severe disease.

INTRODUCTION

Eclampsia has been documented for more than 2400 years, and features of the prodromal syndrome preeclampsia (previously referred to as toxaemia of pregnancy) have been documented for almost 200 years.[1]

Preeclampsia is a frequent disease with an incidence of 5 to 7% among the general population; however, geographic, social, economic and racial differences are responsible for an incidence that is up to three times higher in some populations. Preeclampsia is associated with a five-fold increase in perinatal mortality and its socioeconomic impact on developing countries is huge.[2]

An epidemiological study in the USA over the period 1995-2004 showed that gestational hypertension and Preeclampsia were the most commonly diagnosed hypertensive conditions in pregnancy, whereas pre-existing hypertension was much rarer. [2] Worldwide there is disagreement about many aspects of hypertensive disorders of pregnancy, including the diagnosis, classification, and management. This lack of consensus hampers our ability to study not only the immediate rates of adverse maternal and fetal outcomes for the various hypertensive disorders in pregnancy, particularly preeclampsia, but also the long-term health outcomes of women and babies who survive this condition. It also impacts on research into the pathophysiology of this condition and has almost certainly delayed the development of effective screening tests

and treatments, leading to poorer pregnancy outcomes[3] Pregnancy would lead to a substantial deficiency of calcium were if it was not for adaptation of the maternal homeostatic system which provides for these needs from enhanced intestinal absorption rather than from depletion of the skeletal reserves.[4] Pregnancy is a period of high calcium demand because of fetal requirement .The studies have shown a strong correlation of calcium with preeclampsia. It has been proven that inverse association exists between calcium intake and development of hypertension during pregnancy. Pregnancy entails number of physiological events with implications regarding calcium metabolism: the extracellular fluid expands, the albumin level decreases, the glomerular filtration rate increases causing increase in calciuria and calcium is removed from the maternal system by transfer to fetus. These mechanisms all tend to promote lowering of maternal calcium concentration and present pregnant women for maintaining the levels within the narrow range necessary to preserve homeostasis. During development, as the fetal skeleton forms, more calcium is utilized in forming the bones. To meet these requirements, the mother's calcium absorption rate from gut increases, mainly in the last two trimesters. But in preeclampsia, these compensatory changes do not function adequately or function abnormally. . The calcium supplements in pregnancy reduce hypertension in pregnancy by decreasing smooth muscle contractility and causing vasodilation.[5,6]

AIMS AND OBJECTIVES

- Identify the prevalence of hypocalcemia in pregnant females with hypertensive disorders of pregnancy.

- Assess the compliance of calcium intake in the study group.

MATERIALS AND METHODS

Methodology

Hospital based Descriptive Analytical Study

STUDY DURATION:

The ethical approval was obtained from the institutional ethical committee in the month of April 2019 and the samples were collected from May 2019 to April 2020.The total duration of this study is One Year.

Study Setting

The study was done from the patients in Government Vellore Medical College & Hospital, Vellore, Tamil Nadu.

The patients were recruited from the preeclampsia clinic of the obstetrics OP department as well as from those who were admitted in the labour ward. informed consent was obtained from each patient and or their attenders, and the required investigations were done.

Based on the inclusion criteria, patients were recruited to the study

STUDY POPULATION

Inclusion Criteria

- Age more than or equal to 18 years
- Singleton pregnancy

- Suspected to have, or already diagnosed as gestational hypertension or preeclampsia or preeclampsia with severe features

Exclusion Criteria

- Patients diagnosed with chronic hypertension
- Patients with overt or gestational diabetes mellitus
- Patients with any other chronic illnesses like heart disease, renal failure, or other infectious diseases.
- Those who were reluctant to participate

STUDY SETTING

100 patients were recruited from the gynecology and obstetrics department of Government Vellore Medical College, both from the outpatient as well as those who were admitted in labour ward.

STUDY METHOD

Informed consent was obtained from all the patients and or their attenders. After getting the consent, Each of the participants will be asked pre-specified questions according to the Proforma. Blood pressure was checked for all the patients, and was confirmed again with repeated checking after 4 hours.

.. Required investigations were done in all the patients, which included:

- Complete blood count and hemogram
- Estimation of blood glucose level

- Renal Functoin Test
- Liver Function Test
- Serum calcium
- Urine routine and dipstick for proteinuria

Corrected calcium was derived for all the patients, using the equation, Corrected Calcium = serum calcium+0.8(4- serum albumin)

Patients, according to their disease characteristics, were divided into 3 diagnostic classes,

- Gestational Hypertension
- Pre-eclampsia
- Preeclampsia with severe features (synonymously used as severe preeclampsia and those who have any complications of preeclampsia)

ANALYSIS

A database was setup in Microsoft Excel, based on the collected data. Statistical Analysis was done using IBM SPSS 20.0.

Corrected calcium was divided into 3 categories, 7.5 – 7.9 mg/dl, 8-8.4 mg/dl and >8.5mg/dl.

Analysis using chi-square and pearsons correlation was applied to determine any correlation/ association between the variables. The findings are considered statistically significant if P value <0.05.

REVIEW OF LITERATURE

Definition & classification

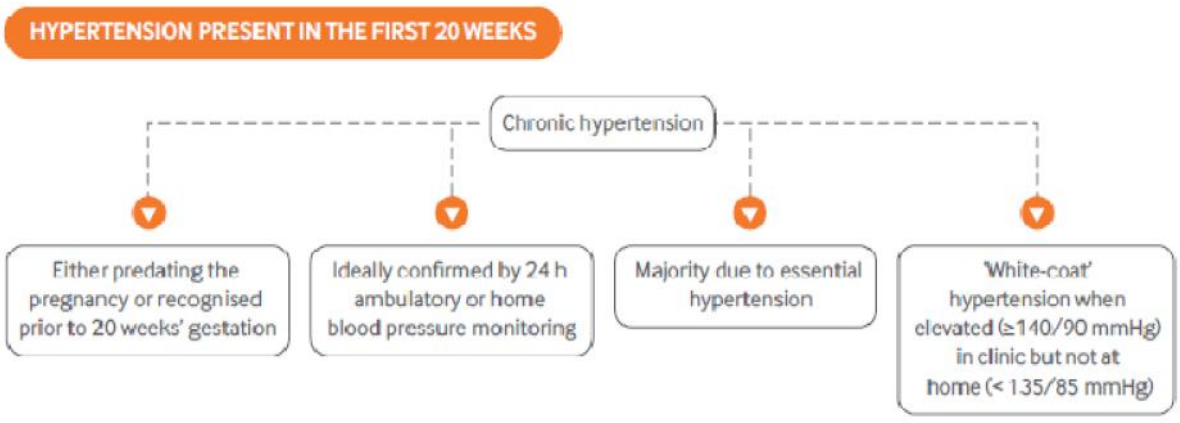
In concordance with the International Society for Study of Hypertension in Pregnancy (ISSHP)2018, the recommended classification for hypertensive disorders of pregnancy is as follows: [3]

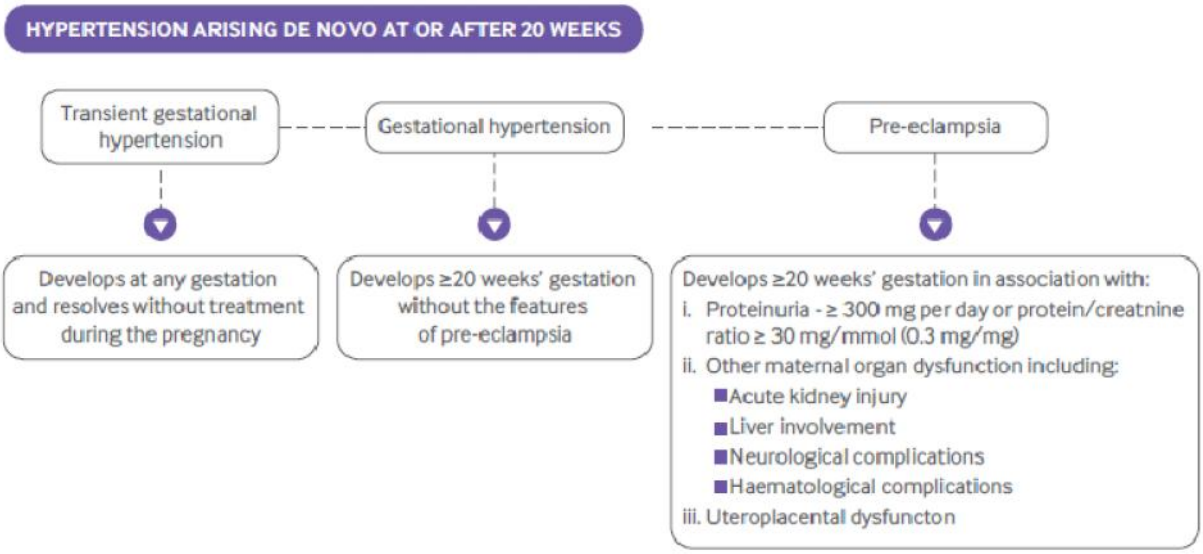
1) Hypertension known before pregnancy or present in the first 20 weeks
    a. Chronic Hypertension
        i. Essential
        ii. Secondary
    b. White coat hypertension
    c. Masked hypertension
2) Hypertension arising de novo at or after 20 weeks
    a. Transient gestational hypertension
    b. Gestational hypertension
    c. Preeclampsia de novo or superimposed on chronic hypertension
    d. Preeclampsia with severe features

- Preeclampsia, transient gestational hypertension, and gestational hypertension are characterized by the *new onset of hypertension (BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic) at or after 20 weeks' gestation*

- *Transient gestational hypertension* is hypertension that arises in the second or third trimester. The hypertension is usually detected in the clinic but then settles with repeated BP readings, such as those taken during the course of several hours in a day assessment unit. This differs from white-coat hypertension that, by definition, must be present from early pregnancy. Transient gestational hypertension is associated with a 40% risk of developing true gestational hypertension or preeclampsia in the remainder of the pregnancy, a fact that highlights the importance of carefully following-up such women
- *Masked hypertension* is another form of hypertension, characterized by BP that is normal at a clinic or office visit but elevated at other times, most typically diagnosed by 24-hour ABPM or automated home BP monitoring. Such a diagnosis is generally sought when a patient has unexplained abnormalities consistent with target organ damage from hypertension but no apparent hypertension. Although this is a form of chronic hypertension, the prevalence of masked hypertension and its significance in pregnancy are less well studied; for now, we do not recommend seeking this diagnosis in the absence of the above features (ie, unexplained chronic kidney disease [CKD], left ventricular hypertrophy, or retinopathy recognized early in pregnancy).

- *White-coat hypertension* refers to elevated office/clinic (≥140/90 mm Hg) BP but normal BP measured at home or work (<135/85 mm Hg); it is not an entirely benign condition and conveys an increased risk for preeclampsia
- Although ISSHP has formerly published a statement documenting severe preeclampsia, they agree with the position of American College of Obstetricians and Gynecologists (ACOG) and others that preeclampsia may become a major threat to mother and baby at any stage, and classification into mild or severe disease can be erroneous or misleading to less experienced clinicians. ACOG has eliminated the diagnosis of severe preeclampsia and instead discusses preeclampsia with or without severe features, a sensible clinical approach.





DIAGNOSIS OF HYPERTENSIVE DISORDERS IN PREGNANCY

Hypertension

- Defined as systolic BP ≥140 and/or diastolic BP ≥90 mm Hg.
- BP should be repeated to confirm true hypertension.
- If BP is severe (systolic BP ≥160 and/or diastolic BP ≥110 mm Hg), then the BP should be confirmed within 15 minutes;
- For less severe BP, repeated readings should be taken for a few hours.

Chronic Hypertension

- Chronic hypertension refers to high BP predating the pregnancy or recognized at <20 weeks' gestation.

In practice, this is often diagnosed for the first time at the first or early second trimesters booking visit.

- The majority of cases are because of essential hypertension.
- Secondary causes are uncommon.

Transient Gestational Hypertension

- Transient gestational hypertension is de novo hypertension that develops at any gestation that resolves without treatment during the pregnancy.

Gestational Hypertension

- Gestational hypertension is persistent de novo hypertension that develops at or after 20 weeks' gestation in the absence of features of preeclampsia.

Preeclampsia

Preeclampsia is gestational hypertension accompanied by ≥1 of the following new-onset conditions at or after 20 weeks' gestation:

- Proteinuria

  Or in the absence of proteinuria, other maternal organ dysfunction, including:
- AKI (creatinine ≥90umol/L; 1 mg/dL)
- Liver involvement (elevated transaminases, eg, alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain
- Neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata)
- Hematological complications (thrombocytopenia–platelet count <1.5lakh cells/mm3, disseminated intravascular coagulation, hemolysis)
- Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery [UA] Doppler wave form analysis, or stillbirth)

Preeclampsia with severe features:

"Preeclampsia with severe features" is diagnosed in a patient with preeclampsia, when any one or more of the following finding is present:

Severe blood pressure elevation

- Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on 2 occasions minimum 4 hours apart while the patient is at bed rest.

Symptoms of dysfunction of central nervous system

New onset visual or cerebral such as

- Photopsia, cortical blindness, scotomata, retinal vasospasm
- Severe headache or headache that persists and progresses inspite of giving analgesics and no alternate diagnosis could be made.

Hepatic abnormality

- Impairment of liver function which cannot be accounted for by another diagnosis and characterized by concentration of serum transaminase more than 2 times the upper limit of the normal range or
- Persisting severe right upper quadrant or epigastric pain not resposive to medication and not accounted for by an alternative diagnosis

Thrombocytopenia : <100,000 platelets/microL

Renal abnormality:

Renal insufficiency (serum creatinine >1.1 mg/dL [97.2 micromol/L] or a doubling of the serum creatinine without any other renal disease.

Pulmonary edema

Preeclampsia Superimposed on Chronic Hypertension

About 25% of women with chronic hypertension will develop superimposed preeclampsia. These rates may be higher in women with underlying renal disease.

- This diagnosis is made when a woman with chronic essential hypertension develops any of the above maternal organ dysfunction consistent with preeclampsia.
- Rises in BP per se are not sufficient to diagnose superimposed preeclampsia, as such rises are difficult to distinguish from the usual increase in BP after 20 weeks' gestation.
- In the absence of preexisting proteinuria, new-onset proteinuria in the setting of a rise in BP is sufficient to diagnose superimposed preeclampsia.
- In women with proteinuric renal disease, an increase in proteinuria in the pregnancy is not sufficient per se to diagnose superimposed preeclampsia.
- Diagnostic biomarkers (particularly PlGF) may assist with diagnosis and prognosis in the future but are not yet recommended for this diagnosis.
- Fetal growth restriction may be part of chronic hypertension per se and cannot be used as a diagnostic criterion for superimposed preeclampsia.

Abnormal Proteinuria in Pregnancy

- Proteinuria is to be assessed initially by automated dipstick analysis of urine if not available, careful visual dipstick analysis can be done.
- Ideal is to measure the 24 hour urine protein.

- If positive (≥1+, 30 mg/dL), then spot urine protein/creatinine (PCr) ratio should be performed.
- A PCr ratio ≥30 mg/mmol (0.3 mg/mg) is abnormal.
- If the dipstick is negative, usually it can be accepted, and further spot sampling is not mandatory.
- Proteinuria is not required for a diagnosis of preeclampsia.
- If the proteinuria is massive (>5 g/24 h) it is associated with more severe neonatal outcomes.

Even with these well defined criteria, diagnosing pre-eclampsia still remains a challenge. There are two main phenotypes, the maternal and the placental. The former is associated with inflammation and endothelial cell activation, while the more severe early onset placental phenotype is associated with fetal growth restriction. Women may present with late-onset hypertension and proteinuria, with an absence of fetal growth restriction near term and they have few long-term consequences for mother or infant. But, early onset, severe maternal disease is often associated with fetal intrauterine growth restriction.

Even when there is severe preterm disease, a woman can be asymptomatic. Douglas and Redman reported absence of hypertension and proteinuria in 38% of patients who presented with an eclamptic seizure pointing out that severe maternal adverse events occur even when the conventional clinical definition of pre-eclampsia is unmet. Unrecognized fetal compromise contributes to the high rate of fetal demise, and 1 in 20 stillbirths without congenital abnormality is complicated by, and/or attributable to, pre-eclampsia[(7)].

New Developments in Prediction (7)

Significant variations have been shown in Mean first-trimester levels of

- pregnancy-associated para protein A (PAPP-A),
- a disintegrin and metalloproteinase 12 (ADAM12),
- and placental growth factor (PlGF);
- placental protein 13;
- angiopoietin 1 and 2;
- inhibin A and Activin A,
- soluble endoglin, and soluble fms-like tyrosine kinase 1 (sFlt-1);
- and human chorionic gonadotropin (hCG) .
- Many studies have shown that levels of cell-free fetal DNA (cffDNA) are increased in women with pre-eclampsia. The hypothesis for raised levels of cffDNA is of, hypoxia reperfusion injury, abnormal placentation and release of apoptotic fragments containing cffDNA into maternal circulation.

Novel Methods of Diagnosis

There is emerging role of angiogenic biomarkers in the diagnosis of pre-eclampsia. Several angiogenic factors have been implicated recently in the pathogenesis of PE. Several studies propose that in those women in whom we clinically suspect pre-eclampsia an sFlt-1:PIGF ratio less than 38 can be used to rule out the short-term development of the pre-eclampsia syndrome[8]

Epidemiology[1]

Since the diagnostic criteria of Pre-eclampsia is very complex, it has affected the accuracy in determining its incidence, especially across various

countries. Ascertainment is not complete in low and/or middle income countries (LMIC), and standardization of diagnostic accuracy is almost not possible. A world-wide estimate derived from data of around 39 million pregnancies suggests an incidence of 4.6% Wide differences are found regionally , with a reported incidence as low as 0.4% in Vietnam. The condition is especially common in women belonging to, or with ancestry from, sub-Saharan Africa. The incidence of eclampsia is lower but very much varying, ranging from 0.015% in Finland15 to an estimated 2.9% in some parts of Africa illustrating that the rate depends to some extend on access to obstetric care. Maternal mortality from pre-eclampsia/eclampsia is highest in LMIC, and worldwide, it accounts for at least 63,000 maternal deaths per annum. Major breakthroughs in clinical management of PE were few, and the substantial improvements in maternal death rates from pre-eclampsia/eclampsia in developed countries were achieved by empirical advances in care, professional education, higher clinical competence, and, more recently, consistent application of national guidelines such as in the UK from the National Institute for Health and Care Excellence (NICE). In LMIC, which lack equivalent resources, preeclampsia accounts for nearly 30% of all maternal deaths in 29 countries (20 per 100 000), a mortality rate of 0.8% for affected women. This is more than 200 times higher than the mortality specific rate of 0.03% in the UK, assuming that the national incidence of pre-eclampsia is about 3%.

Etiology[9]

A study which was designed to elucidate the etiology has come to the conclusion that, preeclampsia is a condition which arises as a result of very complex interaction between economic, nutritional, psychosocial, environmental and genetic factors, that results in a common alteration, that is an imbalance in the release of free radicals, , O2 NO - and peroxynitrate.

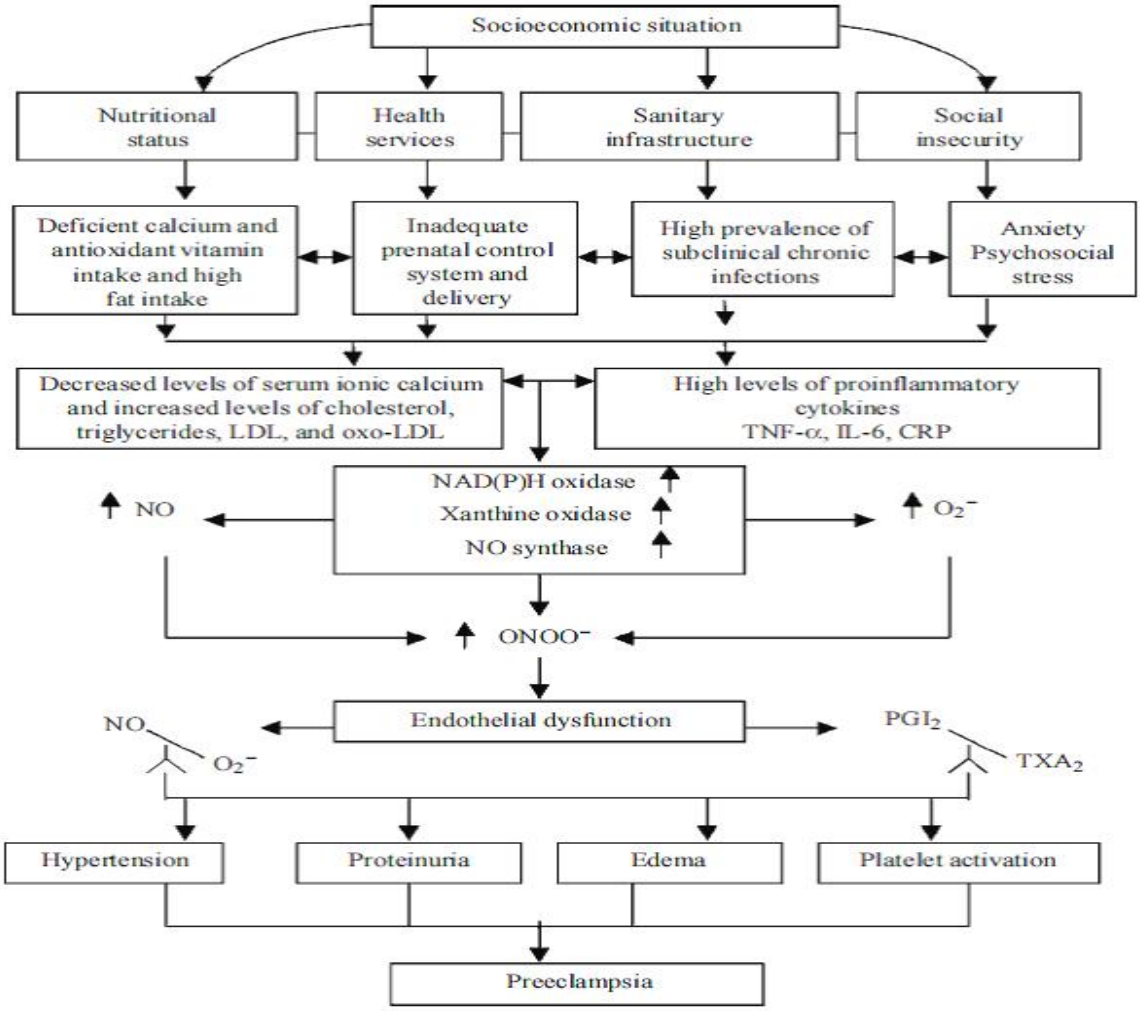


Figure 1 Interaction between different social, economic, nutritional and environmental factors that contribute to creating an imbalance between nitric oxide/superoxide (NO/O2-) that leads to the subsequent development of preeclampsia. (CRP, C-reactive protein; PGI2, prostaglandin I2; TXA2, thromboxane A2)

Risk factors

Stong Risk Factors[7]

- previous pre-eclampsia or hypertension in pregnancy,
- chronic kidney disease,
- chronic hypertension,
- diabetes (type 1 or 2), and
- autoimmune disorders such as SLE or APLA syndrome.

Moderate Risk Factors

- Age more than or equal to 35 years
- Interval between two consequent pregnancy is more than 10 years
- BMI of 35 kg/m2 or more
- history of pre-eclampsia in the family, and
- multiple pregnancy
- Previous stillbirth
- Nulliparity
- Reduced school education
- Assisted reproduction
- Previous intrauterine growth restriction
- Previous placental abruption
- Obstructive sleep apnoea

Recent studies have revealed a reduced level of Vitamin D at initial weeks of gestation is associated with increased risk of preeclampsia. There is a hypothesis that low-circulating 1,25(OH)2D results in an imbalance in immune function, leading to a shift towards a pro-inflammatory internal mileu and disrupted implantation . Increased TNF stimulates catabolism of 1,25(OH)2D,

contributing to the lower circulating calcium levels that are observed in pregnancies diagnosed with PE .[10] But study by Hashemipour et al has failed to establish significant association of vitamin D level with PE, whereas they found out reduced corrected serum calcium was associated with six times increased risk of severe pre-eclampsia.[11]

Pathophysiology [1]

Several mechanisms of disease are proposed in pathogenesis of preeclampsia like: [12]

- Chronic uteroplacental ischemia
- Immune system maladaptation
- VLDL toxicity
- genetic imprinting
- increase in the apoptosis and necrosis of trophoblast and
- an exaggeration in maternal inflammatory response to deported trophoblasts.

There are more recent observations suggesting a possible role of imbalances between angiogenic factors in preeclampsia pathogenesis.

In terms of the pathophysiology, there is emerging evidence that there are at least two sub-types:

Early-onset and late onset pre-eclampsia.

The early onset form is mailny due to defect in the placentation during the first few weeks of gestation, and shares a common initiating pathophysiology like other disorders of placentation, mainly FGR. Evidence

from various studies indicate that the level of insult to the placenta is more in pre-eclampsia than in FGR, stimulating the release of a heavier burden of pro-inflammatory factors from the placenta. The concentration of these factors, and their interactions with the maternal constitution, will determine the inflammatory response that differentiate between the two conditions. In contrast, late onset preeclampsia seems to be driven by oxidative changes in the placenta initiated by a progressive mismatch between maternal perfusion and feto-placental demands, together with a maternal predisposition to cardiovascular disease. Eventhough they are presented as distinct sub-types, in reality the balance between the placental and maternal causations varies among individuals across the spectrum of gestational age at clinical presentation.

Factors originating from the placenta into systemic circulation are thought to result in the maternal syndrome of pre-eclampsia. Oxidative stress of the syncytiotrophoblast, the cell that forms epithelial covering of the placental villi in contact with maternal blood, is one of the hallmarks, especially in the early onset form. When stressed, the syncytiotrophoblast releases a complex myriad of factors, including exosomes , pro-inflammatory cytokines, cell-free fetal DNA,and anti-angiogenic agents, into the maternal circulation. These disturb maternal endothelial function resulting in a systemic inflammatory response, the clinical syndrome of pre-eclampsia. Different stressors can perturb the syncytiotrophoblast, but the important one in early onset pre-eclampsia is uteroplacental malperfusion secondary to defective remodeling of

the uterine spiral arteries. In contrast, in late onset cases the cause is more toward an increasing mismatch between normal maternal perfusion and the metabolic demands of the placenta and fetus, along with a maternal predisposition to inflammation, a high BMI, and/or a high arterial pressure.

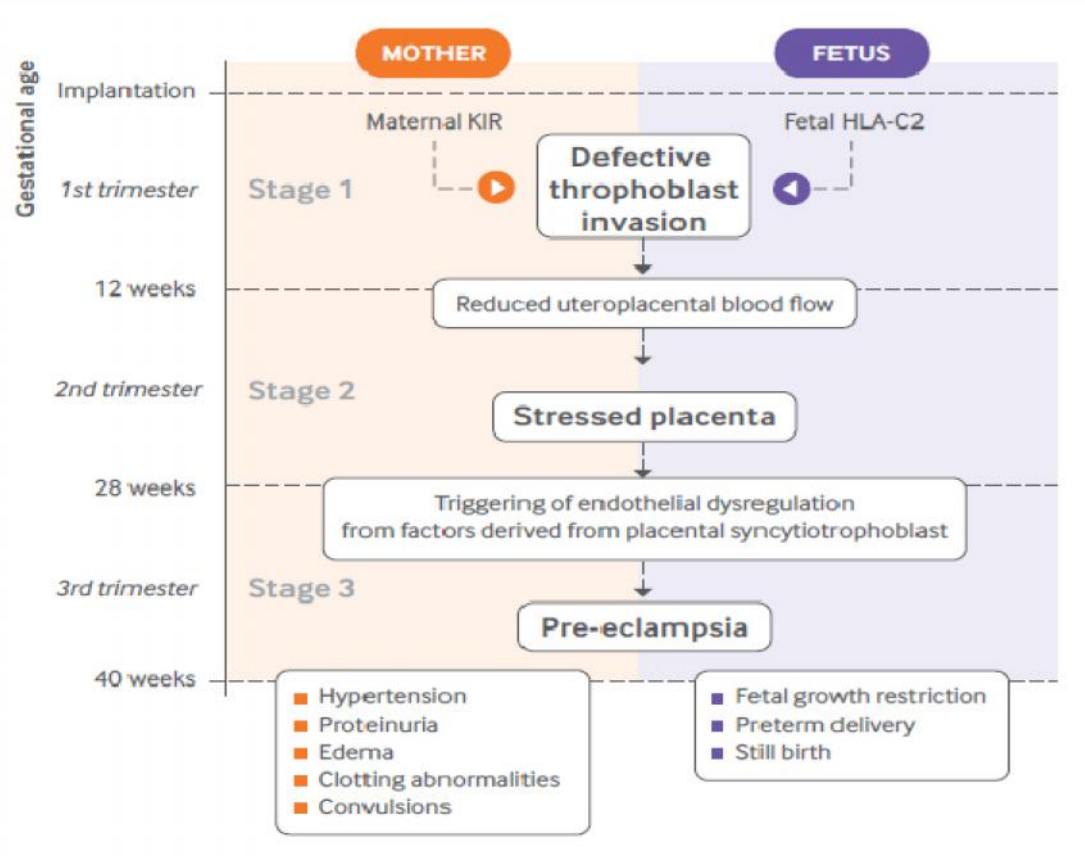


Figure 2 Pathogenesis of pre-eclampsia with the subsequent effects on mother and fetus. The failure of trophoblast uterine interactions in the first trimester leads to a stress response in the placenta. This may affect growth and development of the villous tree, affecting transfer of oxygen and nutrients to the fetus. The stress to the syncytiotrophoblast leads to shedding of a range of factors into the systemic circulation. These factors cause a systemic inflammatory response resulting from disruption of the homoeostatic functions of the maternal endothelium, including regulation of clotting, fluid transfer, and blood pressure

Changes in Placenta

The gross placental lesions mainly reflect maternal malperfusion, villous-free placental lakes, with infarcts of the villous tissue in different stages of resolution, , deposition of fibrin , and inflammation. These changes point toward high level of placental stress at the molecular level. Thus, oxidative stress and activation of the unfolded protein response (UPR) are greater in early than in late onset pre-eclampsia. One consequence of UPR is suppression of synthesis of non essential proteins. And this suppression might explain the presence of fetal growth restriction (FGR) in early onset pre-eclampsia.

From placental stress to maternal syndrome

Placental stress leads to maternal peripheral endothelial cells dysfunction, a systemic inflammatory response and the clinical syndrome of pre-eclampsia. Blood flow to maternal organs is compromised, and physiological assessment indicates activation of the coagulation cascade, vasospasm, and reduced plasma volume before clinical disease.

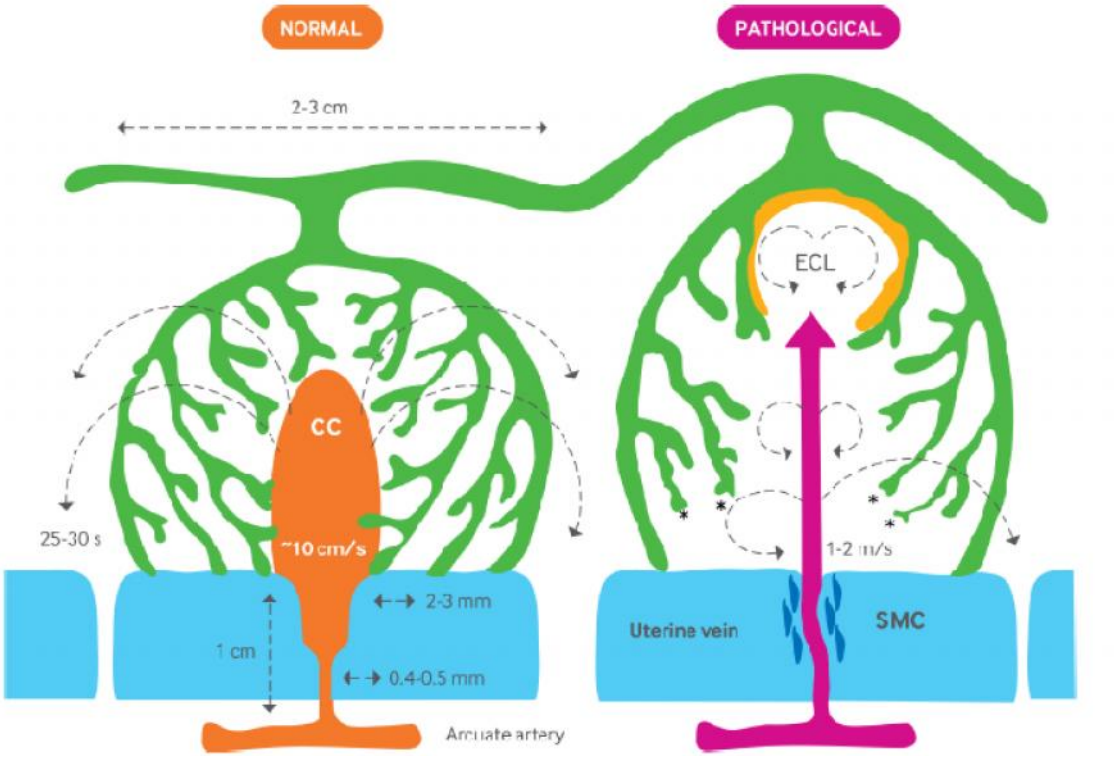


Figure 3 Diagrammatic representation of the effects of spiral artery remodeling on the inflow of maternal blood into the intervillous space in normal and pathological pregnancies. Dilation of the distal segment of the spiral artery in normal pregnancies reduces the velocity of incoming blood, and the residual momentum carries the blood into the central cavity (CC) of a placental lobule, from where it disperses evenly between the villi. Transit time to the uterine vein is estimated to be in the order of 25-30 s, allowing adequate time for oxygen exchange. In pathological pregnancies, where no or very limited conversion occurs, the maternal blood enters the intervillous space in a jet-like spurt at speeds of 1-2 m/s. Flow is likely to be turbulent, indicated by the circular arrows, and the high momentum damages the villi, forming echogenic cystic lesions (ECL) lined by thrombus (stippled). The transit time will be reduced, so that oxygen exchange is impaired. Trophoblastic microparticulate debris may be dislodged from the villous surface. The retention of smooth muscle cells (SMC) around the spiral artery will increase the risk of spontaneous vasoconstriction and ischemia-reperfusion injury

At high levels of activation, the UPR changes from principally homoeostatic to proapoptotic and pro-inflammatory pathways. Therefore , the increased levels of placental senescence, maternal serum pro-inflammatory cytokines, cell-free fetal DNA, leptin, placental apoptotic debris, soluble receptor (sFLT) for vascular endothelial growth factor (VEGF), and the lower levels of placental growth factor (PlGF) reported in early onset pre-eclampsia compared with fetal growth restriction alone may reflect the severity of the initiating maternal malperfusion. Of the potential mediators listed, the balance between sFLT and PlGF is of particular clinical importance. The elevated levels of sFlt are thought to bind and reduce the bioavailability of VEGF to the maternal endothelial cells, impairing their endogenous production of nitric oxide and causing vasoconstriction Because of the endothelial involvemet, preeclampsia is a global systemic syndrome affecting multiple organs including the central nervous system, kidney, liver, and the coagulation cascade to varying degrees in different women. Metabolic abnormalities, including insulin resistance dyslipidaemia, , and inflammatory markers, are also characteristic There are striking differences in rate of progression and the severity of the disorder. Pre-eclampsia can present as a mild disorder that progresses slowly or one that develops rapidly to a life threatening condition.

Physiological Changes in Preeclampsia[12]

Vascular changes[13]

Other than hypertension, females with preeclampsia or eclampsia typically lack the hypervolemia which is normally associated with pregnancy; and hence , hemoconcentration is a frequent finding. In addition, there is interaction of various vasoactive agents, like thromboxane A2 (potent vasoconstrictor), prostacyclin (vasodilator), nitric oxide (potent vasodilator), and endothelins (potent vasoconstrictors) which results in yet another significant change quoted in preeclampsia: that is intense vasospasm. Attempts to correct the contracted intravascular space with vigorous fluid therapy are usually ineffective and could be dangerous due to the presence of capillary leak and reduction in colloid oncotic pressure often associated with preeclampsia. Aggressive fluid therapy can lead to elevation of the pulmonary capillary wedge pressure (PCWP) and increases risk of pulmonary edema.

Hematologic Changes[14]

Various hematologic changes may also occur in women with preeclampsia, mainly in those who have preeclampsia with severe features. Hemolysis and thrombocytopenia usually occur and can reach dangerous levels as a part of HELLP syndrome. Thrombocytopenia is due to increased activation, aggregation, and consumption of platelets and is considered a marker of severity of disease. A platelet count less than 1.5lakhs is seen in almost 20%

of patients with preeclampsia. One should keep in mind that hemolysis and hemoconcentration can occur in pregnancy, while interpreting a hematocrit value. Increased serum LDH of more that 600IU/L should be a sign of hemolysis, as it is present in high concentration in RBCs.

Hepatic Changes[15]

Hepatic function can be significantly altered in women who has preeclampsia with severe features. Alanine aminotransferase(ALT) and Aspartate aminotransferase (AST) may be elevated. In liver dysfunction as a result of preeclampsia, AST is the dominant transaminase released into the peripheral circulation. It is related to periportal necrosis. The fact that increase of AST is more than the rise in ALT in the early stages, usually aids in differentiating preeclampsia from other causes of liver parenchymal injury. in the latter cases, ALT is more elevated than AST. In preeclampsia, increase in LDH can be due to two mechanisms:

- Liver dysfunction (LDH from ischemic or necrotic hepatocytes, or both)
- Hrmolysis(from destructed erythrocytes)

Increased bilirubin secondary to hemolysis develops only in later stages of the disease. Likewise, imbalances in synthetic function of liver also develop only in advanced preeclampsia. Evaluation of these coagulation parameters is useful only when either the platelet count is below 1.5lakhs , there is significant liver dysfunction, or there is suspected abruption of the placenta.

Renal Changes[16]

The classic histopathologic renal changes described in preeclampsia is glomerular endotheliosis. It consists of swollen, vacuolated endothelial cells with fibrils, subendothelial deposits of protein reabsorbed from the glomerular filtrate, swollen mesangial cells, and tubular casts. Due to increase in tubular permeability to LMW proteins like globulin, albumin, haemoglobin or transferring, proteinuria in preeclampsia is nonselective. As there is an increase in tubular reabsorption of calcium, there is reduction in urinary calcium. [17]. In women with preeclampsia, as there is contraction of the intravascular space secondary to vasospasm it leads to worsening renal sodium and water retention. The normally increased renal blood flow and glomerular filtration rate and the expected decrease in serum creatinine might not occur in females with preeclampsia, especially if the disease is severe. Preeclampsia with severe features include acute renal deterioration as part of the clinical spectrum. Oliguria in severe preeclampsia is due to intrarenal vasospasm resulting in an approximate 25% reduction in glomerular filtration rate. In these patients, transient oliguria (less than 100 mL over 4 hours) is a common observation in either during labor or the first 24 hours of the postpartum period. In pregnancy, there is a normal increase in the level of uric acid. And this is due to:

- Increased production from placenta and fetus
- Reduction in binding to albumin
- Reduction in uric acid clearance

There is a significant increase of serum uric acid concentration in preeclampsia.[18]. This is due to increase in the reabsorption and reduction in the excretion of uric acid from the proximal renal tubules.

Complications[2]

Maternal

- ✓ HELLP or partial HELLP syndrome (83.3%) was the most common cause of mortality in Preeclampsia.
- ✓ Eclampsia
- ✓ Haemorrhagic stroke and
- ✓ pulmonary edema are the most common cause of death in patients with eclampsia.
- ✓ Short term complications include :
  - central nervous system dysfunction,
  - Hepatocellular injury,
  - thrombocytopenia,
  - acute disseminated intravascular coagulation (DIC),
  - oliguria,
  - pulmonary edema,
  - cerebrovascular events and
  - placental abruption

Fetal Consequences[19]

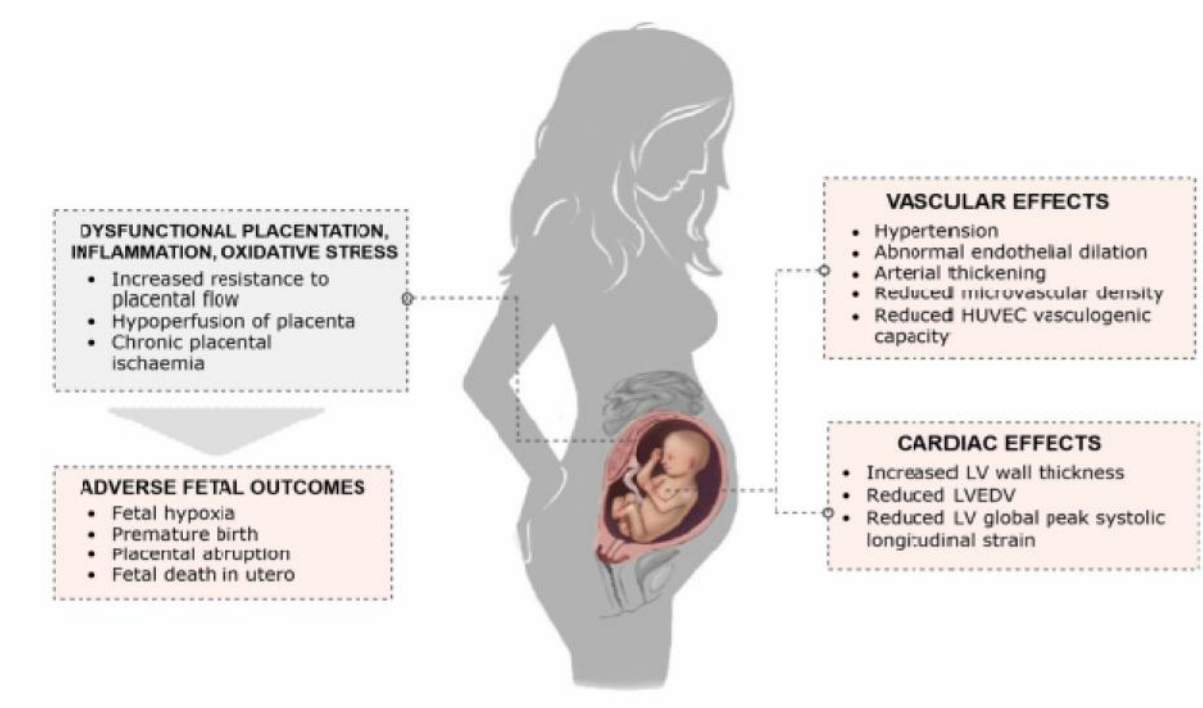


Figure 4 Effects of preeclampsia on the foetus and o_spring. HUVEC stands for human umbilical vein endothelial cells; LV, left ventricle; LVEDV, left ventricular end-diastolic volume[20]

As there is impairement in the blood flow to the uteroplacental unit due to failure of physiologic transformation in the spiral arteries or due to placental vascular insults, or both, manifestations of preeclampsia are seen in the fetal–placental unit. Among preeclamptic women, clinical manifestations that follow from this uteroplacental ischemia are

- fetal growth restriction,(FGR)
- oligohydramnios,
- Abruption of the placenta

- Doubtful status of the fetus on antepartum surveillance
- Consequently, these foetuses are at increased risk of preterm delivery.
- small for gestational age (SGA) neonate,
- low birth weight neonate,
- intrauterine and perinatal death

HELLP SYNDROME[21]

The hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is more severe form of preeclampsia as it is associated with increased maternal morbidity and mortality.

Main clinical feature of HELLP syndrome are generalised tiredness and pain in the right upper quadrant of abdomen in up to 90% of cases along with and nausea and vomiting in 50% of cases.

Following criteria is more commomly used to make a diagnosis of HELLP syndrome:

- lactate dehydrogenase (LDH) elevated to600 IU/L or more,
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated more than twice the upper limit of normal, and
- the platelets count less than 1lakh cells/mm3

HELLP syndrome can also have an insidious and atypical onset, with up to 15% of the patients lacking either hypertension or proteinuria.

Eclampsia

Eclampsia is defined as new-onset tonic-clonic, focal, or multifocal seizures in the absence of any other causative factors such as epilepsy, intracranial hemorrhage, cerebral arterial ischemia and infarction, or drug use. Eclampsia is among the more severe manifestations of the disease**.** Some alternative causes for seizures are likely in cases where new-onset seizures occur after 48–72 hours postpartum or when seizure occurs during the administration of magnesium sulfate. In low-resource settings particularly, Eclampsia is a significant cause of maternal death. Seizures can lead to severe maternal hypoxia, aspiration pneumonia and trauma. Usually residual neurologic damage is rare, but some women can have short and long-term consequences like impaired memory and cognitive function, particularly after recurrent seizures or uncorrected severe hypertension resulting in cytotoxic edema or infarction. In upto one fourth women after eclampsia, Permanent loss of white matter loss has been documented on brain imaging (MRI), however, this does not correlate to significant neurologic deficits. Eventhough eclampsia can occur in the absence of any warning signs, in 78-83% cases, it is preceded by premonitory signs and symptoms of cerebral irritation, like, photophobia, blurred vision, persistent and severe frontal or occipital headache, and altered mental status. Eclampsia can manifest before, during, or after labour. Of note, eclampsia can be the very first manifestation of the disease in 20-38% patients, without any classic signs of preeclampsia(proteinuria or hypertension)

Headaches are believed to be due to the elevated cerebral perfusion pressure, cerebral edema, and hypertensive encephalopathy. The term preeclampsia doesn't generally mean that seizure must occur if no prophylaxis is given. Usually it occurs only in a small proportion, i.e, 1.9% in those with preeclampsia, and 3.2% in those who has preeclampsia with severe features.

Posterior reversible encephalopathy syndrome (PRES) is an array of neurological signs and symptoms such as vision loss or deficit, headache, seizure, and altered sensorium or confusion. Presence of these clinical features arouses a high suspicion of PRES. But it is confirmed in the MRI of brain, where there is vasogenic edema and hyperintensities in the posterior aspects of the brain. Risk of PRES is increased in those women with preeclampsia, who has symptoms of headache, altered mental status or visual abnormalities.

Reversible cerebral vasoconstriction syndrome (RCVS) is another condition that may be confused with eclampsia or preeclampsia. RCVS is characterized by multifocal narrowing of the cerebral arteries which is reversible along with clinical features that typically include thunderclap headache and, less commonly, focal neurologic deficits related to brain edema, stroke, or seizure.

Treatment of women with PRES and RCVS include medical management of hypertension, antiepileptics and long-term neurologic follow-up.

Long Term Implications

There is said to be life-long implications on both the mother and the fetus. There is a meta analysis suggesting nearly two-fold increase in the cardiovascular risk and death in females with history of prior pre-eclampsia.[22] This increase becomes 6-9 fold if preeclampsia occurs in more than one pregnancy. There is another study suggesting increased cognitive dysfunction and white mater lesions in MRI brain formerly pre-eclamptic mothers.[23] Another study reveals a reduced risk of carcinoma breast in previously pre eclamptic women, and this protection is much more if the fetus is a boy.[24]

The infant also is found to have increased risk of cardiovascular diseases. During young adulthood, they have a higher blood pressure and increased risk for stroke later in life[25]. There are also some studies indicating increased psychiatric issues including mood and anxiety disorders[26]. One third of the infants in preeclamptic pregnancy have FGR which itself poses increased risk of obesity, hypertension, diabetes, and other chronic diseases.

Prevention of Preeclampsia[3,12]

Use of low-dose aspirin is advised, (preferably 150 mg/d) started before 16 weeks of pregnancy for those women at increased risk for preeclampsia, particularly if any of the following conditions exist:

- Previous preeclampsia

- Preexisting medical conditions (including chronic hypertension, underlying renal disease, or pregestational diabetes mellitus)
- Antiphospholipid antibody syndrome
- Multiple pregnancy
- Obesity
- Conceived with assisted reproductive techniques

If there is a chance of low calcium intake,(<600 mg/d), use calcium 1.2 to 2.5 g/day in women at increased risk.

Pregnant women are advised to get exercise at least 3 days per week for an average 50 minutes per week using a combination of aerobic, strength exercise, and flexibility training; this is associated with less weight gain and helps in reducing the incidence of hypertensive disorders in pregnancy.

Predicting the course of established Preeclampsia

A clinical predictive model, named the PIERS model (Preeclampsia Integrated Estimate of Risk), is used to predict the likelihood of a composite severe adverse outcome in the mother using the following datas collected from 0 to 48 hours after admission with preeclampsia:

- Gestational age
- Chest pain or dyspnea
- Oxygen saturation

- Platelet count
- Serum creatinine
- Aspartate aminotransferase

In practice, pulse oximetry is used infrequently and defaults to an oxygen saturation of 97% in the risk model when oximetry is not available. ISSHP recommends this as a useful adjunct in the initial assessment of women with preeclampsia.

Management of Preeclampsia[12]

Delivery v/s Expectant Management

At the initial workup, a complete blood count with platelet estimate, serum creatinine, LDH, ALT, AST, and testing for proteinuria should be obtained in adjunct with an elaborate clinical evaluation od the mother and fetus. When the diagnosis is uncertain, for example, in evaluation of possible preeclampsia superimposed upon chronic hypertension, an estimation of serum uric acid may be considered. Evaluation of the fetus should include ultrasonography for estimated fetal weight and amniotic fluid index, as well as fetal antepartum testing. Further management will depend on the results of the above evaluation and gestational age. Decision regarding delivery must be based on the maternal and fetal risk benefit ratio.

Gestational hypertension and preeclampsia without severe features

If a pregnant woman is having only gestational hypertension, or preeclampsia alone (i.e, without any severe features) continued observation is considered appropriate if she is not term. Retrospective data suggest that in the absence of severe features, the management plan should be directed toward prolonging the pregnancy until delivery, at gestation of 37 0/7 weeks if there is no evidence of abnormal antepartum testing, preterm labor, premature rupture of membranes or vaginal bleeding, for the benefit of neonate.

The risks in expectant management in the late preterm period include

- Progression to severe hypertension,
- Development of eclampsia,
- Complication by HELLP syndrome,
- abruption of the placenta
- fetal growth restriction and
- fetal demise

However, these risks are small and counterbalanced when compared to the increased number of admissions to the neonatal intensive care unit, due to neonatal respiratory complications and neonatal death that is associated with delivery prior to 37 0/7 weeks of gestation. Expectant management of women with gestational hypertension or preeclampsia without severe features include continued monitoring with

- determination of fetal growth by serial ultrasonography
- weekly antepartum testing,
- close monitoring of blood pressure, and
- regular laboratory tests for preeclampsia.

The frequency of these tests should be modified based on clinical findings and patient symptoms. Once there is proteinuria and the diagnosis of preeclampsia has been established, further quantification of proteinuria is not necessary.

Women should be advised to report immediately in any case of persistent, concerning, or unusual symptoms.

In women with gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery is recommended upon diagnosis, rather than expectant management.

Preeclampsia with severe features:

This might result in many acute and long-term complications for the woman and her newborn. Complications in the mother include

- stroke, acute respiratory distress syndrome,
- coagulopathy,
- retinal injury.

- myocardial infarction,
- pulmonary edema and
- renal failure.

In the context of a pre-existing medical condition, these complications are more likely. The clinical course of preeclampsia with severe features is typically characterized by progressive deterioration in the condition of both the mother and fetus. Therefore, when there are any of the severe features in patient with gestational hypertension or preeclampsia, delivery is recommended at or after 34 0/7 weeks. It is not ideal to delay the delivery in the late preterm period for the administration of steroids.

If the condition of both the mother and fetus is very stable, then expectant management may be considered in patient with preeclampsia with severe features at less than 34 0/7 weeks of gestation. Close clinical monitoring of the condition of mother and fetus is necessary and laboratory testings done in preeclampsia, to keep an eye on development of any complications should be done serially. The expectant management before 34 0/7 days, is based on very strict selection criteria, and should be done only in setting where there are appropriate resources for the mother and neonate. If at any time there is deterioration in the maternal and fetal condition during the expectant management, delivery is recommended. Below are some of the indications for expedited delivery irrespective of gestational age:

Maternal

- severe range uncontrolled blood pressures (persistent SBP≥ 160mmHg or DBP ≥110mmHg, refractory to antihypertensive medication)
- Persistent headaches, not responding to treatment
- Epigastric or right upper quadrant pain in the abdomen, refractory to repeat dose of analgesics
- Central Nervous System dysfunction in the form of Visual disturbances, motor deficit or altered sensorium
- Cerebrovascular accidents
- Myocardial infarction
- HELLP syndrome
- New onset or worsening of previously present renal dysfunction (serum creatinine greater than 1.1 mg/dL or twice baseline)
- Pulmonary edema
- Progression Eclampsia
- When there is suspected acute placental abruption or bleeding per vaginum in the absence of placenta previa.

Fetal

- Abnormal fetal testing on antepartum surveillance
- Fetal demise
- Fetus not expected to survive at the time of diagnosis (eg, presence of a lethal anomaly, extreme prematurity)
- Persistent reversal of end-diastolic flow in the umbilical artery

Administration of corticosteroids for fetal lung maturation is recommended if delivery is indicated prior to 34 0/7 weeks of gestation however, it not advisable to delay the delivery of optimal corticosteroid exposure.

Inpatient Versus Outpatient Management

Ambulatory management at home (outpatient management) is an option only for those with gestational hypertension or preeclampsia without severe features and it requires frequent fetal and maternal evaluation. Hospitalization is appropriate for women with severe features and for women in whom adequate adherence to frequent monitoring is a doubt. Because assessment of blood pressure is essential for this clinical condition, health care providers are encouraged to follow the recommendations from regulatory bodies regarding the proper technique for blood pressure measurement. In those whom home management is selected, frequent and regular fetal and maternal evaluation are required. Fetal monitoring consists of ultrasonography to determine growth of

the fetus every 3–4 weeks of gestation and amniotic fluid volume assessment at least once in a week.

Maternal evaluation consists mainly of frequent evaluation to pick up either the development of or worsening of preeclampsia. In these women, weekly evaluation of platelet count, serum creatinine, and liver enzyme levels is recommended. In addition, for women with gestational hypertension alone, assessment of proteinuria is recommended once in a week. However, if one is worried about the progression of disease these tests should be repeated more frequently. Also women should regularly be asked about the onset of symptoms of preeclampsia with severe features (eg, severe headaches, visual changes, epigastric pain, and shortness of breath). Blood pressure measurements and assessment of symptoms are recommended serially, using a combination of in-clinic and ambulatory approaches, with at least one visit per week in-clinic.

Intrapartum Management

In addition to appropriate management of labour and delivery, the two important pillars in the management of women with preeclampsia during labour and delivery are

1) Prophylaxis for seizure prevention and

2) management of hypertension.

Prevention of Seizures

Once preeclampsia has been diagnosed, The prevention of eclampsia is empirically based on the concept of timely delivery. A significant body of evidence points toward the efficacy of magnesium sulfate to prevent seizures in women with preeclampsia with severe features and eclampsia. It is recommended that magnesium sulfate should be used for the prevention and treatment of seizures in women with gestational hypertension with severe features and preeclampsia with severe features or eclampsia. There is no consensus about the prophylactic use of magnesium sulfate to prevent seizures in women with gestational hypertension or preeclampsia without severe features.

Magnesium sulfate is more effective than phenytoin, nimodipine, or diazepam in reducing eclampsia and is considered the drug of choice to prevent eclampsia in the intrapartum and postpartum period. Phenytoin and benzodiazepines are used only when the use of antiepileptic is required or in conditions when the use of magnesium sulphate is contraindicated, or it is not available.

Contraindications of magnesium sulphate include

- myasthenia gravis,
- myocarditis
- moderate-to-severe renal failure,

- ischemic heart disease,
- heart block, or
- hypocalcemia

The data regarding the ideal dosage of magnesium sulphate is still inadequate. Therapeutic range is generally considered to be 4.8–9.6 mg/dL (4–8 mEq/L), but that is also doubtful.

Many datas have concluded that the regimen followed in the United States is generally preferred, which is (intravenous [IV] administration of a 4–6 g loading dose over 20–30 minutes, followed by a maintenance dose of 1–2 g/hour). For those who cesarean delivery (before onset of labor), the infusion should ideally begin before surgery and continue through out surgery, as well as for24 hours postpartum. For women who undergo vaginal delivery, the infusion should continue for 24 hours post delivery. In case of difficulties with establishing intravenous, magnesium sulfate can be administered intramuscularly (IM) injection, 10 g initially as a loading dose (5 g IM in each buttock), followed by 5 g every 4 hours. Since the IM injection is painful, it can be mixed with 1 mL of xylocaine 2% solution.

The rate of adverse effects is higher with the intramuscular administration. The adverse effects of magnesium sulfate (respiratory depression and cardiac arrest) are largely due to its action as a smooth muscle relaxant.

- Therapeutic range : 4.8–9.6 mg/dL (4–8 mEq/L
- Loss of deep tendon reflexes : 9 mg/dL (7 mEq/L),
- respiratory depression: 12 mg/dL (10 mEq/L),
- cardiac arrest: 30 mg/dL (25 mEq/L).

In addition to monitoring respiratory status and tendon reflexes, Urine output should closely be measured as magnesium sulphate is almost exclusively excreted in the urine. Dose of magnesium sulphate should be modified in renal dysfunction.. If the renal failure is mild, the loading dose of 4–6g should be followed by only 1hm/hour of maintenance dose. In cases with renal dysfunction, serum magnesium should be assessed every 4 hours. If the serum level exceeds 9.6 mg/dL (8 mEq/L), the infusion should be discontinued and serum magnesium levels should be determined every 2-hours. The infusion can be restarted at a lower rate when the serum level decreases to less than 8.4 mg/dL (7 mEq/L) In those Patients at risk of impending respiratory depression tracheal intubation might be required and emergency correction with calcium gluconate 10% solution, 10 mL IV over 3 minutes, along with intravenous furosemide to accelerate urinary excretion rate.

Control of Hypertension

The objectives of controlling severe hypertension are to prevent occurrence of heart failure, renal injury, myocardial ischemia, and any cerebrovascular accident. Antihypertensives should be started immediately for

acute-onset severe and persistent(≥15minutes) hypertension (SBP ≥160mmHg and/or DBP≥110mmHg).

Three most commonly agents used are Intravenous labetolol or hydralazine and oral nifedipine. Parenteral therapy might be required initially for acute control of hypertension, but it can be changed to oral medications, once it is controlled and as expectant management is continued. Oral labetalol and calcium channel blockers have been commonly used.

One commonly used approach is starting oral labetolol 200 mg 12 hourly, and gradually increasing it upto 800 mg every 8-12 hours, as a required(maximum 2400mg/day). If still BP is not controlled or if there is any side effects, short acting oral nifedipine can be added.

Table 1: Antihypertensives used for urgent BP control in pregnancy[12]

Drug	Dose	Comments	Onset of action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum total dose of 300 mg; or Continuous infusion 1–2 mg/min IV	Tachycardia(less common) Avoid in women with asthma, decompensated cardiac function, preexisting myocardial disease, and heart block.	1–2 minutes
Hydralazine	5 mg IV or IM, then 5–10 mg IV repeated every 20–40 minutes to a maximum total dose of 20 mg; or continuous infusion of 0.5–10 mg/hr	Maternal hypotension, headaches, and abnormal fetal heart rate tracings; (with higher and frequent dosings)	10–20 minutes
Nifedipine	10–20 mg orally, repeat in 20 minutes if required; then 10–20 mg every 2–6 hours; maximum daily dose is 180 mg	reflex tachycardia and headaches	5–10 minutes

Mode of Delivery

The decision regarding mode of delivery in women with hypertensive dirsorders of pregnancy is made on the grounds of routine obstetric considerations.

In women with gestational hypertension and or preeclampsia without severe features, vaginal delivery is preferred. In preeclampsia with severe features, studies have shown that induction of labor can be done and that it was reasonable and was not harmful to low-birth-weight infants. The decision to perform cesarean delivery should be individualized according to the patient conditions.

Management of HELLP syndrome

The HELLP syndrome is characterized by progressive and sometimes sudden deterioration in maternal and fetal health. Due to the serious nature if this condition and increased rates of maternal morbidity and mortality,it is suggested that women with HELLP syndrome should be delivered immediately regardless of their gestational age. They should be transfeered to a tertiary care centre because management of these patients require well experienced obstetric and neonatal intensive care units and experienced specialists. No beneficial effect of using corticosteroids in HELLP was found out with various studies, hence its use is not recommended. Very close monitoring is required in HELLP syndrome until delivery and in the postpartum period.Lab testings should be

done atleast 12 hours apart. AST levels more than 2,000 IU/L or LDH more than 3,000 IU/L indicates an increased mortality risk. The lowest observed platelet count occurs at an average of 23 hours post delivery. Women with HELLP syndrome are at increased risk of renal failure, pulmonary edema, and acute respiratory distress syndrome.

Management of Eclampsia

Basic supportive measures are the initial steps in managing a woman with eclampsia. These include calling for help, prevention of maternal injury, placement in lateral decubitus position, prevention of aspiration, administration of oxygen, and monitoring vital signs including oxygen saturation. Then only is attention directed to the administration of magnesium sulfate. Most eclamptic seizures are self-limited, and role of magnesium sulfate is not in arresting a seizure, but to prevent recurrent convulsions. Magnesium sulfate administered intramuscularly or intravenously is is associated with less maternal and neonatal morbidity and also is superior to diazepam, phenytoin,, or lytic cocktail (usually chlorpromazine, promethazine, and pethidine). If convulsions recur,2–4 grams of magnesium sulfate could be repeated, administered IV over 5 minutes. If seizure is refractory to magnesium sulphate, (still seizing at 20 minutes after the bolus or more than two recurrences), sodium amobarbital ,thiopental, or phenytoin can be used. In these instances, management in the ICU with Endotracheal intubation and assisted ventilation is warranted. Brain imaging

should also be done, to rule out any other cause for seizures that are refractory to magnesium sulphate.

Minerals in Pregnancy [27]

Minerals play many roles in the body among which, participation in the construction of the body and regulation of its function especially in bone construction, regulation of blood sugar , transport of oxygen, , regulation of chemical reactions , as a cofactor for the enzyme activity, protection of cells from oxidative damage and regulation of immune system function. Minerals constitute about 4% to 5% of body weight out of which, 50% is calcium and 25% is phosphorus.

During pregnancy, there is increased need for micronutrients to support increased physiological changes to support body metabolism in the mother and growing foetus. Hence proper availability and intake of these micronutrients from the beginning og pregnancy, i.e fertilization and also prior to pregnancy . deficientcy of any of these micronutrients might lead to increased risks, like gestational hypertension and pre-eclampsia, anemia, foetal growth restriction, increased labour complications anf foetal and maternal mortality.

Calcium in humans.

Dietary sources of calcium include milk, cheese, , legumes, yogurt, tofu, green leafy vegetables and fish with edible bones, e.g., sardines[27]. Calcium

affects many intra and extracellular functions. Some of them include , membrane stability neural transmission, , blood coagulation, bone structure, muscle movement, and intracellular signaling. It is also a major cofactor for hormonal secretion in endocrine organs. Substrate for bone mineralization is calcium. If calcium intake is not sufficient or its loss is excessive, it is dnot possible to built or maintain the skeletal mass. More than 99% of total calcium is stored in bones as hydroxyapatite and the remaining (5–6 g) in the intra-and-extracellular compartments, in which, only 1.3 g is located in the extracellular compartment. Nearly 50% of plasma calcium is in a free or ionized state, and it is this ionized calcium which is metabolically active and takes part in body's physiological functions. In the remaining plasma calcium, 40% is transported bound to plasma proteins (90% of this is bound to albumin), and to small anions such as phosphate, carbonate, etc.

Calcium regulation

Every day, around 10–20 mEq of calcium is utilized by the body. Calcium equilibrium is maintained by the relationship between the intake of calcium, its absorption, and excretion. Calcium removed from bones is replenished by the same amount (500 mg). The amount of calcium normally absorbed by the intestines is almost equally balanced by urinary excretion of calcium. Even when there are gross fluctuation in calcium , in a healthy person, the level of ionized calcium is tightly regulated by the two important calcium

regulating hormones (parathyroid hormone (PTH) and calcitonin) and the prohormone, vitamin D, and three organs (bone, kidney, and small intestine) through complex feedback mechanisms.. Serum pH, anion levels and protein, also play an important role in serum calcium levels

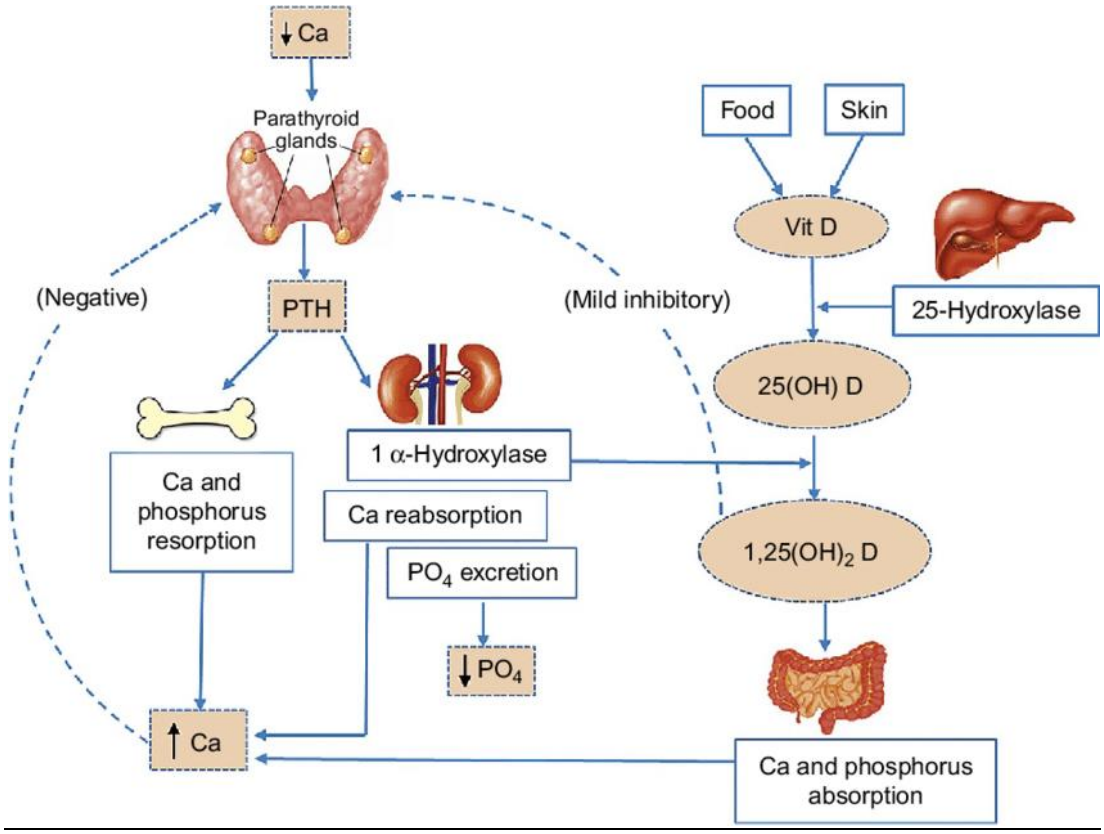


Figure 5 A schematic diagram of calcium metabolism[28]

Calcium defeicinecy in females

Females has increased demand for calcium throughout the time of puberty, pregnancy, and lactation. If there is deficiency in calcium, it can have implications from early foetal life to elderly post menopausal age. Therefore, Inadequate calcium intake can lead to stunted growth, and a reduced peak bone density which increases the risk of osteoporosis in the later life.[29]

Calcium metabolsim in pregnancy

Maternal calcium absorption

Maternal calcium absorption increases significantly, almost doubles during the second and third trimesters. This increase in calcium absorption directly correlates with maternal calcium intake. This early increased absorption of calcium may allow the maternal skeleton to store more calcium in advance of the peak fetal demand that occurs in the third trimester. [29] The mechanism of calcium absorption is by binding of calcium to a specific calcium binding protein. The synthesis of this protein is stimulated by active forms of vitamin D (1,25-dihydroxyvitamin D)[30]

Many studies have reported that calcitriol [1,25(OH)2D] levels increase progressively in each trimester, thereby increasing calcium absorption.

A study of Brazilian women consuming lower amounts of calcium during pregnancy (438–514 mg calcium/day) reported even higher increases in calcium absorption,(69%) during early pregnancy, which increased to 87% during late pregnancy. However, even with this increased rate of absorption, fetal and maternal needs may not be met in women with chronically low calcium consumption (<500 mg/day).

Calcium absorption during pregnancy is mediated by fluctuations in maternal calcitropic hormones. During the first trimester, there is reduction of

the PTH to low normal level, and towards the end of third trimester, it increases to the higher end of normal values. This points toward the increased transfer of calcium in the later gestation, from the mother ot fetus. Eventhough the levels of PTH does not increase more than the normal range, there is increased level of parathyroid hormone receptor protein (PTHrP), a prohormone. PTHrP is recognized by PTH receptors and therefore has effects similar to PTH. This prohormone is secreted both by mammary and fetal tissues.

Important role of PTHrP in pregnancy include:

- Stimulation of placental calcium transport to the fetus.
- It increases the absorption of calcium from intestine, and also its tubular resorption in the kidney. Thus it protects the maternal skeleton from excess resorption.
- PTHrP may also support mineralization of trabecular and cortical bone in the fetus.

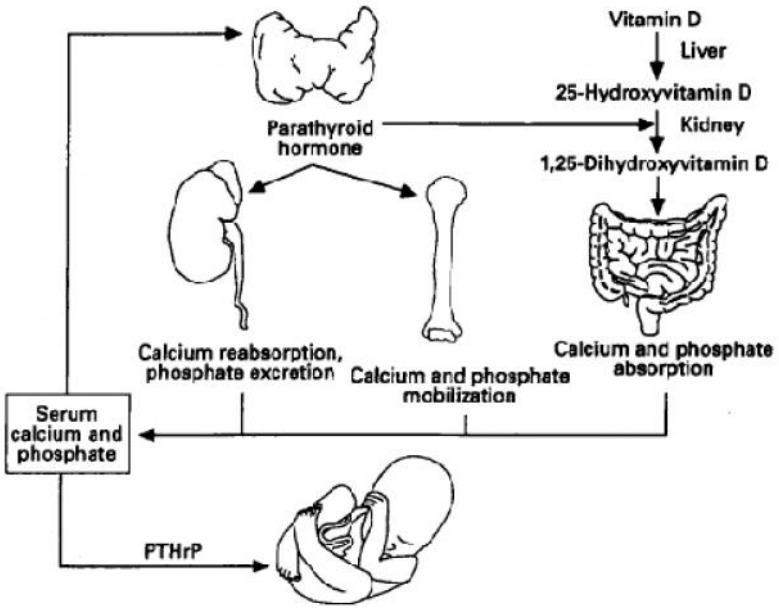


Figure 6Hormonal regulation of **maternal and fetal calcium homeostasis**[(4)]

Other calcitropic hormones affecting maternal calcium metabolism are both the active [1,25(OH)2D] and the inactive [25(OH)D] forms of vitamin D. Serum levels of 25(OH)D s do not change much during pregnancy, but an increase in 1-a-hydroxylase and additional synthesis in the placenta allows for an increase in the conversion of 25(OH)D to 1,25(OH)2D. Maternal 1,25(OH)2D levels increase twofold during pregnancy, thus also doubling the intestinal absorption of calcium. Both free and protein-bound forms of calcitriol increase during pregnancy and subsequently the concentrations of vitamin-D binding protein. Due to the corresponding changes in VDBP and 1,25(OH)2D, the availability of free 1,25(OH)2D do not increase until the third trimester which might explain the significant increase in calcium uptake seen during late gestation. Because maternal 25(OH)D does cross the placenta and because there is a positive association between maternal serum 25(OH)D, cord blood 25(OH)D, and infant 25(OH)D levels at delivery, it is thought that vitamin D plays a role in fetal bone development.

Maternal Calcium Excretion

There is Physiological hypercalciuria during pregnancy due to increased calcium absorption. Surprisingly, urinary calcium is within normal range during fasting but increases in postprandial period, indicating that elevated excretion is related to the increase in calcium absorption. For women with reduced dietary calcium intake (\500 mg/day), urinary calcium level is more tightly regulated.

Although urinary calcium excretion increases during pregnancy, the increase in intestinal calcium absorption is not reduced, so that net maternal calcium retention is positive.

Calcium transfer from mother to fetus[29]

A full-term new born baby has about 30 g of calcium which is acquired during pregnancy from the calcium stores of the mother to meet its needs for skeletal mineralization and to maintain normal physiological processes during gestation. In the first trimester, it is only few milligrams a day, then there is rapid increase of this active transport to more than 250 mg per day in last trimester risking the condition of mothers bones and teeth. This high level of calcium is mostly derived from dietary absorption during pregnancy.

A breastfeeding neonate needs more calcium in breast milk during first six months of exclusive feeding than its fetal requirement, and the baby continues to draw calcium from the mother through breast milk for the duration of lactation. Calcium losses through human breast milk denote ~260 mg/L29 during the breastfeeding period

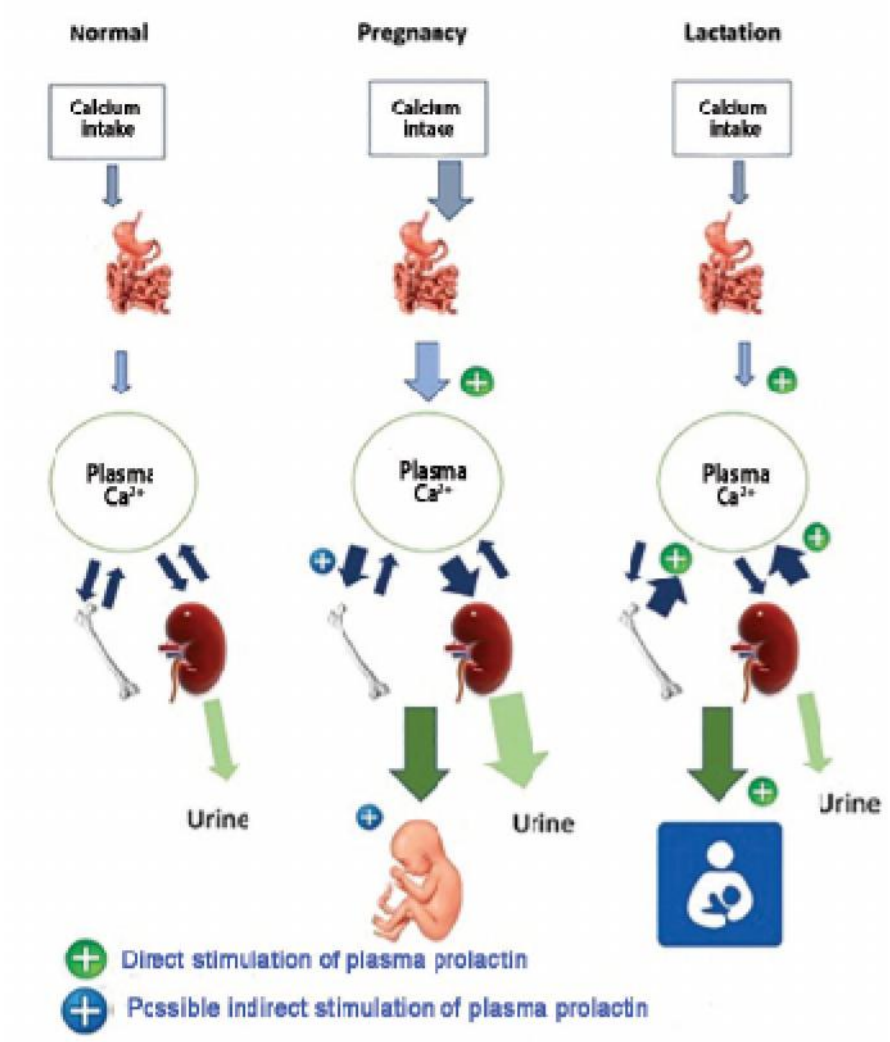


Figure 7 Contrasting calcium homeostasis in normal adults, compared to human pregnancy and lactation. The relative decrease or increase with respect tonon-pregnant and normal state is depicted by the thickness of the arrows. The possibility of a direct and indirect stimulation by prolactin is also depicted.

Calcium and Maternal Health[31]

There are biological limits for a pregnant woman's capacity to increase calcium absorption, and if she do not consume adequate amounts of dietary calcium, she may be at increased risk of complications during gestation, such as preeclampsia, and preterm delivery or long-term morbidities, such as excessive bone loss.

Role of calcium in hypertensive disorders of pregnancy

Low calcium intakes during pregnancy may

1. Stimulate PTH secretion which increases intracellular calcium and thus contractility of the smooth muscle, and/or
2. Stimulates the release of renin from the kidney, resulting in vasoconstriction and retention of sodium and water.
3. extracellular ionic calcium is crucial for synthesis of vasoactive substances in the endothelium such as prostacyclin and nitric oxide[32]

These physiological changes can lead to the development of gestational hypertension and preeclampsia.

A meta-analysis on the role of calcium supplementation during pregnancy for the prevention of hypertensive disorders in pregnancy found a reduction in the development of gestational hypertension in women receiving calcium versus placebo by 45%.

A Cochrane review of 13 trials involving nearly 16,000 pregnant women revealed that the average risk of preeclampsia was reduced in women receiving calcium supplements (RR 0.45) and that the effect was greatest in women with reduced baseline calcium intakes. The review concluded that pregnant women consuming lesser amount of dietary calcium could reduce their risk of developing preeclampsia by 31% to 65% if they consumed an additional 1,000 mg of calcium per day.

Other issues

Pre term Birth

Calcium supplementation has shown to be effective in reducing the risk of preterm delivery in females with reduced calcium intakes. A possible mechanism of action of calcium is that it suppresses parathyroid release and intracellular calcium and thus reduces smooth muscle contractility. By this mechanism, calcium supplementation reduces contractility of uterine smooth muscle and has a role in preventing preterm labor and delivery.[30]

Post Partum Hemorrhage

Postpartum hemorrhage (PPH) is one of the leading cause of maternal morbidity and mortality worldwide and is most commonly caused by uterine atonicity following delivery. The first-line agent used for the prevention and treatment of PPH is oxytocin, which, by binding with the oxytocin receptor found on myometrial cells, cause uterine contraction. Oxytocin acts by

increasing levels of intracellular calcium within the myometrial cell, which promotes contraction. Prolonged exposure to oxytocin desensitizes myometrium to oxytocin. This results in a significant reduction in contractility upon administration of further oxytocin. Calcium is an important messenger within the uterine myometrium to cause muscle contraction following oxytocin administration. A physiological level of calcium is required to provide optimal contractility of normal myometrium. Determination of low, normal or high calcium levels when there is a need of prolonged exogenous oxytocin administration can provide guidance for the use of exogenous calcium as a uterotonic adjunct. In a study done on 36 women, Talati et al.[33]concluded that in a myometrium which is oxytocin naïve, normocalcemia provides superior oxytocin-induced contractility compared to those with hypocalcemic conditions.

Effect of hypocalcemia on the fetus

A study found that pregnant women with the hypocalcemia with lowest calcium levels (among those on normal diet and calcium supplements) also had the highest lead level in the blood. During pregnancy, when there is hypocalcemia, it accelerates the production of new bone to replace olf bone. Since nearly all the body's lead is stored up in skeleton, the lead 'leaks' into the bloodstream when there is high bone turnover and thus it can drive up levels of lead in the blood, which might be harmful to the fetus.[34]

Studies have suggested that very low maternal calcium levels may be a risk for newborns to have a lesser bone mass. Another study states that maternal calcium metabolic stress, has an adverse influence on fetal growth. A positive correlation between serum ionized calcium levels of the mother and the crown-heel length of the newborn suggests that maternal vitamin D deficiency could interfere with fetal growth.

Neonatal hyperparathyroidism may develop in response to maternal hypocalcemia, causing demineralization of fetal bones and growth restriction. Birth weight, mean length at birth, , and one-minute Apgar score were higher in those newborns born to mothers whose calcium and vitamin D intake was adequate, compared to those whose intake was inadequate.

Short term bone changes

In a study by Kumar and Kaur , biochemical markers of bone turnover were found to be increased in preeclampsia compared with normal pregnancy. This must be due to the multisystem involvement of preeclampsia which occurs in response to circulating factors released during the development of disease . Increase in levels of proinflammatory cytokines and presence of endothelial dysfunction in preeclampsia is being implicated in stimulating osteoclast activity and hence increased bone resorption. The levels of NTx (N-telopeptide of type 1 collagen), marker of bone resorption is significantly increased during pregnancy in women with preeclampsia . This further necessitates the

supplementation of elemental calcium during pregnancies complicated with preeclampsia, for preservation of maternal skeleton.[30] Few studies, comparing the BMD preconception and 4-6 weeks postpartum have shown a reduction in the maternal lumbar spine bone density reduce by an average of 4%. [35]

The BMD values of the anteroposterior lumbar spine (L2–L4) and femoral neck using DXA in multiparous North Indian women from 20–60 years of age showed decline with advancing age indicating that pregnancy probably adds up to the bone loss in the women with faulty dietary pattern and quality.[36]

Osteoporosis and pregnancy[30]

To meet the demand of rapidly mineralizing fetal skeleton, significant transplacental calcium transfer occurs, especially in the last trimester during pregnancy. Similarly, there is an inevitable loss of calcium in the breast milk during lactation. Both these result in an eventual stress on the bone mineral homeostasis in the mother. In India, a significant proportion of pregnancies occur in the initial twenties when peak bone mass is usually not yet achieved. Furthermore, protein energy malnutrition, deficiency of calcium and vitamin D are also commonly encountered in this age group. Poor preconceptional BMD, reduced calcium and vitamin D intake during pregnancy and poor socioeconomic status poses increased risk of low bone mass and later developing osteoporosis in these women.

HYPOCALCEMIA: CAUSES IN PREGNANCY[29]

Table 2 Hypocalcemia causes in pregnancy

Major causes	Sub Causes
Hypoparathyroidism	**Acquired** • Iatrogenic(post surgical) • Infiltrative disease (e.g., hemochromatosis, thalassemia, granulomatous disease (sarcoidosis), and amyloidosis) • Infiltration of parathyroid gland by metastasis or heavy metals.(iron, copper) • Autoimmune disease (usually as a component of polyglandular autoimmune syndromes) • Pseudohypoparathyroidism types 1a, 1b, and 2 **Genetic cause** • Congenitally absent or defective gland (DiGeorge's syndrome) • Autosomal dominant hypocalcemia where there is activating mutation of the calcium receptor gene)
Pseudohypoparathyroidism	Lack of normal response to PTH
Calcium disorders	• Mutation in the calcium-sensing receptor • Inadequate dietary intake/ allergy to cow's milk protein • As a part of natural ageing • Disorders that result in sequestration of calcium(by decreasing absorption, increased binding in vascular space, or increased deposition in tissues) as in short gut, hyperphosphatemia, coeliac disease, tufting enteropathy • Renal disease resulting in hypercalciuria • Hungry bone syndrome • Acid-base • Hyperkalemia
Actual vitamin D deficiency and dependency	• Malabsorption, especially pancreatic disease and coeliac disease • Dietary deficiency • Lack of sunlight exposure
Functional vitamin D	• Renal disease (reduced 1- α hydroxylation)

deficiency and dependency	• Liver disease (reduced 25-hydroxylation)
Medication effects	• Corticosteroids alter vitamin D function • Transfusion of phosphate or citrated blood • antiepileptics and proton pump inhibitors.
Severe hypomagnesemia (by inhibiting response of PTH to hypocalcemia)	• Immunosuppressants • Diuretics, especially loop diuretics • Miscellaneous drugs, e.g., proton pump inhibitors
Gastrointestinal	• Malnutrition • Severe diarrhea • Alcoholism
Other causes	• Sclerotic metastases • Septic shock (due to suppression of parathyroid hormone release and decreased vitamin D conversion) • Acute pancreatitis (when lipolytic products released from the inflamed pancreas chelate calcium) • Fanconi syndrome • Surgery **Hyperphosphatemia (mechanism by which it causes hypocalcemia is poorly understood)** • Rhabdomyolysis • Renal failure • Tumor lysis syndrome • Phosphate administration **Hypoalbuminemia (most common cause of hypocalcemia)** Cirrhosis, nephritic syndrome, malnutrition, burns, chronic illness, and sepsis **Widespread osteoblastic metastases** • Breast cancer

Measurement of serum calcium[29]

Normal calcium levels reported by the laboratories are actually the total serum calcium. The normal range of this is 8.5–10.5 mg/dL (2.12 to 2.62

mmol/L). A decrease in total serum calcium can also be due to any condition, which can reduce the serum albumin like malnutrition, chronic liver disease, nephrotic syndrome etc. Therefore, before diagnosing a ‘true’ case of hypocalcemia, one must check the ionized calcium (Ca). The formula used to estimate corrected calcium is, corrected calcium = serum calcium +0.8(normal albumin-patients albumin)

In the practical situation, the major concern is only level ioionized calcium, which can be measured directly or by estimation, but since it requires special handling of the blood sample, an ionized calcium test is more sophisticated to perform than serum calcium and it is only done in certain cases. The normal range of ionized calcium is 4.65–5.25 mg/dL (1.16–1.31 mmol/L). Thus a ‘true’ hypocalcemia is actually, reduction in ionized calcium, which need not always occur when the total serum calcium is reduced.

In pregnant mothers, alterations in the serum chemistries and calciotropic hormones can easily be mistaken for an abnormality in calcium homeostasis. During pregnancy, there is hemodilution which causes the serum albumin and hemoglobin to come down, and the albumin levels remains low until birth. This fall in albumin causes the total serum calcium to fall to levels which, in normal non pregnant individuals, can result in symptomatic hypocalcemia. Therefore, here is the importance of calculating the corrected calcium values or, to be more precise, measuring the ionized calcium.

Prevalence of hypocalcaemia in pregnancy

Severe dietary inadequacy and hypoparathyroidism are the most common etiology of hypocalcemia in pregnancy. Decreased levels of calcium and magnesium have been associated with hypertensive disorders in pregnancy.

A study from India determined the prevalence of hypocalcaemia in pregnant women to be 66.4% (n = 362/545); and all of them were asymptomatic.(37) The average daily dietary intake of calcium, and serum calcium level, corrected for serum albumin, for the group was 325±198 mg and 8.1±1.5 mg/dL, respectively. In this study population, the reduced daily dietary intake of calcium, compared to the recommended daily intake must have been the cause for hypocalcaemia. In a study in Algeria, hypocalcemia in pregnant women was 70.55%.(38) A study done recently in Pakistan found the prevalence of hypocalcaemia in pregnant women with preeclampsia to be 60% (39).

Recommended Daily intake of calcium and calcium supplementation

The recommended dietary allowance (RDA) of elemental calcium in pregnant and lactating women is 1000 mg/day, which remains unchanged compared to the non-pregnant state and depending on maternal age[(40)] A study conducted among North India on pregnant women reported a low calcium intake of less than 300 mg/day in almost half of the study population [(30)].

Moreover, calcium absorption could be hampered by deficiency vitamin D as it is the major factor required for absorption of calcium from the gut. A study in 418 North Indian pregnant women reported vitamin D deficiency (\32 ng/ml) in 95.4% population with severe deficiency (\10 ng/ml) in 34.4% of the population. Women with severe vitamin D deficiency had low mean serum calcium levels of 7.13 ± 1.41 mg/dl due to poor absorption of calcium. Thus, in a population where vitamin D deficiency is very much prevalent, and with low dietary calcium intake, the problem is very likely to worsen during pregnancy because of the increased transplacental transport of calcium to the developing fetus.

Therefore, it is recommended that women who has reduced dietary intake of calcium should either increase the intake of calcium rich food sources, such as milk or cheese, and/or, along with that, add a supplement that gives around 600–1000 mg of calcium per day. Increased calcium intake is associated with better and improved calcium balance, which will provide a protective effect against bone loss that happens during pregnancy. Studies have suggested that bone resorption during late pregnancy can be attenuated by increased calcium intake[31]. WHO makes a strong recommendation for supplementation for pregnant women with 1.5grams to 2.0grams of elemental calcium perday in area s where dietary calcium intake is low and for women at high risk of developing hypertensive disorders during pregnancy.

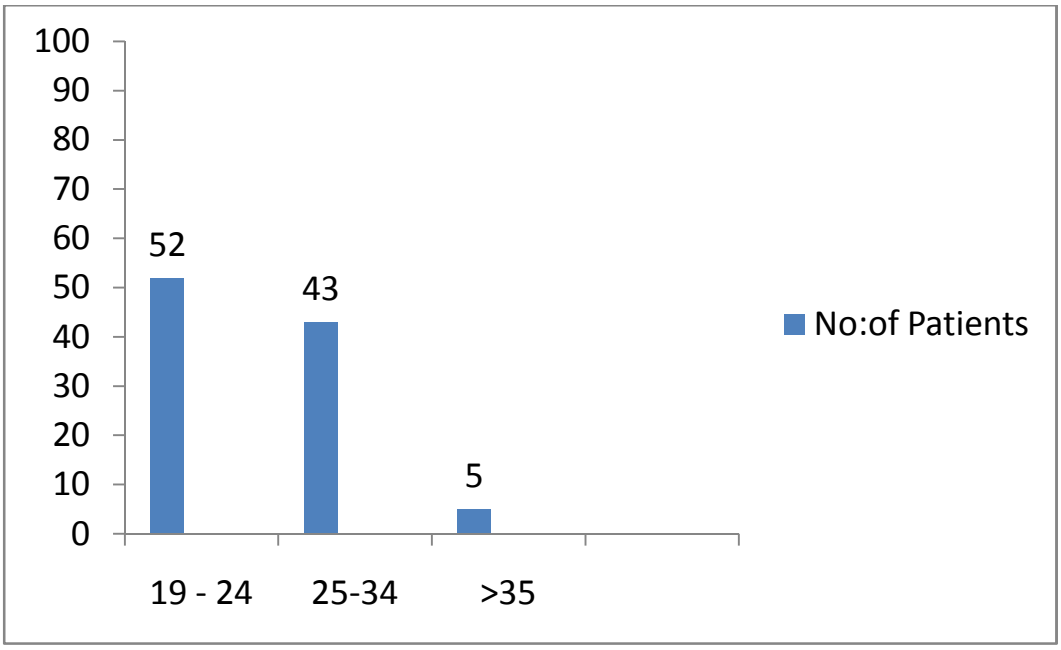
RESULTS

1. Age Distribution

Mean age of the study group is 25.3±1 years. The distribution of age group is as following:

Age Distribution		
Age group	**Number of patients**	**Percentage**
19 to 24	52	52.0
25 to 34	43	43.0
more than 35	5	5.0
Total	100	100.0

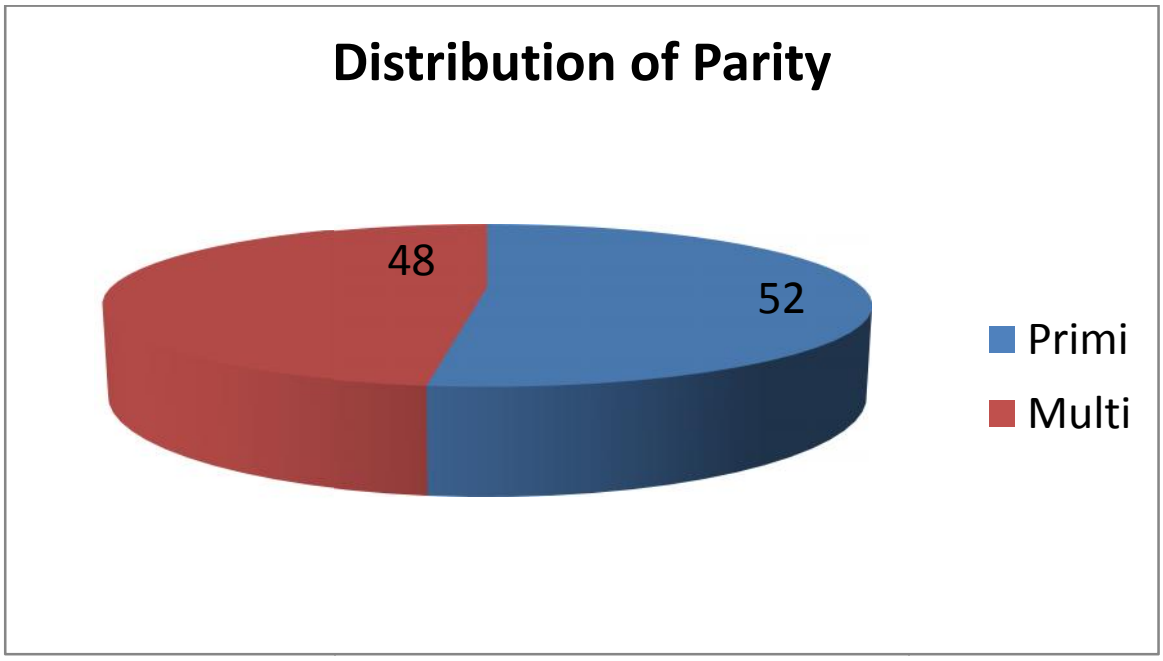
AGE DISTRIBUTION



2. Distribution of parity among the study group.

Parity		
Parity	**No of Patients**	**Percentage**
Multi	48	48.0
Primi	52	52.0
Total	100	100.0

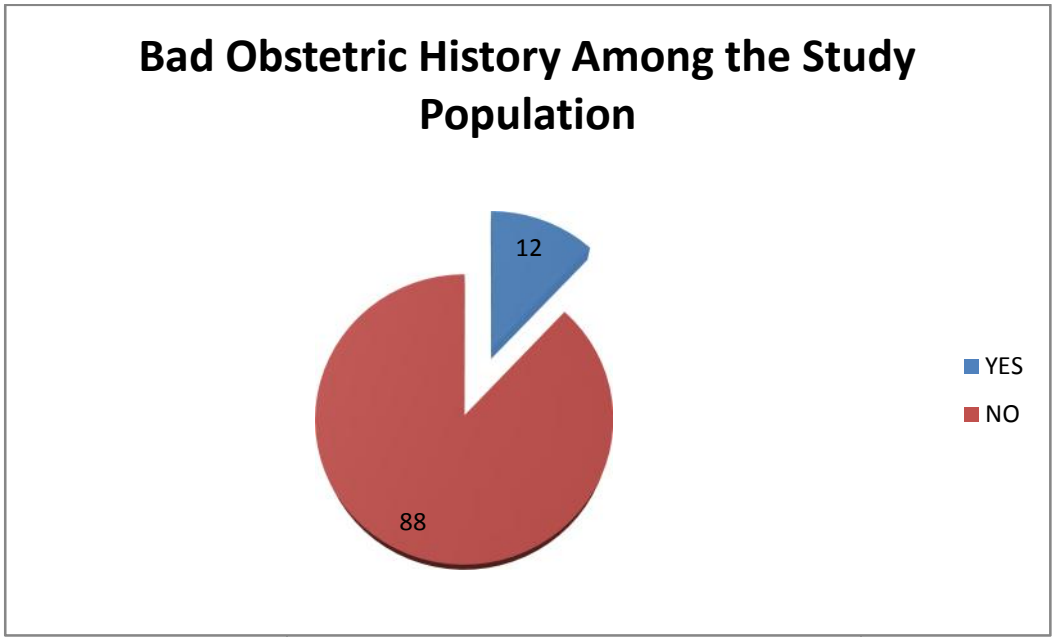
52 out of 100 patients were primiparous and the remaining were all multiparous.



3. Presence of bad obstetric history.

12 out of 100 patients had a past bad obstetric history in terms of at least one abortion, other than medical termination of pregnancy.

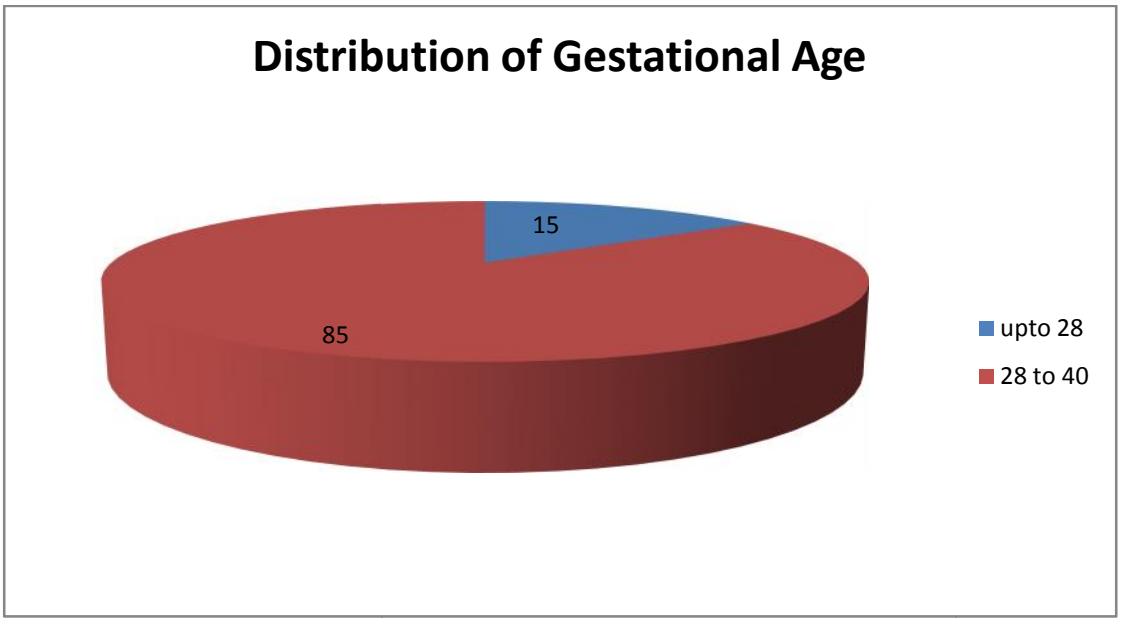
Bad obstetric history		
Presence of boh	**Frequency**	**Percent**
No	88	88.0
Yes	12	12.0
Total	100	100.0



4. Distribution of gestational age.

Gestational Age		
GA in weeks	**No of Patients**	**Percent**
28 to 40	85	85.0
upto 28	15	15.0
Total	100	100.0

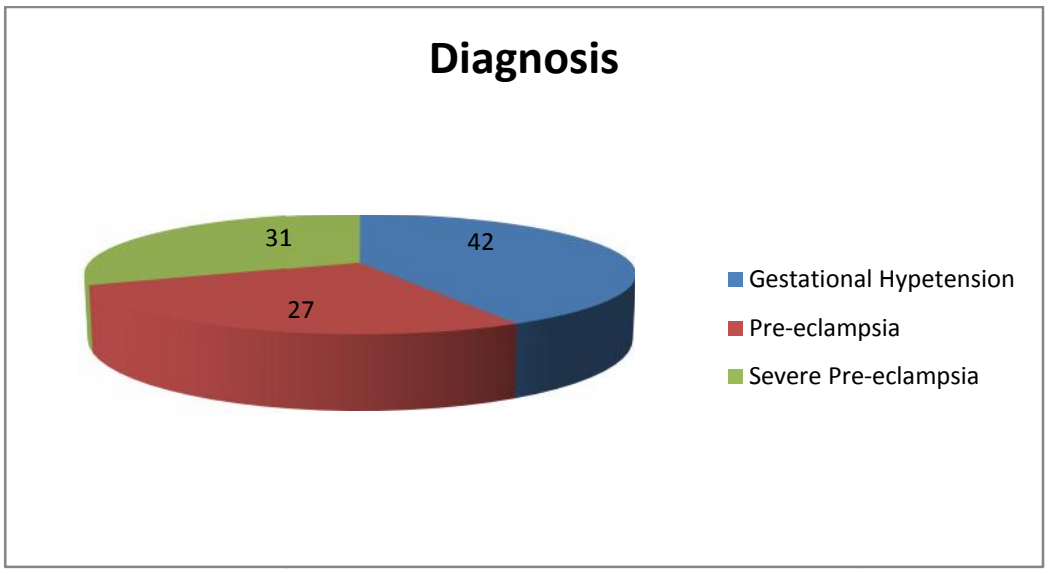
15 out of 100 patients belonged to second trimester and the remaining to the third trimester.



5. Diagnosis among the study population

Diagnosis		
Diagnosis	**No of Patients**	**Percent**
G.HTN	42	42.0
PE	27	27.0
Severe PE	31	31.0
Total	100	100.0

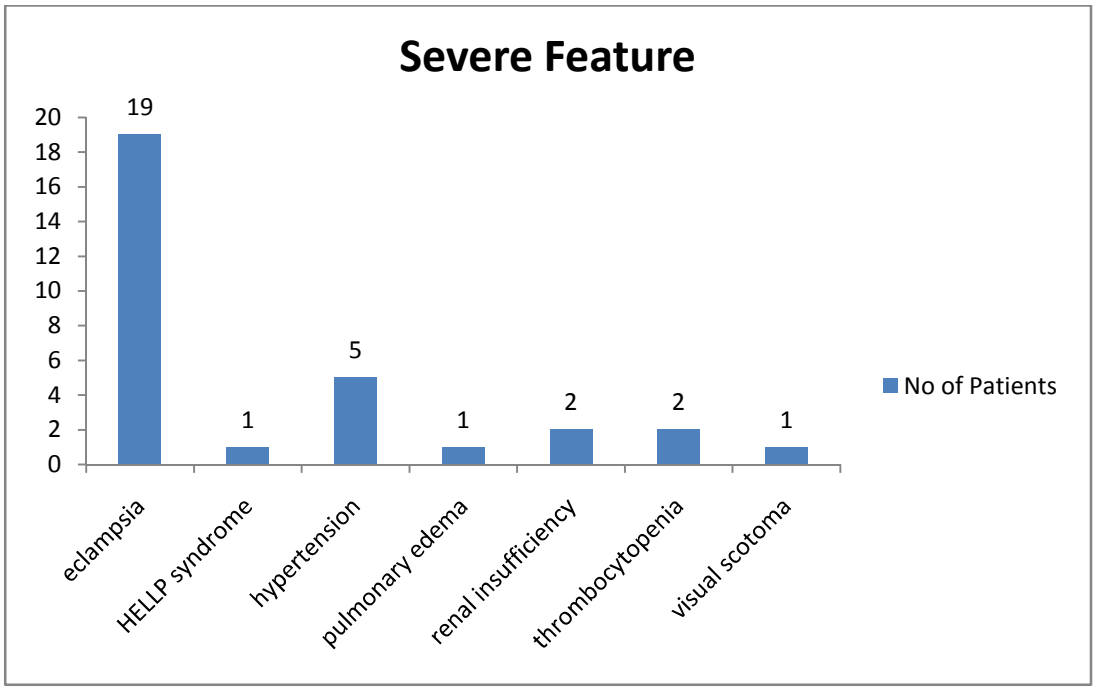
In the study population, 42 % had Gestational Hypertension, 27% had Preeclampsia and 31% had severe preeclampsia (including those who had complicated preeclampsia)



6. Out of 31 patients with severe disease, characteristics which attributed to severity/complication are as follows:

Feature		
	Frequency	**Percent**
Eclampsia	19	61.2
HELLP Syndrome	1	3.2
Hypertension	5	16.1
Pulmonary Edema	1	3.2
Renal Insufficiency	2	6.4
Thrombocytopenia	2	6.4
Visual Scotoma	1	3.2
Total	31	100

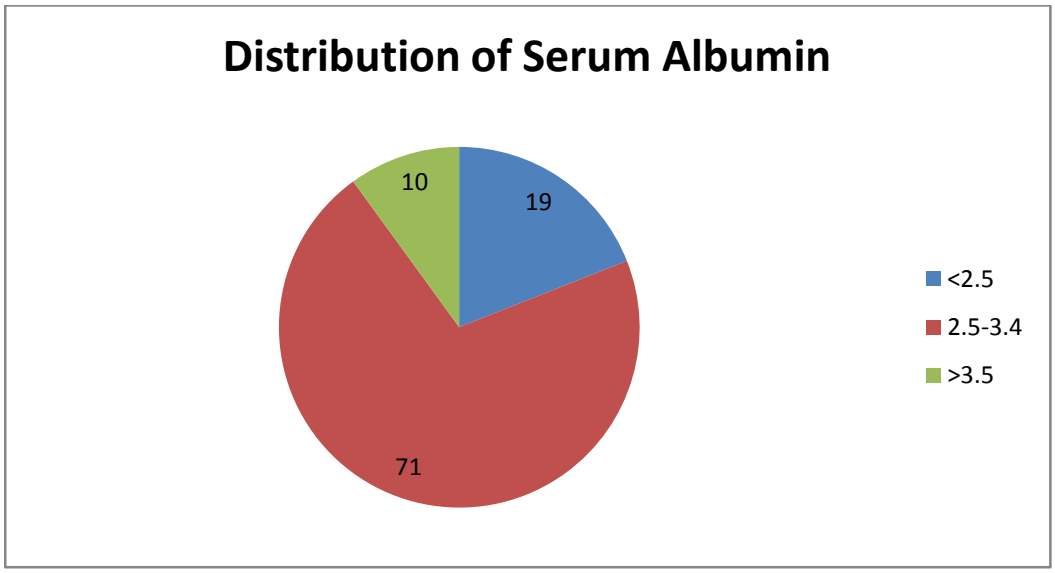
Eclampsia was the major contributor to the spectrum of severe disease in this study group (61.2%)



7. Distribution of serum albumin

Mean serum albumin in the study group is 2.81±.08g/dl.

Distribution of serum albumin		
S.albumin(g/dl)	**No of patients**	**Percent**
<2.5	19	19.0
>3.5	10	10.0
2.5-3.4	71	71.0
Total	100	100.0

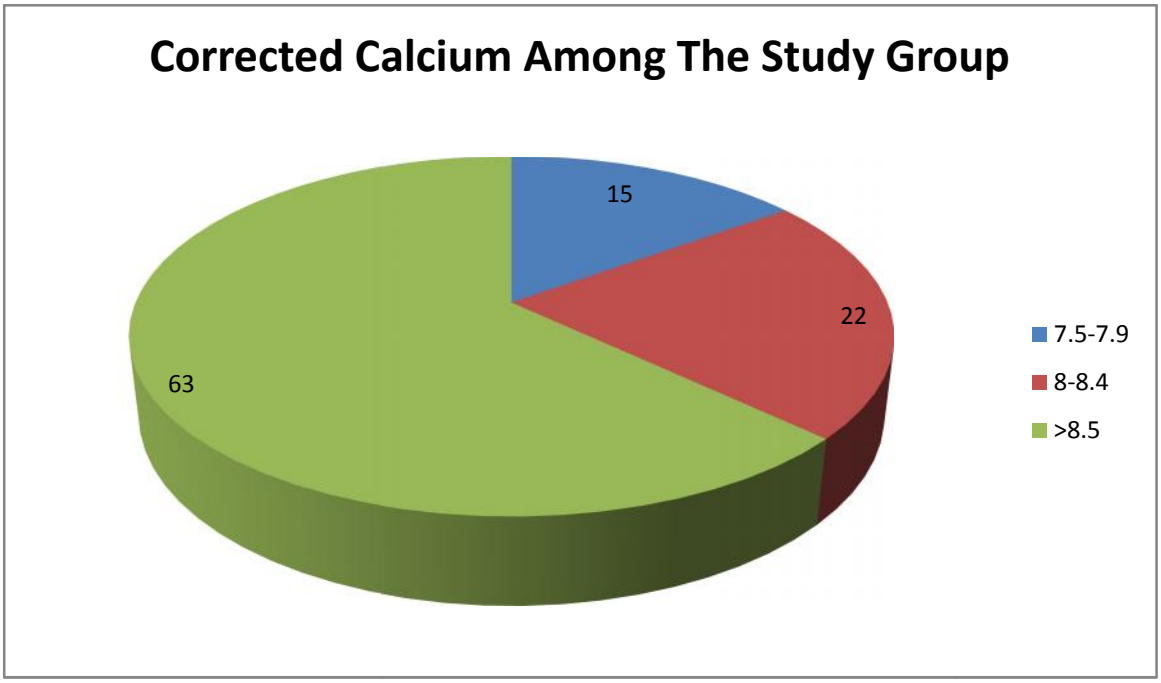


8. Distribution of corrected calcium in the study group

Mean level of corrected calcium in the study population is 8.876 mg/dl ±0.16

Distribution of corrected calcium		
Corrected calcium (mg/dl)	**No of patients**	**Percent**
7.5 to 7.9	15	15.0
8 to 8.4	22	22.0
More than 8.5	63	63.0
Total	100	100.0

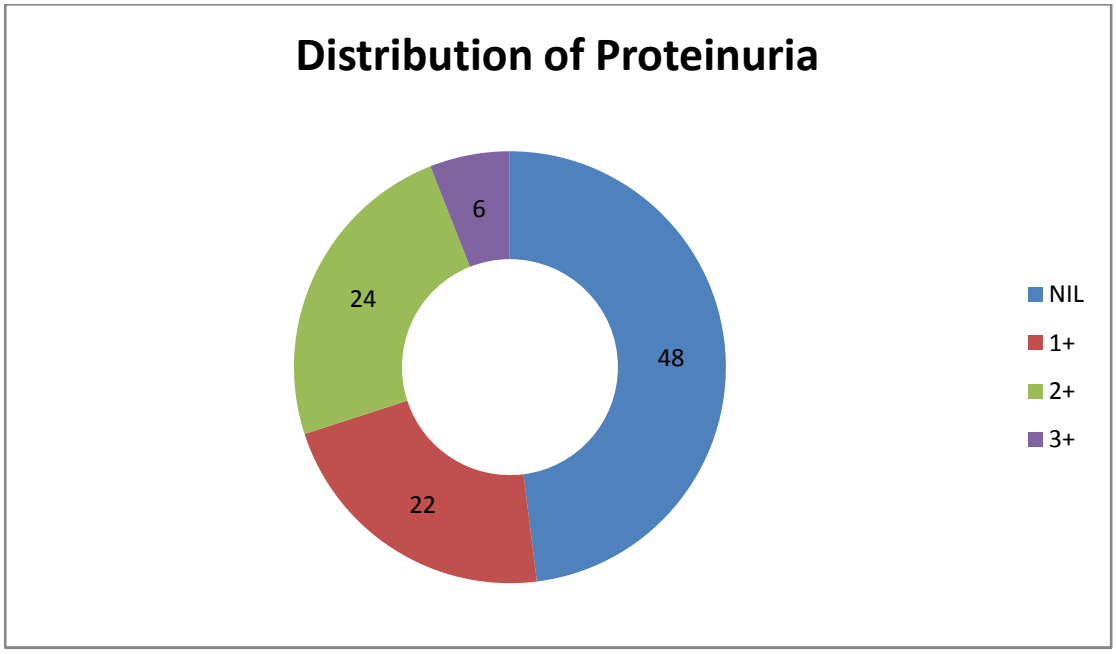
63% had corrected calcium more than 8.5mg/dl and 15% had less than 8mg/dl



9. Distribution of proteinuria

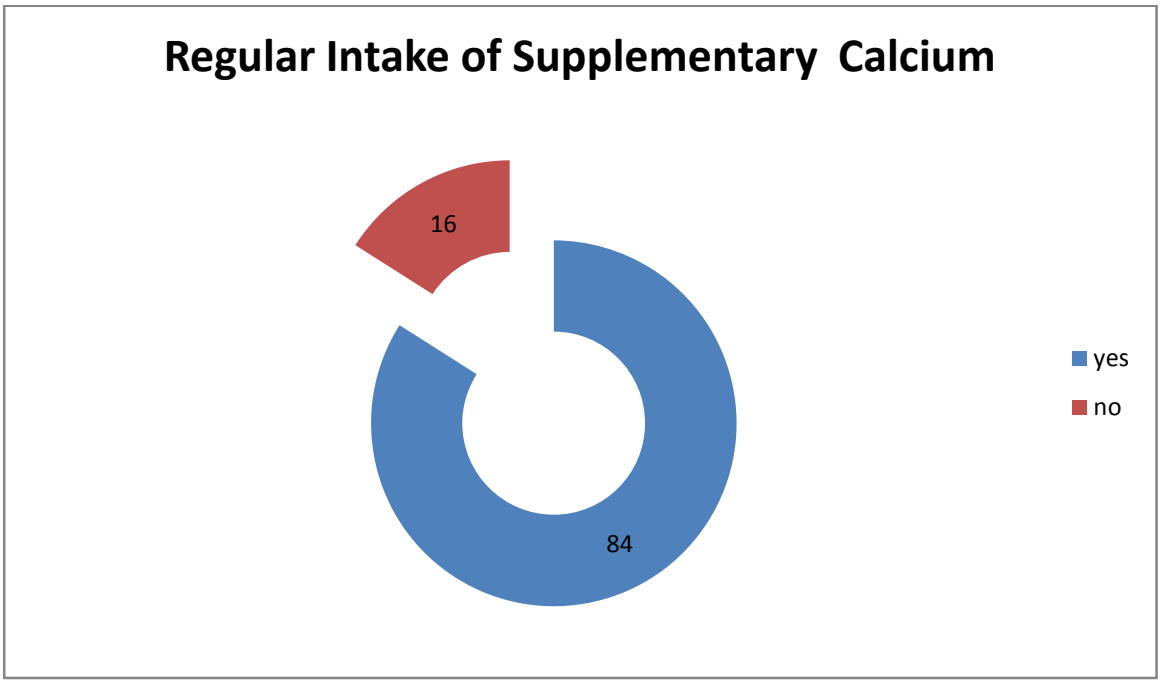
Distribution of serum albumin		
Urine dipstick for albumin	**No of patients**	**Percent**
1+	22	22.0
2+	24	24.0
3+	6	6.0
NIL	48	48.0
Total	100	100.0

48% of the study group had no proteinuria while 6% had 3+ proteinuria and remaining had 1+ or 2+ proteinuria.



10.Compliance among the group

Compliance to Drug Intake		
On regular intake of supplementary calcium	**Frequency**	**Percent**
No	16	16.0
Yes	84	84.0
Total	100	100.0



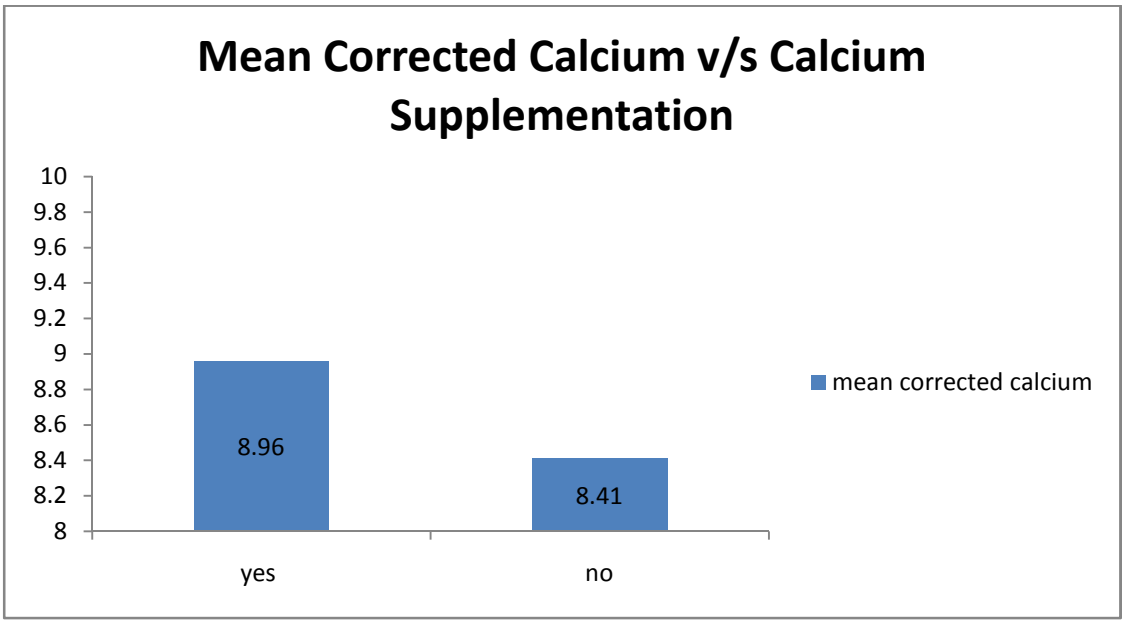
16% of the study group was not taking regular calcium supplement.

11. Association of compliance and serum calcium

Compliance	Corrected calcium			Interpretation
	7.5 to 7.9	8 to 8.4	More than 8.5	
Yes	9	18	57	Pearsons correlation coefficient 0.253 P value 0.011
No	6	4	6	

There is a positive correlation between compliance and serum calcium level, that is better the compliance more will be the calcium level and this was statistically significant (P value <0.05)

Regular intake of calcium supplement	Mean corrected calcium
Yes	8.9643
No	8.4125



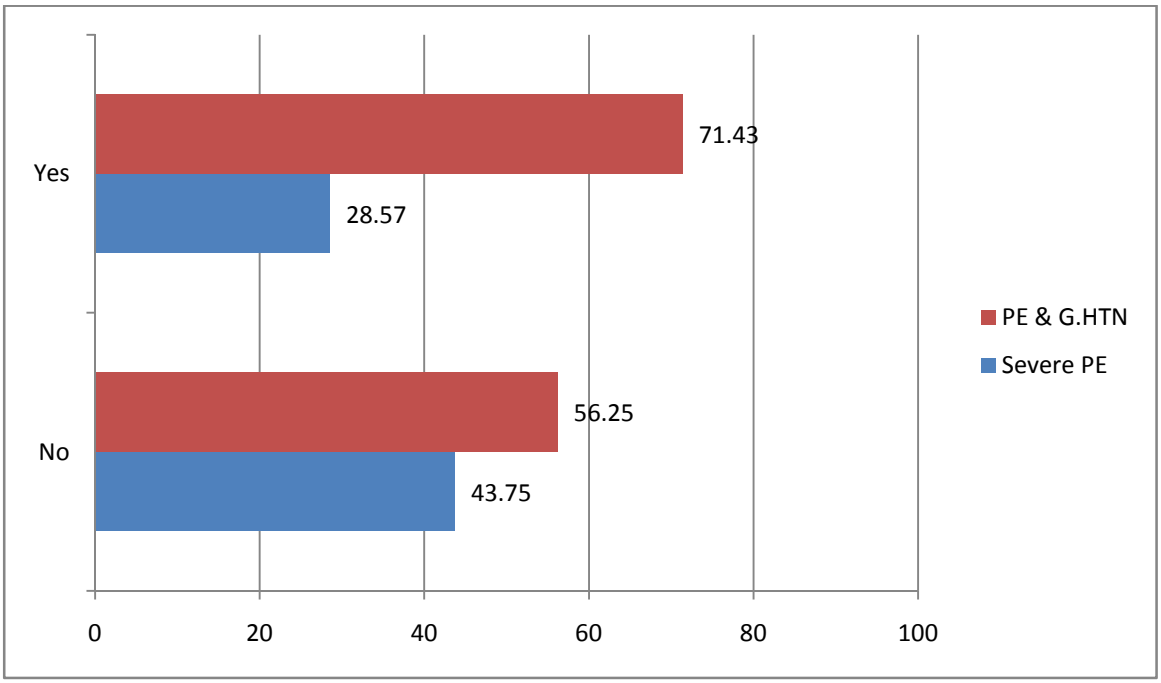
It clearly shows that the serum calcium level is better in patients who are regularly taking a calcium supplement.

12.Compliance and severity of illness.

Compliance	Severe PE(%)	PE and G.HTN	Total	Interpretation
No	7(43.75)	9(56.25)	16	Chi-square : 0.82 P value : 0.36
Yes	24(28.57)	60(71.43)	84	
Total	31	69	100	

Odds ratio is 1.94 (.65-5.81, 95% CI)

There is 1.94 times increased risk of contracting severe preeclampsia if a patient is not regularly taking calcium supplementation.But since P value is >0.05, this association is statistically insignificant

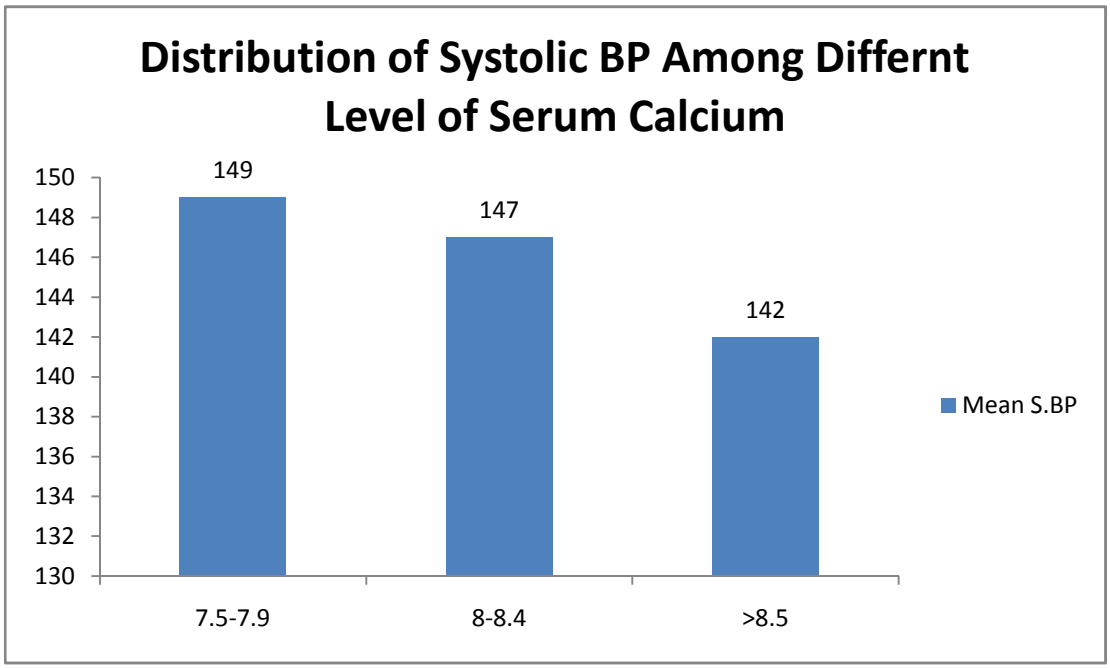


13.Association between corrected calcium and systolic BP

The mean systolic blood pressure among the study group was 144.2± 3.5mm Hg

Corrected ca	Mean systolic blood pressure	Interpretation
7.5-7.9	149	Pearsons correlation coefficient -.265
8-8.4	147	
>8.5	142	P value 0.008

There was a negative correlation between serum calcium level and systolic BP,i.e, lesser the corrected calcium, more was systolic blood pressure, and this was statistically significant (P value <0.05)

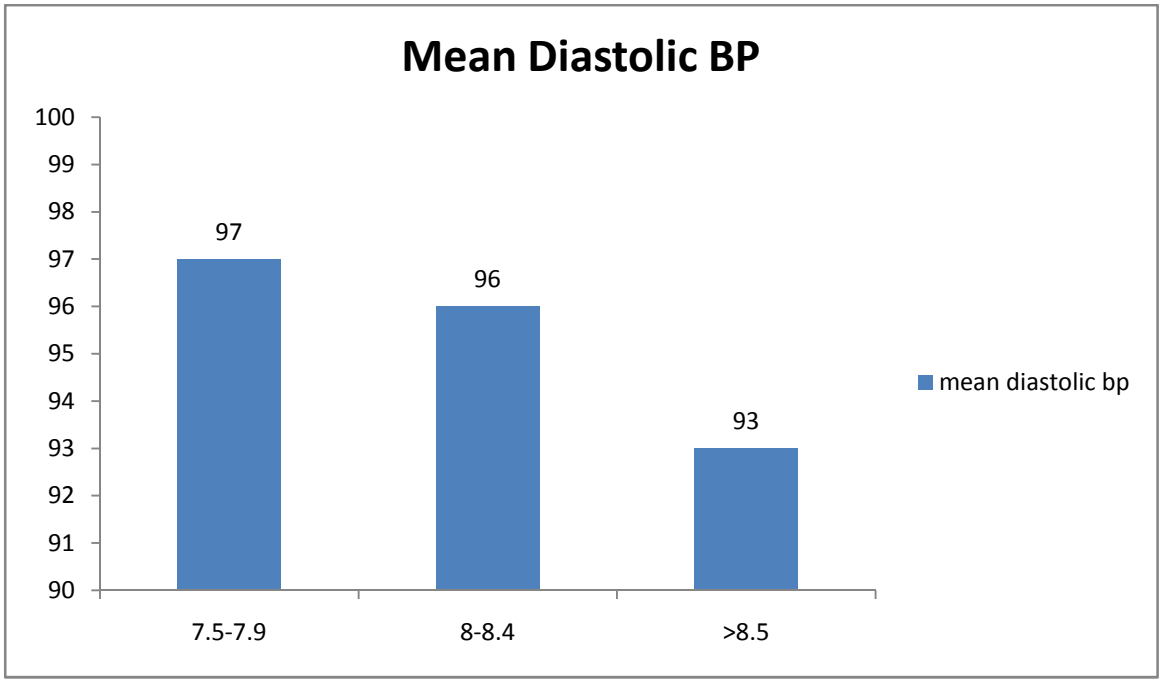


14.Association between corrected calcium and diastolic bp

The mean diastolic blood pressure was 94.7± 1.6mm Hg

Corrected ca	Mean diastolic blood pressure	Interpretation
7.5-7.9	97	Pearsons correlation coefficient -.280 P value 0.005
8-8.4	96	
>8.5	93	

There was a significant correlation between serum calcium level and diastolic BP of the patient, i.e, lesser the serum calcium, more was the diastolic blood pressure. (P value <0.005)

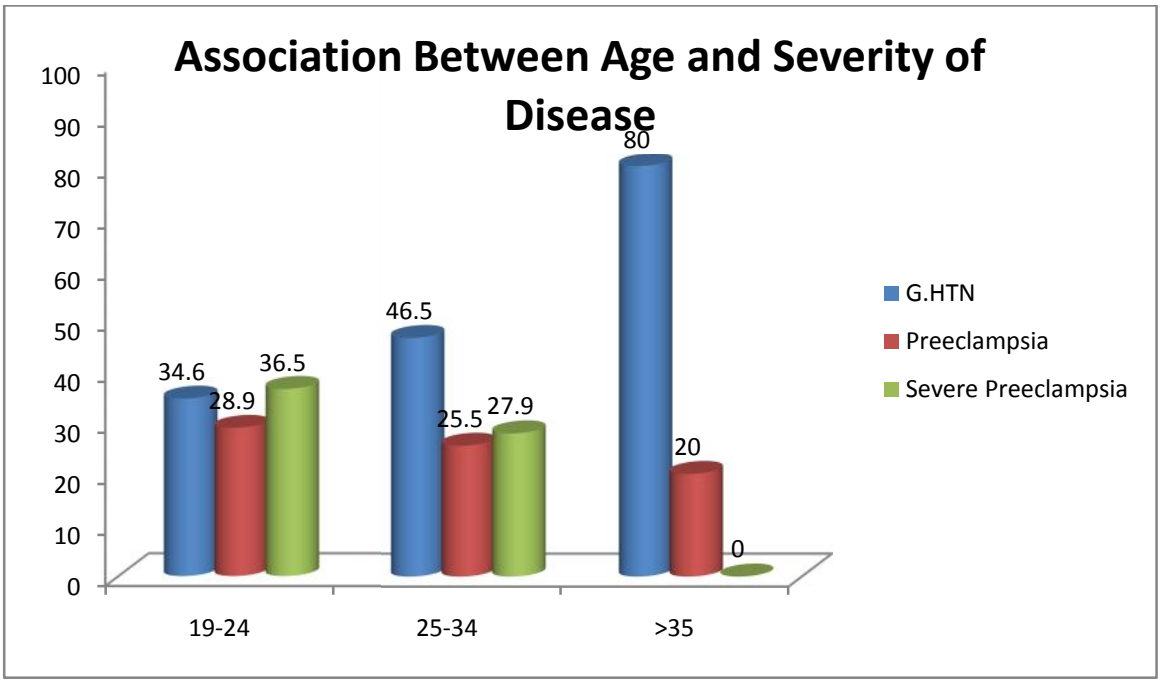


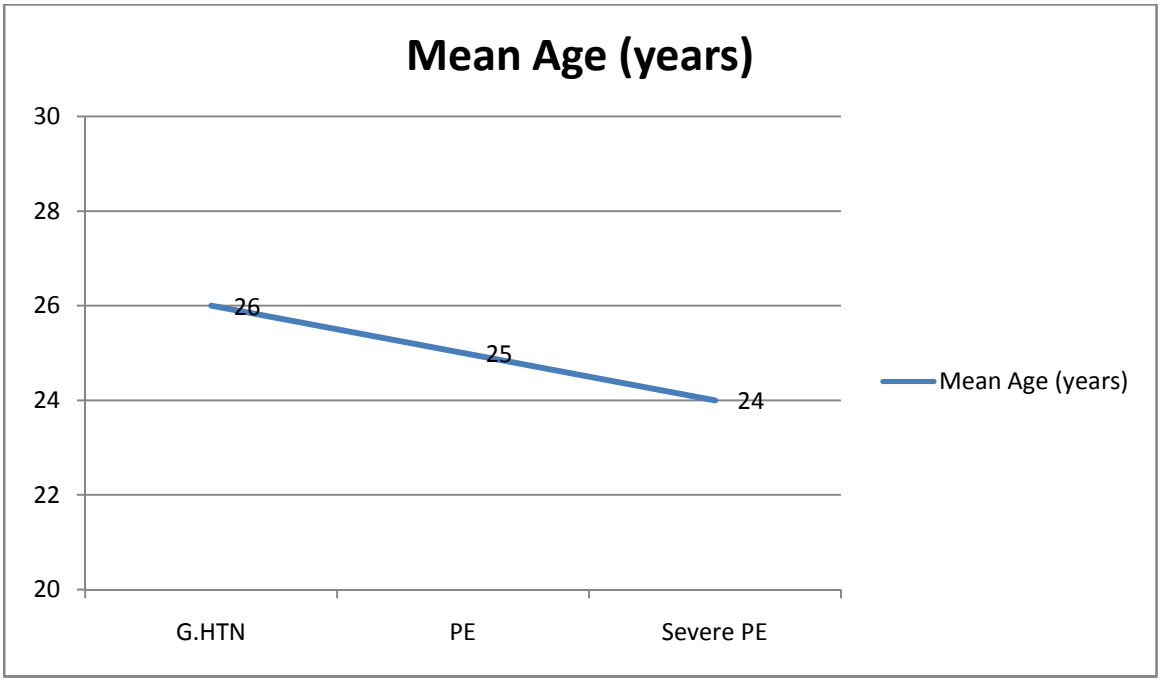
15.Association between age and severity of the disease

Age group	Diagnosis			Total	Interpretation
	G.HTN	Preeclampsia	Severe Preeclampsia		
19 to 24	18(34.6)	15(28.9)	19(36.5)	52	Pearsons correlation coefficient : -0.190 P value 0.059
25 to 34	20(46.5)	11(25.5)	12(27.9)	43	
more than 35	4(80)	1(20)	0	5	

Diagnosis	Mean Age
G.HTN	26
PE	25
Severe PE	24

There was a slight negative correlation of 19% between age and severity of the disease, in this study, but was statistically not very significant (P value>0.05)

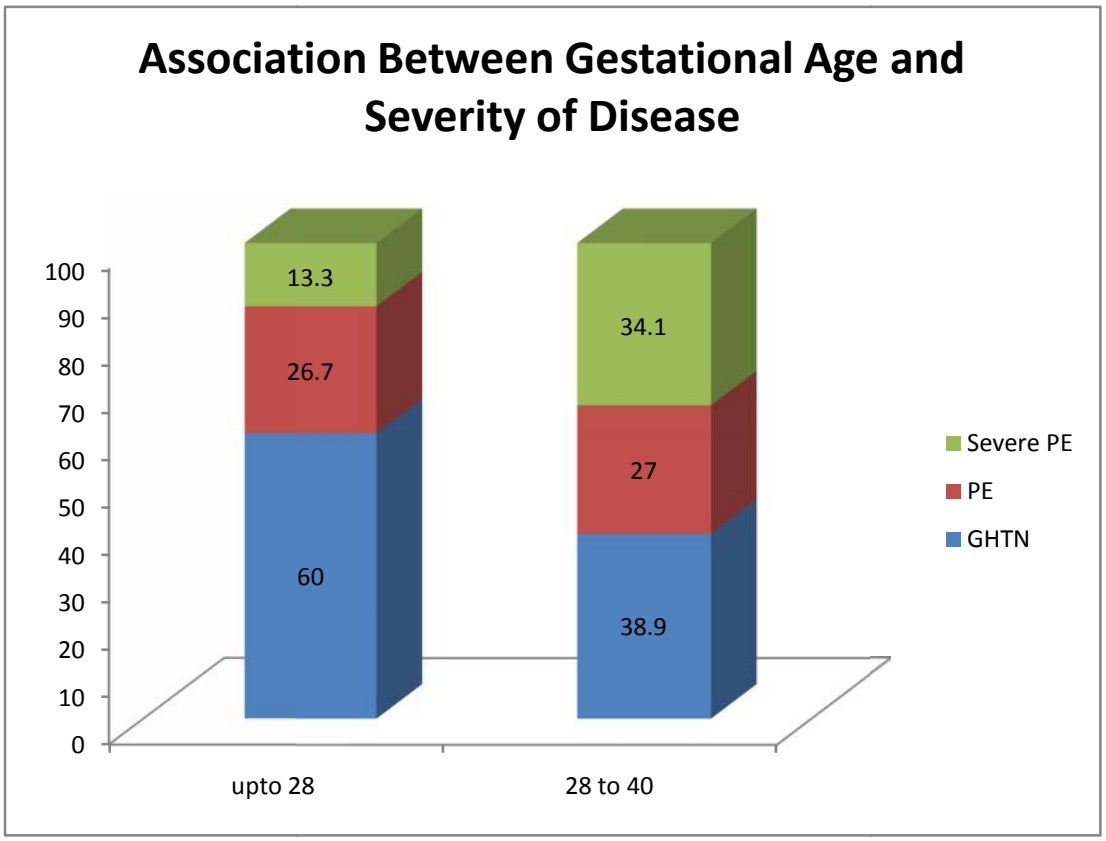




So in this study, there was a negative correlation with the age and severity of the disease, that is lesser the age of the patient, it was likely that the she will get severe spectrum of the illness. (P value 0.056) though it was not statistically very significant.

16. Association of gestational age and severity of the disease

Gestational age in weeks	DIAGNOSIS				Interpretation
	G.HTN	PE	Severe PE	Total	
28 to 40	33(38.9)	23(27)	29(34.1)	85	Pearson correlation coefficient 0.099 P value 0.328
upto 28	9(60)	4(26.7)	2(13.3)	15	



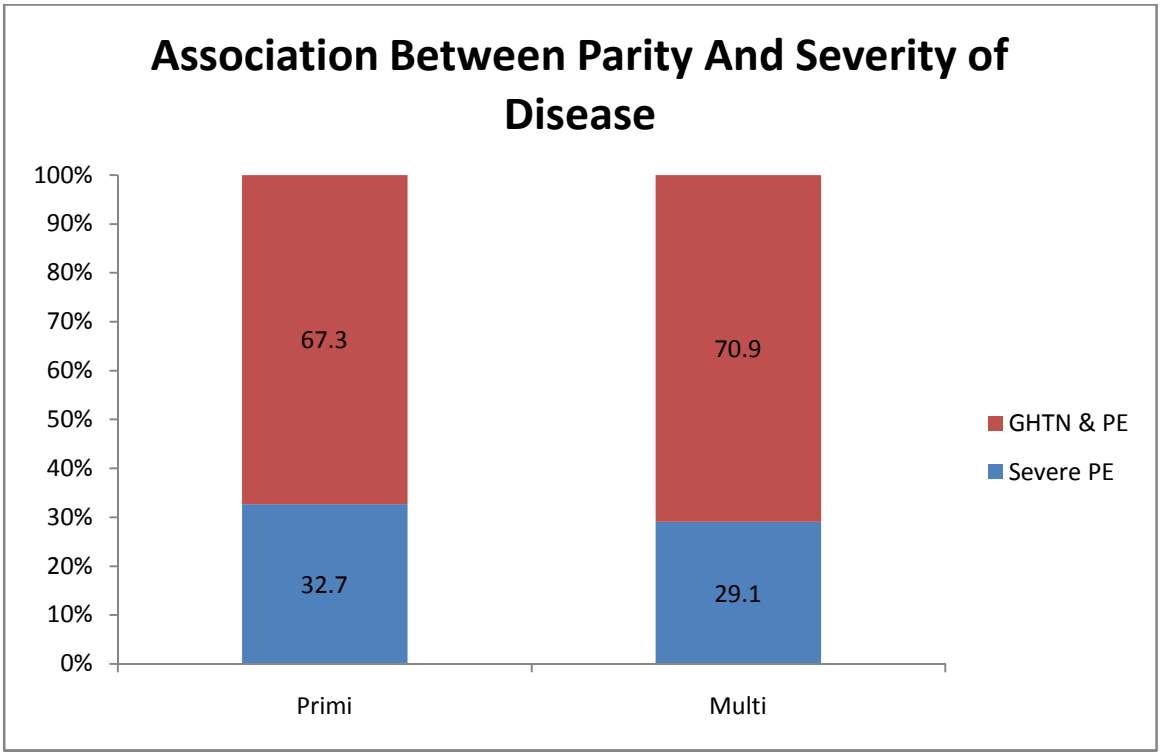
There was only a slight positive correlation between gestational age and severity of disease spectrum in the study group and since p value was >0.5, this correlation was not significant.

17.Association between parity and severity of disease

Parity	Severe PE	PE & GHTN	Total	Interpretation
Primi	17(32.7%)	35(67.3%)	52	
Multi	14(29.1)	34(70.9%)	48	Chi square : .03 P value : 0.87
Total	31	69	100	

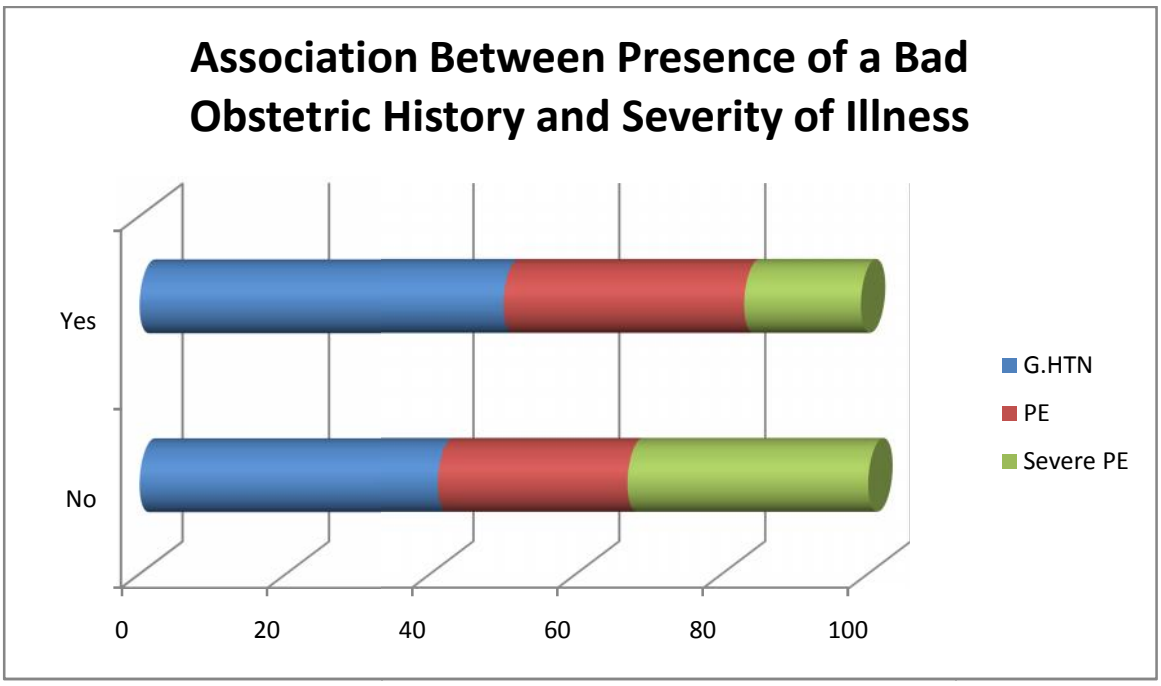
In this study, there was no significant association between parity and severity of the disease, as P value was >0.05.

Odds Ratio is 1.18, (0.5-2.76, 95% CI) , hence, not significant



18 Association between bad obstetric history and severity of disease

Presence of bad obstetric history	Diagnosis			Interpretation
	G.HTN	PE	Severe PE	
No	36(41%)	23(26%)	29(33%)	Pearsons correlation coefficient: 0.097 P value : 0.335
Yes	6(50%)	4(33%)	2(16%)	

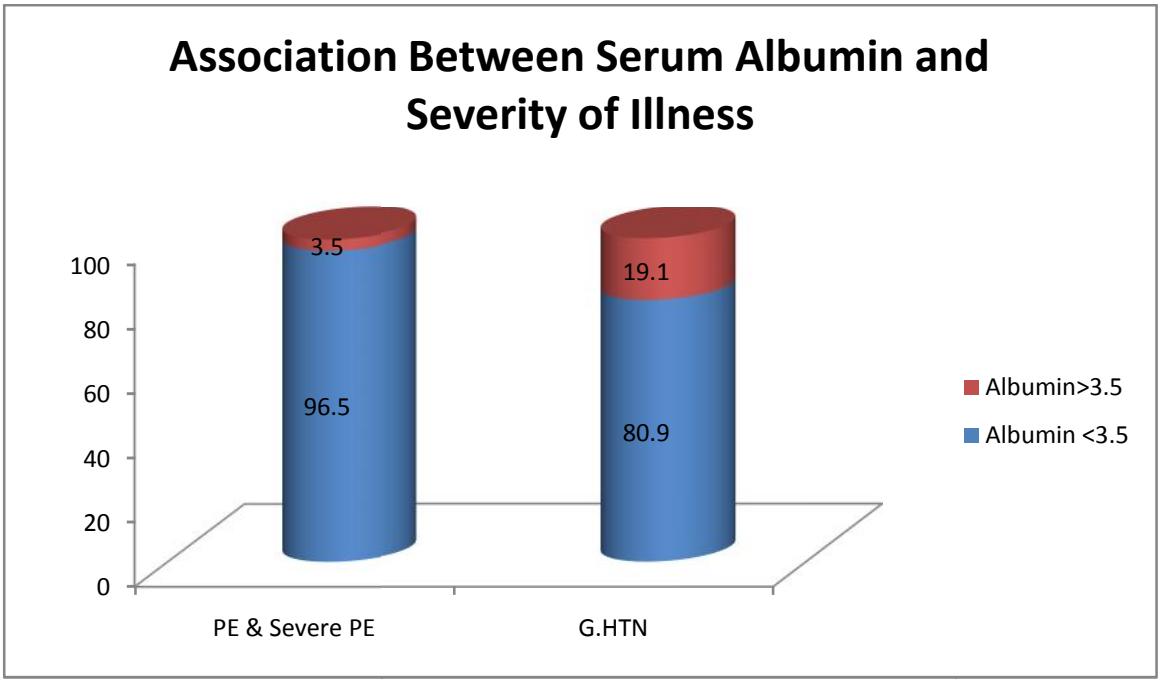


There was no statistically significant correlation between the presence of a bad obstetric history and severity of the disease spectrum in the study group (P value >0.33)

19 Association between serum albumin and severity of disease

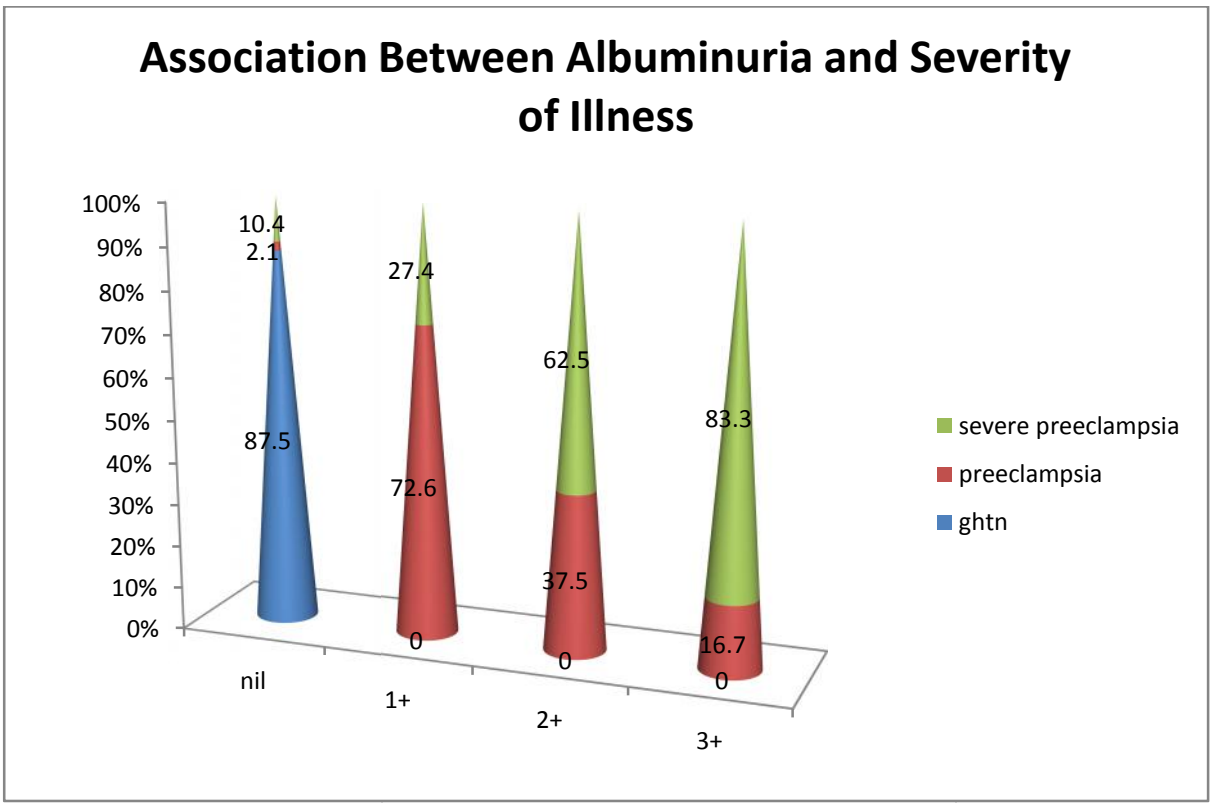
Diagnosis	S. Albumin <3.5	S.Albumin >3.5	Total	Interpretation
PE and Severe PE	56(96.5)	2(3.5)	58	Chi-square 4.967 P value 0.02
GHTN	34(80.9)	8(19.1)	42	
Total	90	10	100	

Odds ratio was 6.5 (1.32-30.6 with 95% CI) with p value <0.05, indicating that there is a significant correlation between severity of the disease and serum albumin



20. Association between albuminuria and severity of the disease

Urine albumin (dipstick reading)	Diagnosis			Total	Interpretation
	G.HTN	PE	Severe PE		
NIL	42(87.5)	1(2.1)	5(10.4)	48	Pearsons correlation coefficient 0.736
1+	0	16(72.6)	6(27.4)	22	
2+	0	9(37.5)	15(62.5)	24	
3+	0	1(16.7)	5(83.3)	6	P value : 0.001

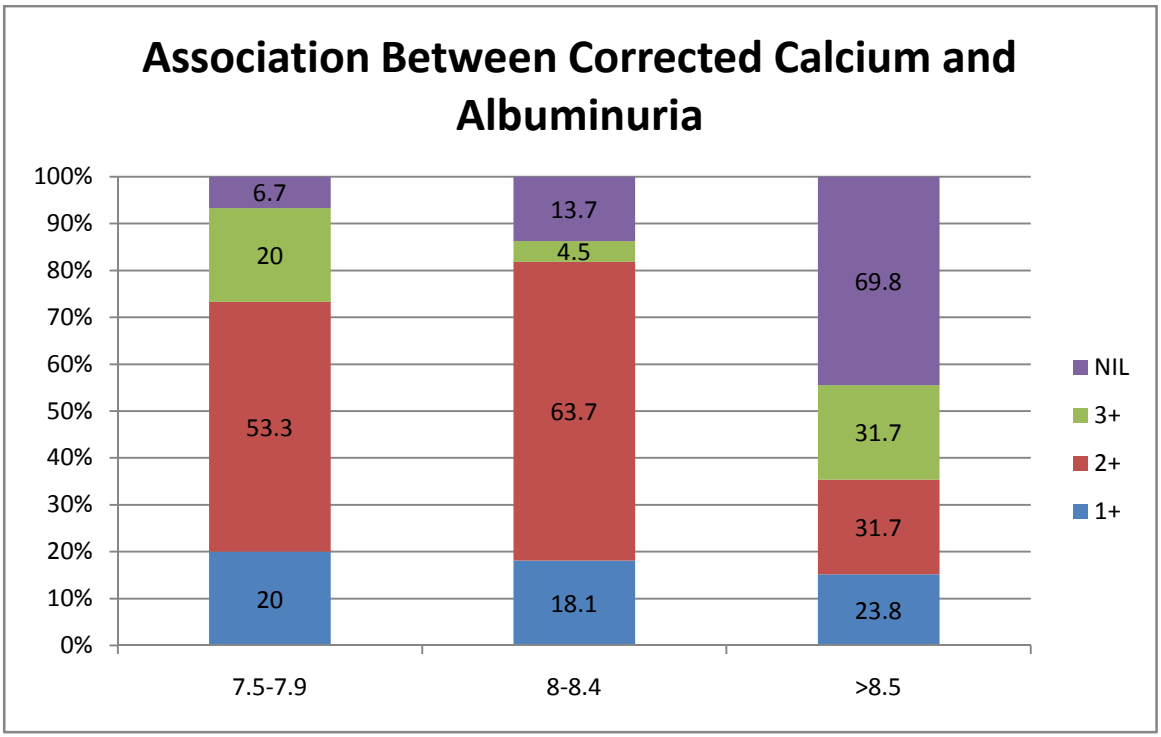


There was a positive correlation between albuminuria and severity of the disease, and this was statistically significant (P value <0.05)

21 Association between serum corrected calcium and albuminuria

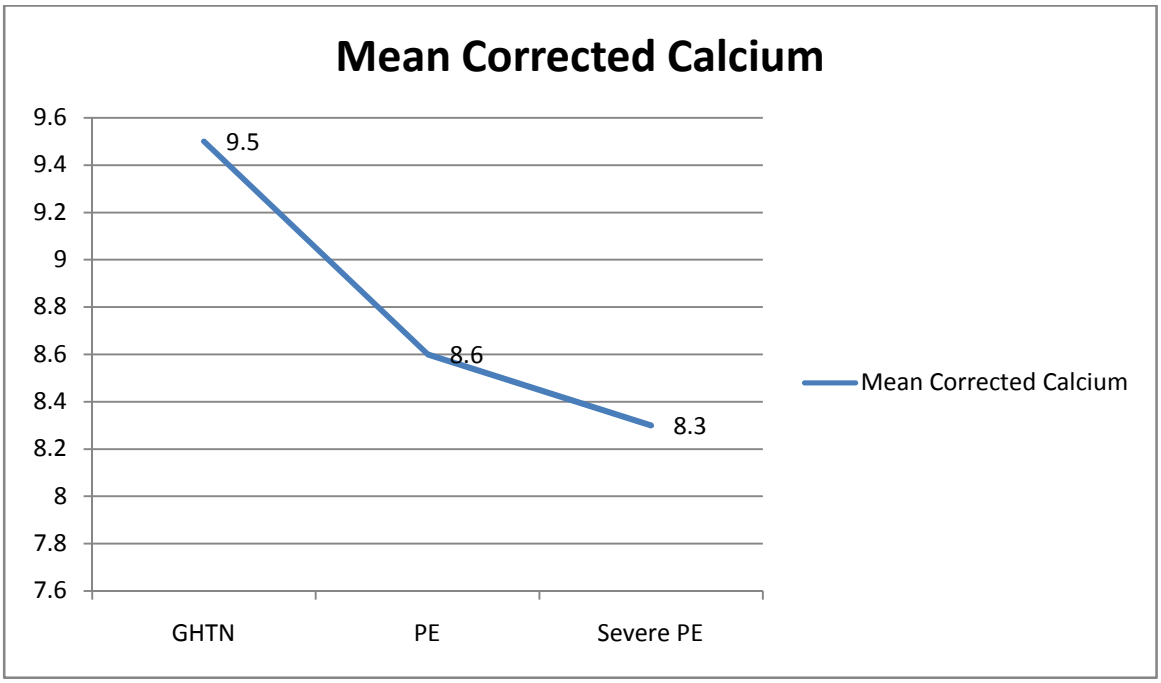
Corrected serum calcium (mg/dl)	Urine Albumin				Total	Interpretation
	1+	2+	3+	NIL		
7.5 to 7.9	3(20)	8(53.3)	3(20)	1(6.7)	15	Pearsons correlation coefficient : -.605 P value : 0.001
8 to 8.4	4(18.1)	14(63.7)	1(4.5)	3(13.7)	22	
More than 8.5	15(23.8)	2(31.7)	2(31.7)	44(69.8)	63	

There is a negative correlation between serum calcium level and severity of albuminuria and the level of negative correlation is 60% with significant p value of 0.001



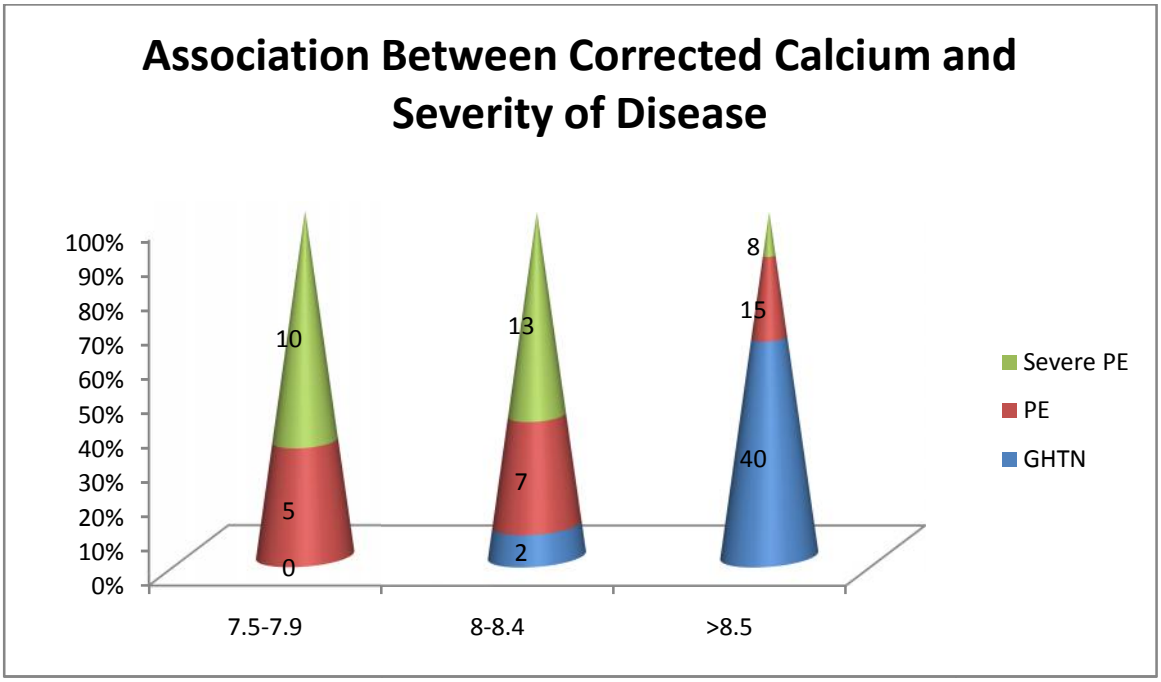
22. Aassociation between calcium and severity of the disease

	DIAGNOSIS		
	G.HTN	**PE**	**Severe PE**
Mean serum corrected calcium	9.4881	8.6111	8.2774



There is a decline in the mean value of corrected calcium value, as the severity of the disease spectrum is advancing.

Corrected Serum Calcium	Diagnosis			Interpretation
	G.HTN	PE	Severe PE	
7.5 to 7.9	0	5	10	Pearsons coefficient : -.652 P value : 0.001
8 to 8.4	2	7	13	
More than 8.5	40	15	8	



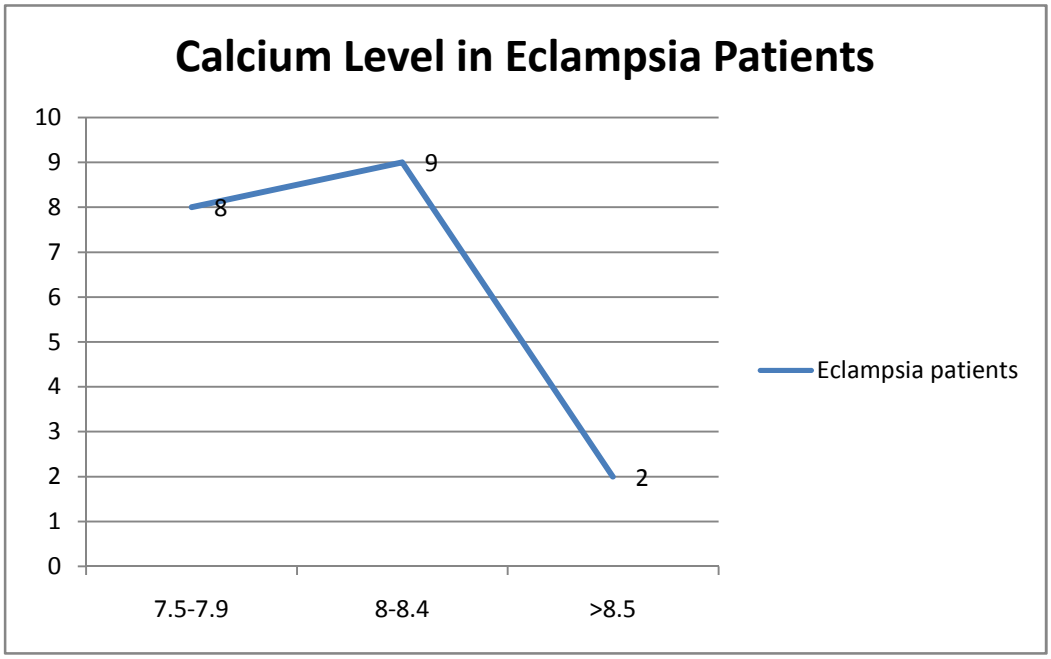
There is significant negative correlation between corrected calcium and severity of the disease, with P value < 0.05

Corrected serum calcium	Severe preeclampsia	Preeclampsia and gestational hypertension	Total
<8.5	23	14	37
>8.5	8	55	63
Total	31	69	100

Odds ratio was found to be 11.2 (4.1-30.5, 95% CI)
A patient with serum calcium level of <8.5 is 11.2 times at a higher risk of severe preeclampsia as compared to those with calcium >8.5mg/dl.

23 Association between eclampsia and serum calcium

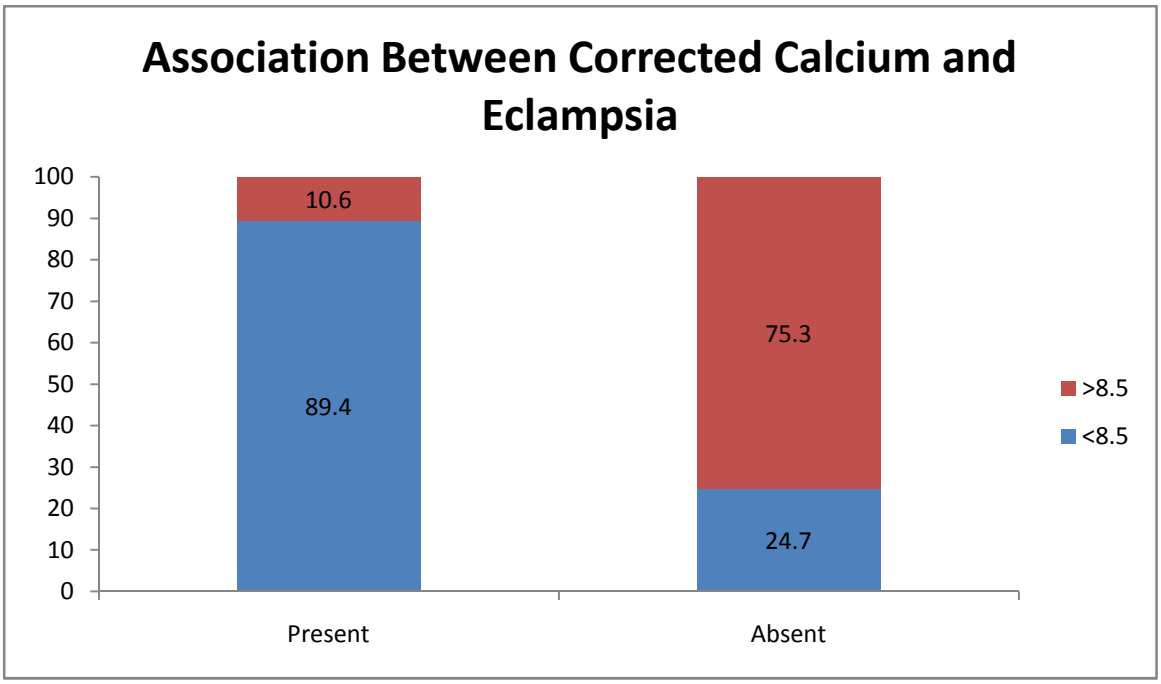
Corrected Calcium	Eclampsia
7.5 to 7.9	8
8 to 8.4	9
More than 8.5	2
Total	19



Mean serum calcium in patients with eclampsia is 8.10±0.16

Serum calcium (corrected)	Eclampsia present	No Eclampsia	Total	Interpretation
<8.5	17(89.4)	20(24.7)	37	Chi square :24.999 P value 0.001
>8.5	2(10.6)	61(75.3)	63	
Total	19	81	100	

There is an increased risk of contracting eclampsia if serum corrected calcium is <8.5 mg/dl, and this is statistically significant (P value <0.05)



DISCUSSION

In this study, 100 patients were recruited from the obgyn opd/ ward, who were suspected or diagnosed to have hypertensive disorder of pregnancy.

- Mean age of the study group was 25.3±1 years.
- 52% of the study group was primiparous and remaing multiparous, and in them, 12 patients had a bad obstetric history in the form of atleast one spontaneous abortion in the past.
- 15% of the study group belonged to the second trimester and 85% were in their third trimester of pregnancy.
- 42% had Gestational Hypertension, 27% had Pre-Eclampsia and 31% had severe or complicated preeclampsia.
- Out of 31 patients who had severe preeclampsia, 19 (61.2%) had Eclampsia, 5 (16.1%) had severe hypertension, 2 (6.4%) had acute renal insufficiency, 2(6.4%) had thrombocytopenia, 1 patient (3.2%) had pulmonary edema and 1(3.2%) patient had a visual scotoma.
- Eclampsia (61.2%) was the major contributor to the spectrum of severe disease in this study group.
- In this study, there was a negative correlation between age and severity of the disease, i.e, lesser the age of the patient, she was 19% more likely to contract a more severe spectrum of the disease. But this was statistically not very significant (P value 0.056). A study by Saftlas et al, concluded that maternal age <20 years was a strong risk factor for preeclampsia and eclampsia[41]. But in a study by Sheen et al, With a changing demographic profile of preeclampsia, older women accounted for an increasing

proportion of preeclampsia and related adverse outcomes, in contrary to finding of this study[42].

- There was no statistically significant correlation between gestational age and severity of the disease observed in this study, infact, a study by Moldenhauer et al, :concluded that Placentas in women with preeclampsia have higher degree of pathological changes, and this is further increased with lower gestational ages at the time of delivery for patients with preeclampsia[43]
- No significant association was seen between parity and severity of the disease in this study, though nulliparity is a well known moderate risk factor for development of preeclampsia.
- Mean serum albumin in the study group is 2.81±0.08g/dl, with majority between level of 2.5-3.4 g/dl. Analysis to find any association between severity of disease and serum albumin revealed a statistically significant association (P value <0.05), i.e, more severe the disease, lesser was the serum albumin level. This finding was similar to a study by Gojnic et al [44] and Basima et al[45] where they found that degree of hypoalbuminemia could used as a marker of severity of the preeclampsia and associated disorders.
- 48% of the group had no proteinuria on urine dipstick, while 6% had 3+ proteinuria. Analysis showed a significant relation between degree of proteinuria and severity of the disease, i.e more severe the proteinura, there was 73% chance for the patient to get a severe form of preeclampsia.(P value <0.05) This finding was similar to a study in the literature, by Tanacan et al in whose study they observed that Patients

who had higher levels of 24-h proteinuria was being diagnosed with preeclampsia at earlier gestation, and also had higher incidence of features of severe preeclampsia .Also, patients with massive proteinuria had more severe clinical symptoms of preeclampsia, and higher incidence abnormalities in laboratory tests than in those who had mild proteinuria.[46]

- Mean level of corrected calcium was 8.876±0.16mg/dl. 63% had corrected calcium more than or equal to 8.5mg/dl and 37% had less than 8.5mg/dl. Maximum was 10.6mg/dl and minimum was 7.5mg/dl. Not many studies similar to this have been conducted in south india. Similar finding was observed in study by Kanagal et al,Karnataka in which mean serum calcium in preeclamptic patients was 7.84 ± 0.87 mg/dl.[47]

  A study from Northern part of India by Chaurasia et al., found significantly lower levels of serum calcium and magnesium in pre-eclamptic pregnant women compared to normal pregnant women[48]) many other studies from different parts of the world have also come to a similar conclusion i.e, there was significantly reduced level of serum calcium in pregnant women with hypertensive disorders of pregnancy, when compared to normotensive pregnancies.[5,49–56]. but very few studies have also failed to find significant difference of calcium level between preeclamptic and normotensive pregnancies.[57–59]

- On assessing the relation between serum calcium level and severity of the disease, there was a significant correlation, i.e, there was 65% chance of getting severe spectrum of preeclampsia, if serum corrected calcium level was less than 8.5mg/dl and this was highly significant (P value <0.001).

If a patient had corrected serum calcium <8.5mg/dl, there was 11.2 times (4.1-30.5, 95%CI) increased risk of getting preeclampsia with severe features.

- Also, the mean serum corrected calcium in those who had eclampsia was 8.10±0.16mg/dl.
- Studies from literature have shown similar finding of significantly reduced serum calcium level as the severity of preeclampsia was increased. Study by Kumar and Singh concluded that there was significant correlation between maternal serum calcium and severity of hypertensive disorder of pregnancy, adverse perinatal and maternal outcome.[60] Study by Patel et al and Punthumapol et al, also drew similar conclusion.[61,62]
- Analysis to find association between level of corrected calcium and severity of proteinuria, revealed a statistically significant negative correlation of 60% , i.e, lesser the serum calcium level, more severe was the proteinuria ((P value < 0.001).
- 16% of the study population was not regularly taking calcium supplement, as advised by the health care facility. Mean level of corrected calcium those who were on regular calcium supplement was 8.96±0.68mg/dl, and in those who were not regularly taking, was 8.41±0.07mg/dl. this difference was found to be statistically significant (P value < 0.05) It was also found that, there was a 1.94 times increased risk of contracting severe Preeclampsia, if the patient is not regularly taking calcium supplement. But this association was statistically insignificant (P value >0.05).

- A major trial, Calcium in Preeclampsia Prevention (CPEP) found that, Calcium supplementation during pregnancy to those who were having near adequate dietary intake of calcium did not prevent preeclampsia, pregnancy-associated hypertension, or adverse perinatal outcomes in healthy nulliparous women.[63] So to find out the effect of supplemental calcium in women with low dietary intake of calcium, WHO conducted a study among low calcium intake pregnant women, and deducted that A 1.5-g calcium/day supplement did not prevent preeclampsia but did reduce its severity, maternal morbidity, and neonatal mortality,[64] another metaanalysis also concluded that Calcium supplementation appears to be beneficial for women at high risk of gestational hypertension and in communities with low dietary calcium intake[65]
- The mean systolic blood pressure in the group was 144.2±3.5mmHg. there was a negative correlation of systolic blood pressure with corrected calcium level (correlation coeffiecient -.265, P value 0.008) and this was statistically significant.
- Mean diastolic BP was 94.7±1.6mmHg, and similar to systolic BP, there was a statistically significant negative correlation between serum calcium and diastolic blood pressure(correlation coefficient -.280, P value 0.005) This finding was similar to those by Deokar et al, where, there was negative correlation between serum calcium with systolic**(**r = - 0.3963, p value of r = 0.005) and Diastolic BP. (r = - 0.5123, p value of r < 0.001) and was significant.[66] Similar finding was also observed in a study by Haleema et al, where the correlation coefficient was -0.81 in third trimester, between serum calcium and systolic blood pressure.[6]

- On looking up any association between presence of a bad obstetric history and severity of the disease, there was a slight positive correlation, i,e presence of bad obstetric history poses a 9% increased risk of getting severe preeclampsia, but this was statistically insignificant.(P value >0.05). similar finding was observed in two studies, one by Dadhich et al, where there was an association between bad obstetric history and preeclampsia of 11.53%, as compared to normotensive pregnant patients and BOH, of 4.5%.[67]. In another study by Xiong Xu et al, they found an increase in the incidence of preeclampsia, who have had a history of two abortions, and also, a previous term pregnancy is actually a protective factor against the development of preeclampsia in subsequent pregnancies.[68]

CONCLUSION

- The mean age of the study group was 25.3±1 years
- There was a negative, but statistically insignificant correlation between age and severity of the disease.
- 52% was primiparous, 12% had a bad obstetric history in the past.
- No significant association was found between parity and severity of disease.
- 15% was in their second trimester and 85% in their third trimester.
- No significant correlation was found between gestational age and severity of disease.
- 42% had Gestational Hypertension, 27% had Pre-Eclampsia and 31% had severe or complicated preeclampsia
- Eclampsia (61.2%) was the major contributor to the spectrum of severe disease in this study group
- Mean serum albumin in the study group is 2.81±0.08g/dl.
- The association between serum albumin level and severity of disease was statistically significant.
- 48% of the group had no proteinuria on urine dipstick, while 6% had 3+ proteinuria. There was statistically significant association between severity of proteinuria and severity of the disease

- There was a negative correlation of 60% between proteinuria and severity of the disease, i.e, more severe the proteinuria, more severe was the disease. This was highly significant (P value <0.001)
- Mean level of corrected calcium was 8.876±0.16mg/dl.
- Mean corrected calcium in Gestational hypertension, Preeclampsia and Preeclampsia with severe feature were 9.5±0.12mg/dl, 8.6±0.08mg/dl and 8.3±0.24mg/dl , respectively. Mean serum corrected calcium in those who had eclampsia was 8.10±0.16mg/dl
- This difference was highly significant statistically (P value <0.001)
- 16% of the study group was not taking calcium supplement regularly, and mean serum corrected calcium in these patients were 8.41±0.07mg/dl and in the compliant group, it was 8.96±0.68mg/dl. This difference was statistically significant (P value <0.05)
- The mean systolic blood pressure in the group was 144.2±3.5mmHg. there was a negative correlation of systolic blood pressure with corrected calcium level and this was statistically significant.
- Mean diastolic BP was 94.7±1.6mmHg, and similar to systolic BP, there was a statistically significant negative correlation between serum calcium and diastolic blood pressure.
- Presence of bad obstetric history poses a 9% increased risk of getting severe preeclampsia, but this was statistically insignificant.(P value >0.05)

RECOMMENDATIONS

India, being a low-middle income country (LMIC), where in majority of the population, the daily dietary intake of calcium does not reach in par with the recommended daily intake, especially in pregnant/ lactating population, in whom the RDI is even more, the need for adequate and early initiation of calcium supplementation is very high. The relevance of adequate calcium supplementation is shown from this study, where there was increased severity of disease, who were poorly compliant to the drug intake. So this should start from the community level, where the high risk population should be adequately educated to increase dietary consumption of calcium rich foods, and also to regularly adhere to the supplement programmes. There is also a need for early admission to the medical facility, for timely prevention of complications,like in this study population, there was a significant number of patients who presented with eclampsia. Inspite of many novel modalities which have come up for prediction, and diagnosis of pre-eclampsia and related disorders, like PIGF and sflt, importance of minerals like calcium still remains to linger due to its role in many metabolic pathways, and thence in maintaining a normal homeostatis in pregnancy.

LIMITATIONS

- The sample size was very small, compared to the actual required size
- Ionised calcium which is the physiologically active form of calcium was not measured in this study
- Since dietary pattern was not studies, the dietary intake of calcium could not be assessed.
- Instead of measuring 24 hour urine protein, Proteinuria was assessed using only urine dipstick, which has high rates of false positivity as well as false negativity.
- Uterine artery umbilical artery Doppler was not studied in any of the cases

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PROFORMA

1.NAME :

2.AGE :

3.SEX :

4.OCCUPATION :

5.ADDRESS :

6. OP/IP NO. :

7.PAST HISTORY :

8.FAMILY HISTORY :

9. OBSTETRIC SCORE :

10.GESTATIONAL AGE :

11.CLINICAL EXAMINATION

WEIGHT BP

12. OBSTETRIC EXAMINATION :

13. OTHER SYSTEM EXAMINATION

- ✓ CARDIOVASCULAR SYSTEM
- ✓ RESPIRATORY SYSTEM
- ✓ ABDOMEN :
- ✓ CNS :

14. LAB INVESTIGATIONS

CBC, RFT, LFT

SERUM CALCIUM

URINE PROTEIN DIPSTICK

15. COMPLIANCE TO DRUG INTAKE

PATIENT CONSENT FORM

STUDY DETAIL:

STUDY CENTRE:

PATIENT'S NAME:

PATIENT'S AGE:

IDENTIFICATION NUMBER:

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that the sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However I understand that my identity would not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests.

Signature/thumb impression:

Patient's name and address: Place: Date:

Signature of the investigator:

Name of the investigator: Place: Date:

CONSENT FORM

ஒப்புதல் படிவம்

முழுப்பெயர் :

தந்தை / தாயாரின்பெயர் :

பாலினம்/வயது :

I. நான் மேலே குறிப்பிடப்பட்ட ஆராய்ச்சி குறித்த விளக்க உரையினை படித்துபுரிந்து கொண்டேன். எனது , எனக்கு கேள்விகேட்க விளக்கம் அளிக்கப்பட்டது எனது உறுதி செய்கிறேன்.

II. நான் இந்த ஆராய்ச்சியில் பங்குபெறுவது தன்னிச்சையானது என எனது , நான் எப்போது வேண்டுமானாலும் , காரணம் ஏது விதிவிலக்கின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழு சுதந்திரம் எனது , அப்படி செய்வதனால் என் சட்ட ரீதியான மற்றும் சமூகரீதியான உரிமைகள் பாதிக்கப்படமாட்டாது எனது நான் அறிகிறேன்.

III. இந்த ஆராய்ச்சியில் புரவலர் மற்றும் அவரின் சார்பில் பணிபுரிபவர்கள் மற்றும் முழு கட்டுப்பாட்டில் ஆகியோரி, இந்த ஆராய்ச்சியில் போது , என் இந்த சம்பந்தமான விளக்கம் ஆராய்ச்சி செயலும்போது , என் சம்பந்தப்பட்ட சமூகரீதியான விஷயங்களை வெளியிடும் என் அல்லது இல்லை காண அல்லது அளிக்கப்படுகிறேன். மேலும் நான் இந்த ஆராய்ச்சியில் பற்றி விளக்கம் போது , இந்த ஆராய்ச்சியில் முடிவுகள் பங்கேற்பு போது என் அவர்களால் வெளியிடப்பட்டது எனது நான் அறிகிறேன்.

IV. இந்த ஆராய்ச்சியில் மூல அறியப்படு விஷயங்கள் மற்றும் முடிவு அறிவியல் சார்ந்த காரணங்களுக்காக வெளியிடப் படுவதை நான் எப்போது தடுக்கமுடியாது எனது உறுதி அளிக்கிறேன்.

V. நான் இந்த ஆராய்ச்சியில் பங்கு பெற சம்மத விதிக்கிறேன்.

1) ஆராய்ச்சியில் பங்கு கொள்பவர் / சட்டபூர்வ பிரதிநிதியின் கையெழுத்து / ஆள்காட்டி விரல் பதிப்பு

பெயர் / உறவுமுறை

2) ஆராய்ச்சியாளர் சாட்சி கையெழுத்து , தேதி

MASTER CHART

Sl No	Name	Hosp. No:	Age	Obst Score	Gest Age	S.BP	D.BP	U.ALB	S. CALCIUM	S. ALBUMIN	Corr Calcium	DIAGNOSIS	Feature	compliance
1	Shabiyabegam	68830	23	G2P1L1	28.4	200	110	1+	7	3	7.8	Severe PE	eclampsia	Y
2	Zahitha	66288	24	G3P2L2	34.4	130	90	NIL	9.5	2.9	10.4	G.HTN		Y
3	Mageswari	78200	22	G2P1L1	35	160	100	2+	7.5	2.6	8.6	Severe PE	eclampsia	Y
4	Kavitha	81545	22	G2A1	27	170	110	3+	7.2	3.4	7.7	Severe PE	eclampsia	N
5	Sangeetha	80426	20	G1P0	35	150	100	2+	6.8	2.9	7.7	Severe PE	eclampsia	Y
6	Abirami	68117	22	G1P0	38.3	150	100	NIL	7.9	2.6	9	G.HTN		Y
7	Kavari	65939	20	G1P0	32.3	140	80	1+	8.3	2.8	9.3	PE		Y
8	Anitha	69685	20	G1P0	39.7	130	90	NIL	7.5	2.5	8.7	G.HTN		Y
9	Aafrin Banu	68256	21	G1P0	33	130	90	1+	8	3.1	8.7	PE		Y
10	Resma	69796	42	G2P1L1	2	130	90	NIL	8.1	3.4	8.6	G.HTN		Y
11	Ayesha	72164	30	G3A2	21.4	120	90	NIL	8.3	3.6	8.6	G.HTN		Y
12	Usharani	81760	20	G1P0	37	150	100	2+	7.3	3	8.1	Severe PE	thrombocytopenia	N
13	Valli	76846	36	G2P1L1	33	140	100	NIL	8.2	3.1	8.9	G.HTN		Y
14	Priyadarshini	77370	32	G2P1L1	33.6	130	90	NIL	8.5	2.4	9.8	G.HTN		Y
15	Vani	69531	23	G1P0	36.3	160	100	1+	9	2.6	10.1	Severe PE	hypertension	Y
16	Sheela	78788	25	G3P1D1A1	38	190	120	2+	7.1	2.9	8	Severe PE	eclampsia	Y
17	Jansirani	68366	28	G3P2L2	28.7	130	90	1+	7.4	3.4	7.9	PE		Y
18	Megala	77979	30	G2P1L1	36.3	130	90	NIL	8.6	2.2	10	G.HTN		Y
19	Chitra	79255	28	G3P2L2	23	140	90	NIL	8.5	3.7	8.7	G.HTN		Y
20	Roja	80611	23	G2P1L1	35.6	130	90	NIL	7.8	3.5	8.2	G.HTN		Y

21	Uma	80661	25	G1P0	34.4	120	90	NIL	8	3.6	8.3	G.HTN		Y
22	Ellammal	68693	19	G1P0	36.3	130	90	1+	7.9	2.5	9.1	PE		N
23	Vaishnavi	70262	26	G2P1L1	38.3	140	90	2+	7.4	3.6	7.7	PE		Y
24	Kalaiarasi	82631	40	G4P3L3	25.3	150	100	NIL	8.2	3.5	8.6	G.HTN		N
25	Sangeetha	83215	20	G1P0	36.3	140	90	NIL	8.9	3.6	9.2	G.HTN		Y
26	Sasikala	83996	28	G1P0	38	150	90	NIL	8.6	2.5	9.8	G.HTN		Y
27	Sasikala	84627	22	G1P0	36.4	150	90	2+	6.9	2.5	8.1	Severe PE	eclampsia	Y
28	Kumutha	66578	26	G1P0	35.3	160	110	NIL	8	2.9	8.9	Severe PE	hypertension	Y
29	Famidha	87162	32	G4P3L3	37	140	90	NIL	8.1	2.5	9.3	G.HTN		Y
30	Kasthori	86098	27	G3P2L2	37	150	100	NIL	8.4	2.7	9.4	G.HTN		Y
31	Poonkodi	9820	22	G1P0	36.3	140	100	NIL	7.3	3.4	7.8	Severe PE	visual scotoma	N
32	Dharani	13360	25	G2P1L1	34	150	110	3+	6.7	2.6	7.8	Severe PE	eclampsia	Y
33	Neelufar	70288	29	G1P0	36.4	140	100	1+	8	3.5	8.4	PE		Y
34	Ranjitha	71392	22	G3P2L2	35	150	100	2+	7.9	2.7	8.9	PE		Y
35	Jeenath	14912	31	G2P1L1	34.4	170	100	2+	7.4	2.9	8.3	Severe PE	eclampsia	Y
36	Kalaiselvi	91184	25	G3P1D1A1	35.3	150	90	NIL	8.5	3.2	9.1	G.HTN		Y
37	Sakthi	73202	34	G2P1L1	36.6	150	90	1+	8.8	3	9.6	PE		Y
38	Jeevadarshini	91126	26	G3P1L1A1	26	130	90	NIL	8.9	2.6	10	G.HTN		Y
39	Saritha	73563	32	G3P2L1D1	35	140	80	2+	7.2	3	8	PE		Y
40	Meena	72743	23	G1P0	33.3	150	100	1+	6.8	3.1	7.5	PE		N
41	Shalini	4094	24	G1P0	30	130	90	NIL	8.9	2.4	10.2	G.HTN		Y
42	Agila	8443	20	G1P0	28	140	80	NIL	9	3.2	9.6	G.HTN		Y
43	Mohana	8519	26	G4P1L1A2	33	130	90	NIL	9.1	3	9.9	G.HTN		Y
44	Vasanthi	15738	20	G1P0	36.6	160	90	2+	7.4	3	8.2	Severe PE	hypertension	N

45	Thavapriya	7818	23	G1P0	35	130	90	NIL	8.6	2.5	9.8	G.HTN		Y
46	Abirami	76327	24	G1P0	35.3	140	90	2+	6.5	2.7	7.5	PE		N
47	Buvaneswari	15940	23	G2P1L1	29	160	90	2+	6.9	2.8	7.9	Severe PE	eclampsia	Y
48	Divya	79110	31	G2P1L1	31.3	140	100	2+	7.2	2.9	8.1	PE		Y
49	Lavanya	8199	19	G1P0	36.7	130	90	NIL	8.6	2.4	9.9	G.HTN		N
50	Dhanalakshmi	15743	20	G1P0	35.4	160	110	1+	7.4	2.7	8.4	Severe PE	hypertension	Y
51	Savitha	12100	28	G2P1L1	33.3	200	110	2+	7.4	2.8	8.3	severe PE	eclampsia	N
52	Hajira Banu	16830	32	G1P0	34	130	90	2+	6.7	2.4	8	Severe PE	eclampsia	Y
53	Kavitha	8223	25	G3P1L1A1	36.6	120	90	NIL	8.3	2.7	9.3	G.HTN		Y
54	Bhagyalakshmi	9319	30	G3P2L2	22.4	140	100	NIL	8.9	3.6	9.2	G.HTN		Y
55	Priya	16084	21	G1P0	34	130	90	3+	6.4	2.2	7.8	Severe PE	eclampsia	Y
56	Sabrin	82281	23	G1P0	29	150	90	1+	7.8	2.9	8.7	PE		Y
57	Asheena	10043	20	G1P0	37.4	130	90	NIL	8.6	2.3	10	G.HTN		Y
58	Indhumathi	86032	26	G1P0	38	150	100	1+	8.1	2.9	9	PE		Y
59	Selvi	17066	24	G2P1L1	32.4	170	100	2+	7	3.2	7.6	Severe PE	eclampsia	Y
60	Suganthi	9078	23	G4P1L1A2	35	140	100	1+	7.9	2.6	9	PE		N
61	Archana	11454	24	G1P0	34	150	100	NIL	8.6	2.9	9.5	G.HTN		Y
62	Sheen	22248	30	G5P4L4	36.6	130	90	2+	6.5	2.5	7.7	Severe PE	thromboc ytopenia	Y
63	Sumathi	17680	30	G2P1L1	33	140	100	NIL	7.2	2.7	8.2	Severe PE	eclampsia	Y
64	Sidhisha	11173	23	G1P0	33.6	140	100	2+	6.8	2.9	7.7	PE		N
65	Ammu	11359	19	G1P0	37	130	90	NIL	8.6	2.5	9.8	G.HTN		Y
66	Vennila	10506	21	G1P0	36	130	90	NIL	8.9	2.2	10.3	G.HTN		Y
67	Sathya	5390	21	G1P0	34.7	240	130	NIL	7.8	3	8.6	Severe PE	pulmonary edema	Y

68	Nadhiya	11398	30	G1P0	36.7	140	90	1+	7.3	2.6	8.4	PE		Y
69	Veerabanu	10719	19	G1P0	33.6	150	90	NIL	7.8	2.2	9.2	G.HTN		Y
70	Babyshalini	13524	27	G1P0	32.7	140	90	NIL	8.3	2.9	9.2	G.HTN		Y
71	Rabekkal	13861	19	G1P0	36.6	150	80	NIL	8.6	2.4	9.9	G.HTN		Y
72	Sujatha	8735	24	G1P0	24.4	160	110	NIL	7.9	3.2	8.5	Severe PE	hypertension	Y
73	Salmabee	13928	32	G3P2L2	29.6	150	90	NIL	8.6	3	9.4	G.HTN		Y
74	Sandhiya	12715	26	G2P1L1	34.7	130	90	3+	8.4	2.5	9.6	PE		Y
75	Rajalakshmi	18918	22	G3P2L2	36	130	90	3+	7.4	2.8	8.4	Severe PE	eclampsia	Y
76	Shobana	16184	35	G4P3L3	27.4	150	100	NIL	8.2	2.9	9.1	G.HTN		Y
77	Pavithra	13562	35	G3P2L1D1	37	130	90	1+	7.9	2.1	9.4	PE		Y
78	Gayathri	13799	22	G3P0A2	37	140	100	2+	7	2.5	8.2	PE		Y
79	Kiruba	17321	32	G2P1L1	38	130	90	NIL	8.9	2.2	10.3	G.HTN		Y
80	Aliya	16712	33	G3P1L1A1	38	150	100	NIL	9	2	10.6	G.HTN		Y
81	Latha	19536	21	G1P0	32	140	90	2+	6.8	2.8	7.8	Severe PE	eclampsia	N
82	Rani	15477	29	G2P1L1	36.7	130	90	1+	6.9	2.4	8.2	Severe PE	HELLP syndrome	N
83	Vijayalakshmi	15271	27	G1P0	34.4	140	90	NIL	7.9	2.9	8.8	PE		Y
84	Nasrin	19261	32	G3P2L2	30	130	90	NIL	8.1	2.8	9.1	G.HTN		Y
85	Valli	19614	19	G1P0	25.4	130	90	1+	8.2	3.3	8.8	PE		N
86	Priya	20356	23	G1P0	26.6	150	100	1+	8.5	3.1	9.2	PE		Y
87	Sherin Banu	23504	20	G1P0	27.4	140	90	2+	7.6	3	8.4	PE		Y
88	Kalpana	21384	20	G2P1L1	30.6	150	100	2+	7.4	2.9	8.3	Severe PE	eclampsia	Y
89	Rajeswari	22428	25	G1P0	34.3	140	90	1+	8.2	2.6	9.3	Severe PE	eclampsia	Y
90	Alifa Banu	21181	27	G1P0	36.4	150	90	NIL	8.9	2.4	10.2	G.HTN		Y
91	Suveka	22635	21	G1P0	37	130	90	NIL	8.9	2.1	10.4	G.HTN		N

92	Saitha	18412	24	G1P0	36	140	100	3+	8.2	2.3	9.6	Severe PE	renal insufficiency	Y
93	Sangeetha	6657	19	G1P0	32.4	150	90	1+	8	2.7	9	PE		Y
94	Kanimozhi	21555	28	G1P0	35	150	100	2+	7.2	2.5	8.4	Severe PE	eclampsia	Y
95	Ammu	14848	21	G2P1L1	30.4	140	100	NIL	8.8	2.6	9.9	G.HTN		Y
96	Naregee Banu	73973	19	G1P0	26.4	130	90	1+	8.6	3.2	9.2	PE		Y
97	Renuka	74890	26	G3P2L2	36.7	140	90	2+	7.1	2.4	8.4	PE		Y
98	Anusuya	13201	29	G2P1L1	33.4	150	100	NIL	8.3	2.1	9.8	G.HTN		Y
99	Sathya	18371	27	G1P0	31.7	160	90	1+	7.6	2.9	8.5	Severe PE	renal insufficiency	Y
100	Kurshit Beegum	18228	20	G1P0	25.4	130	90	NIL	9.1	3.7	9.3	G.HTN		Y