STUDY OF CALCIUM TO CREATININE RATIO IN A SPOT SAMPLE OF URINE FOR EARLY PREDICTION OF PRE ECLAMPSIA.

TAMILNADU

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Dissertation submitted to in partial fulfillment of the requirements for the degree of

M.S.(OBSTETRICS AND GYNAECOLOGY)

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

COIMBATORE MEDICAL COLLEGE HOSPITAL,

COIMBATORE.

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UNIVERSITY REGISTRATION NUMBER-221716304

<center>**DECLARATION**</center>

I hereby declare that this dissertation entitled "**STUDY OF CALCIUM TO CREATININE RATIO IN A SPOT SAMPLE OF URINE FOR EARLY PREDICTION OF PRE ECLAMPSIA"** is a bonafide and genuine research work carried out by me under the guidance of **Prof. DR.MANONMANI. R, MD, DGO.,** Professor and the HOD, Department of Obstetrics & Gynaecology, Coimbatore Medical College & Hospital, Coimbatore.

Date: **Dr.G.NITHYA.**

Place: Coimbatore

CERTIFICATE

This is to certify that the dissertation entitled "**STUDY OF CALCIUM TO CREATININE RATIO IN A SPOT SAMPLE OF URINE FOR EARLY PREDICTION OF PRE ECLAMPSIA**" is a bonafide and genuine research work carried out by **Dr.G.NITHYA** in partial fulfilment of the requirement for the degree of Master of Surgery in Obstetrics & Gynaecology.

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CERTIFICATE OF APPROVAL

To
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Department of Obstetrics & Gynecology,
Coimbatore Medical College & Hospital
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Dear **Dr.Nithya G**

The Institutional Ethics Committee of Coimbatore Medical College, reviewed and discussed your application for approval of the proposal entitled **"Study of Calcium to Creatinine Ratio in a Spot Sample of Urine for Early Prediction of Pre Eclampsia."**No.068/2017.

The following members of Ethics Committee were present in the meeting held on 25.11.2017.conducted at MM - II Seminar Hall, Coimbatore Medical College Hospital Coimbatore-18.

1	Dr.S.Ramalingam MD, Dean, PSG IMS&R, Cbe	Chairman
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11	Mrs.A.Sharmila BA., BL., Advocate	Legal Expert
12	Dr.K.P.Sampath Kumar M.Pharm, Ph.D., Asst. Prof. of Pharmacy, CMC, Cbe	Scientific Member
13	Dr.G.Vani Ganesh M.Sc.,Ph.D., Tutor in Medical Surgical Nursing, CMCH, Cbe	Scientific Member
14	Mr.V. Balasubramani MA,MA,MBA,LLB,M.Phil,PG.D.M, DLLAL, Chief Executive, Avinashilingam JSS Self Finance Courses, Cbe	Social Worker
15	Mr.V.A.Shahul Hameed, +2	Lay-Person

We approve the Proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary Ethics Committee

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Last but not least I would like to thank all my patients without whose cooperation; this dissertation would never have seen the light of the day.

Date: **Signature of the Candidate**

Place: Coimbatore   **Name Dr.G.NITHYA**

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LIST OF ABBREVIATIONS:

CCR	-	CALCIUM CREATININE RATIO
GA	-	GESTATIONAL AGE
PIH	-	PREGNANCY INDUCED HYPERTENSION
BP	-	BLOOD PRESSURE
BMI	-	BODY MASS INDEX
HELLP	-	HEMOLYSIS,ELEVATED LIVER ENZYMES,LOW PLATELETS
VEGF	-	VASCULAR ENDOTHELIAL GROWTH FACTOR
PIGF	-	PLACENTAL GROWTH FACTOR
NO	-	NITRIC OXIDE
DIC	-	DISSEMINATED INTRAVASCULAR COAGULATION
PAPP A	-	PREGNANCY ASSOCIATED PROTEIN
ADAM -12	-	A DISINTEGRIN AND METALLOPROTEASE
ANP	-	ATRIAL NATRIURETIC PEPTIDE
AT-3	-	ANTITHROMBIN 3
NST	-	NON STRESS TEST
FKC	-	FETAL KICK COUNT
ACOG	-	AMERICAN COLLEGE OF OBSTETRICS AND GYNAECOLOGY
NICE	-	NATIONAL INSTITUTE FOR CARE AND EXCELLENCE
LSCS	-	LOWER SEGMENT CAESAREAN SECTION
NVD	-	NORMAL VAGINAL DELIVERY
PICME	-	PREGNANCY AND INFANT COHORT MONITORING AND EVALUATION
PMSMA	-	THE PRADHAN MANTRI SURAKSHIT MATRITVA ABHIYAN

INTRODUCTION

Hypertension is one of the commonest medical complication during pregnancy. Despite so much research, Pre-eclampsia is one of the leading cause of maternal morbidity and mortality in India and worldwide. Incidence is 5-15% in pregnancy. High blood pressure is a sign ,not a disease.

About 5-15% of the pregnancy are affected by hypertensive disorder and pre eclampsia, of which pre eclampsia constitute of about 70% and chronic hypertension of about 30%. Its incidence in primi gravida is about 10-15% and in multi gravida is 5%.

Pre -eclampsia is one of the leading causes of maternal morbidity and mortality.It accounts for more than 40% premature deliveries and 18% maternal mortality.

Pre eclampsia is a multi system disorder, pathology behind is reduced perfusion to organs due to vasospasm. It is usually associated with proteinuria or oedema or both. Oedema in pregnancy is no longer used as diagnostic criteria, because it is common accompaniment of normal pregnant women and the presence of isolated oedema doesn't indicate the risk of developing hypertension .

Pre eclampsia is a progressive and multi organ disorder ,it can progress to eclampsia leading to seizures and HELLP syndrome if left untreated.

Various predictors for pre eclampsia have been proposed till date, but none of them proved ideal either because of high false positivity or complexity in study interpretation. Therefore many randomized control trails are to be conducted to prove the test which is both sensitive and specific to predict pre eclampsia.

A Calcium creatinine ratio in a spot sample of urine has been found that decreased excretion of calcium may be considered as an useful tool for early diagnosis of pre eclampsia. Therefore the study was done to determine the relationship between the hypocalciuria, calcium to creatinine ration and pre eclampsia for an early predictor of pre eclampsia in a random urine sample.

AIMS AND OBJECTIVES

AIM:

To study the calcium creatinine ratio in a spot sample of urine in a low risk women with less than 20 weeks gestation .

OBJECTIVES:

To evaluate the calcium creatinine ratio for the early diagnosis of pre eclampsia.

To identify the population at greater risk and to follow up and thereby helps in reduction of maternal mortality and morbidity association with the hypertension of pregnancy.

REVIEW OF LITERATURE

Hypertensive disorders in pregnancy, such as pregnancy induced hypertension and pre-eclampisa are most commonly encountered by obstetrician nowadays.

DIAGNOSIS OF HYPERTENSIVE ORDER:

Hypertension is usually diagnosed when the blood pressure exceeds 140 mm Hg systolic or 90 mm Hg diastolic. Previously incremental increase in blood pressure of 30 mmHg systolic or 15 mmHg diastolic from the baseline value taken at midpregnancy also had been used as diagnostic criteria, its no longer used to define Hypertension at present. Also sudden increase in mean arterial blood pressure but still in normal range called DELTA HYPERTENSION, some of these women will have obvious pre eclampsia, some other develop even eclamptic seizures or HELLP (Hemolysis,elevated liver enzymes and low platelets) syndrome while still <140/90 mm Hg, Normotensive.

GESTATIONAL HYPERTENSION:

This diagnosis is made when the blood pressure of more than or equal to 140/90 mm Hg for the first time after 20th week of gestation documented on two occasions 4-6 hours apart without proteinuria.

Its clinical outcome may be

- 15-25% develops pre eclampsia syndrome with proteinuria

- 5% develops eclampsia even before proteinuria

- While in others pre eclampsia doesn't develop, and the blood pressure resolves within 12 weeks post partum-reclassified as Transient hypertension.

- Sometimes it may persists 12 weeks after delivery -reclassified as chronic hypertension.

- When gestational hypertension develops late in third trimester, progression to pre eclampsia is less and its had good prognosis, while the women develops early progression to pre eclampsia is more likely leads to increased morbidity and mortality.

PRE ECLAMPSIA SYNDROME:

It's a pregnancy specific syndrome that can virtually affect every organ system.

New onset hypertension that develops after 20 weeks gestation with proteinuria.

Proteinuria is defined as excretion of 300mg or more of protein in 24 hours sample of urine or >1+ dipstick in random urine sample.

And with or without evidence of multi organ involvement.

In some women with pre eclampsia ,neither overt proteinuria nor fetal growth resistriction are features.

Multi organ involvement such as headache ,visual disturbances epigastric pain,elevated liver enzymes,thrombocytopenia along with Gestational hypertension is considered pre eclampsia.

CLASSIFICATION AND DIAGNOSIS OF PREGNANCY ASSOCIATED HYPERTENSION:

GESTATIONAL HYPERTESSION:

BP >140/90 mm Hg after 20 weeks of gestation in previously normotensive women.

PRE ECLAMPSIA:HYPERTENSION PLUS:

PROTEINURIA:

- ♣ More than or equal to 300mg/24 hour (or)
- ♣ Urine protein:creatinine ratio more than or equal to 0.3 (or)
- ♣ Dipstick 1+ persistent.

OR

THROMBOCYTOPENIA-platelet count <100,000/micro litre

RENAL INSUFFICIENCY -creatinine level of >1.1 mg/dl or doubling of baseline

LIVER INVOLVEMENT-serum transaminase level twice normal

CEREBRAL SYMPTOMS-headache,visual disturbance,convulsions

PULMONARY EDEMA

INDICATORS OF SEVERITY OF GESTATIONAL HYPERTENSIVE DISORDERS:(17)

Abnormality	Nonsevere[b]	Severe
Diastolic BP	< 110 mm Hg	≥ 110 mm Hg
Systolic BP	< 160 mm Hg	≥ 160 mm Hg
Proteinuria[c]	None to positive	None to positive
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia (< 100,000/μL)	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal-growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

BP-Blood Pressure

RISK FACTORS FOR PRE ECLAMPSIA:

Age < 18 years

Advanced maternal age>35 years

Low socio economic status

Environmental factors

Primiparity

High body mass index >35kg/m2 or BMI >30

Multiple pregnancy

Rh isoimmunisation

Hydatiform mole

Diabetes

Hypertesnsion

Renal disease-chronic kidney disease

Connective tissue disorder

Anti phospholipid antibody syndrome

Prior pre eclampsia/abruption/still birth

Assisted reproductive technology

ETIOPATHOGENESIS:

The currently accepted plausible mechanisms include-

ABNORMAL TROPHOBLAST INVASION:

The trophoblastic invasion in normal pregnancy takes place in the following two stages:

Stage 1-invasion of the decidual segment of spiral arterioles at 10-12 weeks of gestation.

Stage 2-invasion of the myometrial segment of spiral arterioles at 16-18 weeks of gestation.
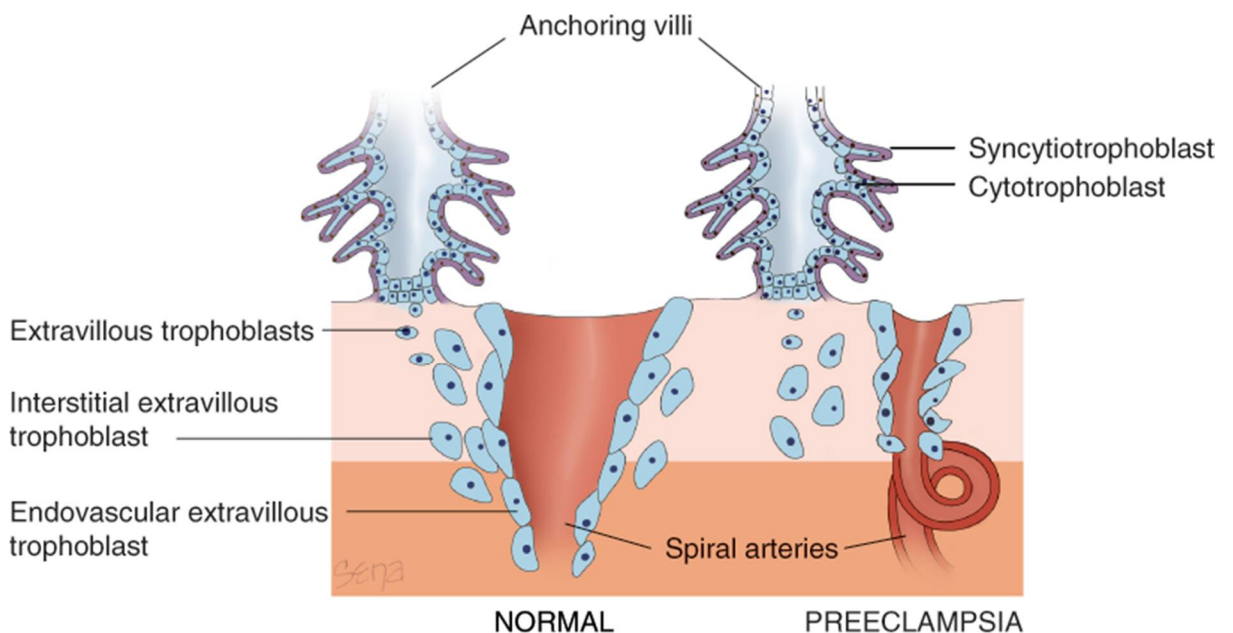
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Normally,The endovascular cytotrophoblast penetrate the walls of the spiral arteriole in the decidua and myometrium to create a dilated low resistance vessel.

Whereas in pre eclampsia defective implantation characterised by the absence of secondary wave of invasion of the wall of myometrial segment of the spiral arteriole.This results in small calibre vessels with high resistance flow.

PLACENTAL UNDERPERFUSION/HYPOXIA:

Failure of trophoblastic invasion and vasodilataion results in placental hypoperfusion, the resultant ischemia and hypoxia in the placenta leads to liberation of substances in to the maternal circulation leads to endothelial dysfunction.

MATERNAL VASCULAR ENDOTHELIAL DYSFUCTION AND INFLAMMATION:
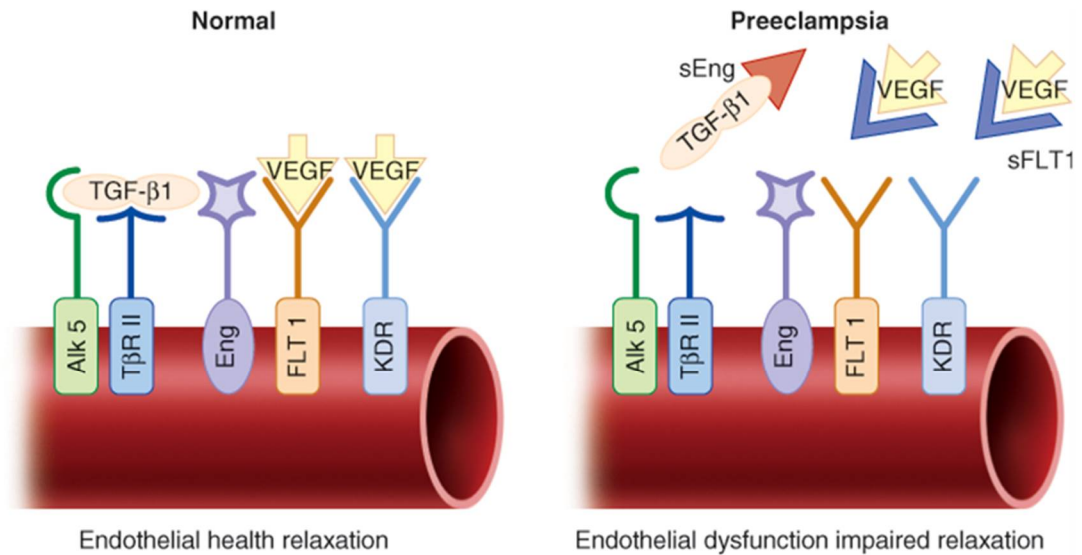
Normal — Endothelial health relaxation

Preeclampsia — Endothelial dysfunction impaired relaxation

Several pro-angiogenic and anti-angiogenic factors are released by the placenta and the balance between these two determines normal endothelial function.

- Pro-angiogenic factors-VEGF-vascular endothelial growth factor

   PIGF-placental growth factor

- Anti-angiogenic factor-soluble fms like tyrosine kinase-1(sFlt-1).

In pre eclampsia there is increased release of anti angiogenic factor due to placental hypoperfusion results in decreased production of vasodilator prostaglandin & NO(nitric oxide) by the endothelium,endothelial damage and dysfunction.

GLOMERULAR CAPILLARY ENDOTHELIOSIS:

During normal pregnancy renal blood flow and glomerular filtration rate rises .With pre eclampsia several anatomical and pathophysiological changes ensue.

NORMAL   PREECLAMPSIA
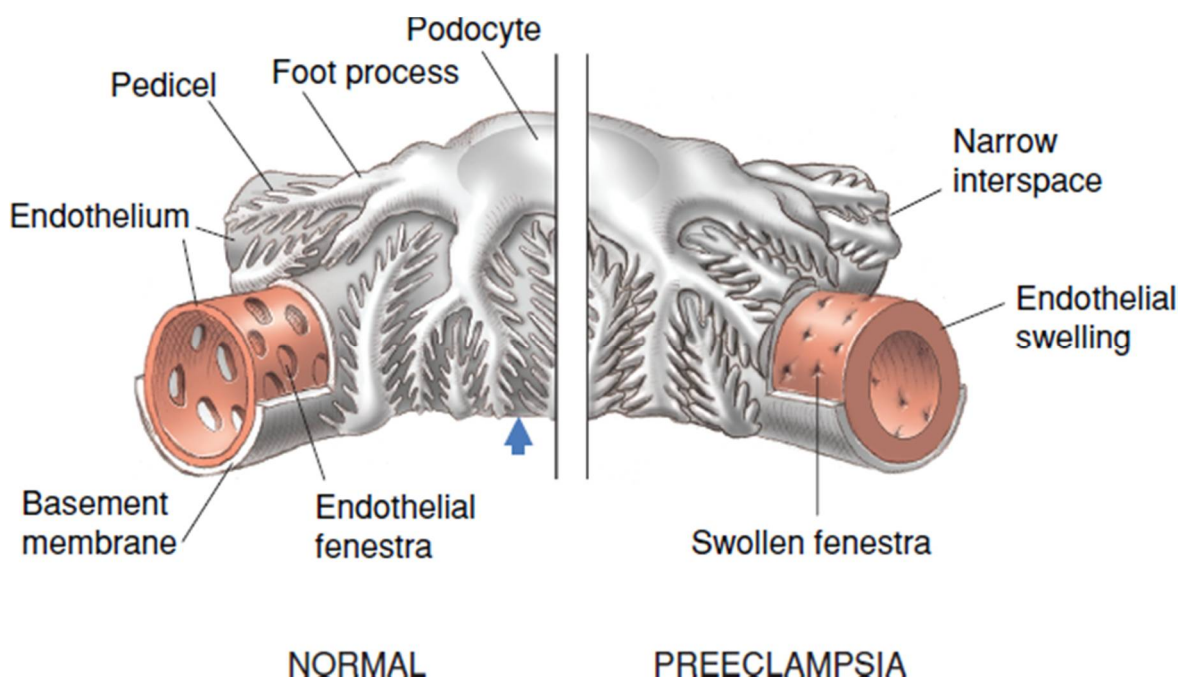
MORPHOLOGICAL CHANGES-The capillary of the normal glomerulus on left side has wide endothelial fenestration and the pedicles emanating from the podocytes are widely spaced.

Where as in right side the endothelial swelling leads to narrowed fenstra and the pedicles that now about each other there by the renal perfusion and glomerular filtration are reduced.

- Proteinuria occurs due to increased glomerular permeability to proteins.

- Serum creatinine level increases.

- Elevation in uric acid level due to decrease clearance of uric acid by kidneys.

- Activation of renin angiotension system leads to sodium retention.

- Acute tubular necrosis occur due to profuse haemorrhage,hypotension,and hypovolemia.

ETIOLOGY OF HYPOCALCIURIA IN PRE ECLAMPTIC PATIENTS:

Its has been speculated that hypocalciuria may be due to decreased dietary intake, decreased intestinal absorption, increased calcium uptake by fetus and placenta or intrinsic renal tubular dysfunction.

Taufieldet et al suggested increased distal tubular reabsorption of calcium as a possible mechanism for hypocalciuria in pre eclampsia.(18)

Pedersen et al did a longitudinal study report that urinary excretion of calcium is considerably lower in third trimester of pre eclamptic women than in both pregnant and non pregnant controls. They suggest that it could be partly be related to decrease glomerular filtration in pre eclampsia.(25)

Atallah et al suggested that low calcium intake leads to stimulation of PTH production ,which increases intracellular calcium level,this causes vascular smooth muscle cell contraction leads to hypertension.so the calcium supplementation inturn would reduces the development of pre eclampsia.(29)

OTHERS –

IMMUNOLOGICAL AND

GENETIC FACTORS ALSO PLAY A ROLE IN THE ETIOPATHOGENESIS OF PRE ECLAMPSIA.

COMPLICATIONS IN PRE ECLAMPSIA:

MATERNAL:

SHORT TERM COMPLICATIONS INCLUDE-

- Placental abruption

- Preterm labour-spontaneous/induced

- Pulmonary edema

- Rupture of liver due to hematoma

- HELLP syndrome

- DIC

- Eclampsia

- Acute renal failure

- Operative vaginal delivery

- Caesarean section.

LONG TERM COMPLICATIONS INCLUDE-

- Recurrent preeclampsia

- Chronic hypertension

- Cardiovascular disease

- Metabolic syndrome.

FETAL COMPLICATIONS:

SHORT TERM COMPLICATIONS INCLUDE-

- Fetal growth restriction

- Prematurity

- Intrauterine death

- Intrapartum asphyxia

- Hypoxic ischemic encephalopathy

- Perinatal mortality

LONG TERM COMPLICATIONS INCLUDE-

- Cerebral palsy

- And other neurological disorders.

MULTI SYSTEM INVOLVEMENT AND CHANGES IN

PRE ECLAMPSIA:

PATHOLOGY	CLINICAL MANIFESTATIONS
HEPATIC CHANGES- Periportal hemorrhages Vasospasm and infarction around sinusoids Hematomas Stretching of liver capsule	Elevated SGOT,SGPT Nausea, vomiting Spontaneous rupture Epigastric pain
CNS CHANGES- Cortical and subcortical haemorrhage Softening,infarction,necrosis Focal and generalized edema Posterior reversible encephalopathy	Convulsion ,confusion,coma, Visual disturbances and headache.
RETINAL CHANGES- Vasospasm Hemorrhages and exudates Papilledema Retinal detachment	Visual disturbances Blindness.

PLACENTAL CHANGES IN PRE ECLMAPSIA:

SPIRAL ARTERIES IN MYOMETRIUM:

Lack of trophoblastic invasion

Narrowing of the arteries   Fetal growth restriction

Obstruction of the lumen   Preterm labour

Placental infarction   Placental abruption

Necrosis of vessel wall

TROPHOBLAST CHANGES :

Apoptosis   Release of

synctiotrophoblast

Necrosis   Release of microparticles

Degeneration   Endothelial inflammation
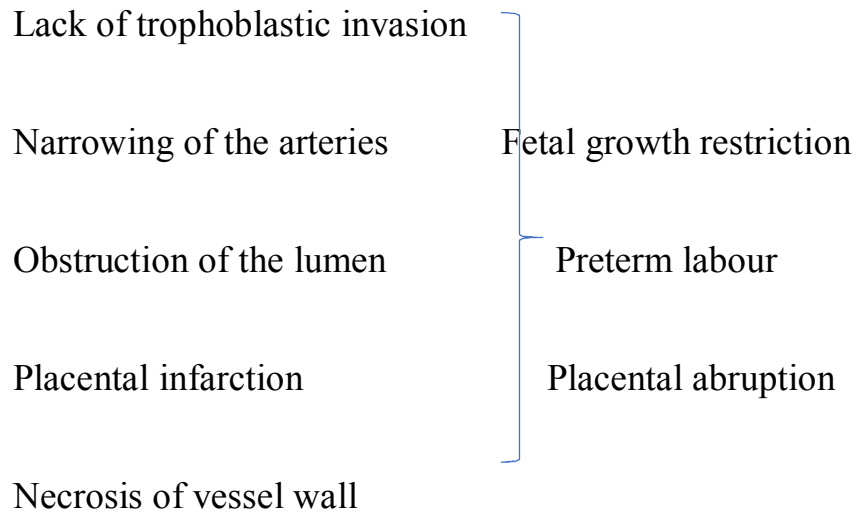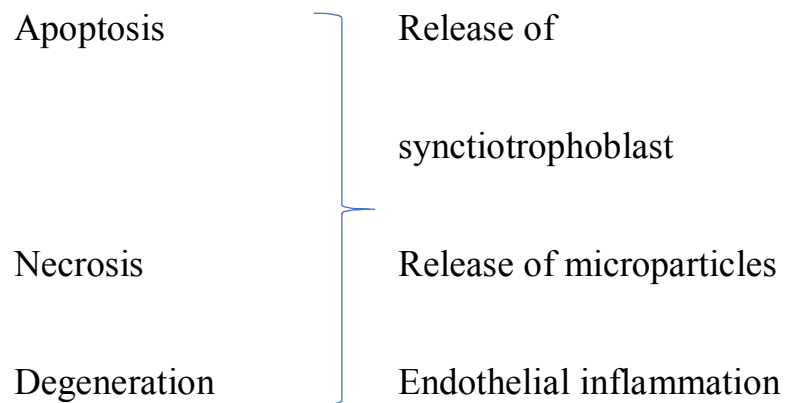
PREDICTIVE TESTS FOR PRE ECLAMPSIA SYNDROME:

TESTING RELATED TO:

PLACENTAL PERFUSION /VASCULAR RESISTANCE-

- Roll over test

- Isometric handgrip or cold pressor test

- Pressor response to aerobic exercise

- Angiotensin -II infusion

- Mid trimester mean arterial pressure

- Placental angiotensin -II binding

- Renin

- 24 hour ambulatory blood pressure monitoring

- Uterine artery or fetal transcranial doppler velocimetry.

FETAL-PLACENTAL UNIT ENDOCRINE DYSFUNCTION:

- Human chorionic gonadotropin

- Alpha-fetoprotein

- Estriol

- Pregnancy associated protein (PAPP A)

- Inhibin A,Activin A

- Placental protein 13

- Corticotropin releasing hormone

- A disintegrin

- ADAM-12

- Kisspeptin

RENAL DYSFUNCTION:

- Serum uric acid

- Microalbuminuria

- Urinary calcium or kallikrein

- Microtransferrinuria

- N acetyl beta-glucosaminidase

- Cystatin C

- Podocyturia

ENDOTHELIAL DYSFUNCTION /OXIDANT STRESS:

- Platelet count and activation

- Fibronectin

- Endothelial adhesion molecules

- Prostaglandins

- Prostocyclin

- Matrix metallopeptidase domain -9

- Thromboxane

- C- Reactive protein

- Cytokines

- Endothelin

- Neurokinin B

- Homocysteine

- Lipids

- Insulin resistance

- Antiphospholipid antibodies

- Plasminogen activator inhibitor

- Leptin

- P-selectin

- Placental growth factor

- Vascular endothelial growth factor

- Fms-like tyrosine kinase receptor-1(sFlt-1)

- Endoglin

OTHERS-

- Anti thrombin -III(AT-3)

- Atrial natriuretic peptide(ANP)

- Beta 2 -microglobulin

- Haptoglobin

- ♣ Transferrin

- ♣ Ferritin

- ♣ 25-hydroxyvitamin D

- ♣ Genetic markers

- ♣ Cell -free fetal DNA

- ♣ Serum and urinary proteomics

- ♣ Metabolomic markers

- ♣ Hepatic aminotransferases

MONITORING OF PATIENTS WITH NON SEVERE PRE-ECLAMPSIA:

MATERNAL	FETAL
1.H/o imminent symptoms	1.Daily fetal kick count
2.Look for imminent signs	2.NST-Biweekly
3.BD BP Monitoring	3.Biophysical profile-
4.Daily weight	Weekly and as backup test if NST is non reassuring
5.Daily urine albumin	
6.Urine output	4.Amniotic fluid index-Atleast weekly once
7.Lab investigations-	5.Fetal growth-every 3 weeks
Biweekly complete blood count with platelets	
Renal function test	
Liver function test	
8.Fundus opinion-	
At admission and review if necessary	

MONITORING OF PATIENTS WITH SEVERE PRE ECLAMPSIA:

MATERNAL	FETAL
1.H/o imminent symptoms	1.Daily fetal kick count
2.look for imminent signs	2.Non stress test-daily
3.Blood pressure -4th hourly	3.Biophysical profile-
4.Daily weight	Twice weekly and as backup test if non stress test is non reassuring.
5.Daily urine albumin	
6.Urine output	4.Amniotic fluid index-daily
7.Lab Investigations-	5.Fetal growth-every 2 weeks.
Daily complete blood count,	
Renal function test	
Liver function test	
8.Fundus examination - At admission and review if necessary	

MANAGEMENT OF GESTATIONAL HYPERTENSION:

```
                    ┌─────────────────┐
                    │   Gestational   │
                    │  Hypertension   │
                    └────────┬────────┘
              ┌──────────────┴──────────────┐
        ┌──────────┐                   ┌──────────┐
        │  Severe  │                   │   Non    │
        │          │                   │  Severe  │
        └────┬─────┘                   └────┬─────┘
   ┌──────────────┐                 ┌──────────────┐
   │  Manage as in│                 │ Weekly twice │
   │  severe pre  │                 │antenatal visits│
   │  eclampsia   │                 └──────┬───────┘
   └──────────────┘
```

Maternal monitoring

blood pressure

Signs and symptoms of severe pre eclampsia

Platelet count and liver enzymes

Fetal monitoring

Daily fetal movement count

Biweekly NST,BPP

Fetal growth once in 3 weeks

No bed rest

No corticosteroids

Antihypertensives if BP > 150/100mmhg

if BP < 150/100, deliver at 39-40 weeks

if BP is between 150/100 and 160/109,

deliver at 37-38 weeks

MANAGEMENT OF NON SEVERE PRE ECLAMPSIA :

Non severe preeclampsia

Hospitalise

Maternal monitoring

Daily BP

Proteinuria

Signs and symptoms of severe pre eclampsia

Weekly platelet count and liver enzymes

Fetal monitoring

Daily fetal movement count

NST, BPP weekly

fetal growth monitoring once in 3 weeks

Restricted activity

Antihypertensive if BP > 150/90

No Corticosteroids

No maternal /fetal compromise

Deliver at 37 weeks

Maternal/fetal compromise

Deliver <37 weeks

MANAGEMENT OF SEVERE PRE ECLAMPSIA:
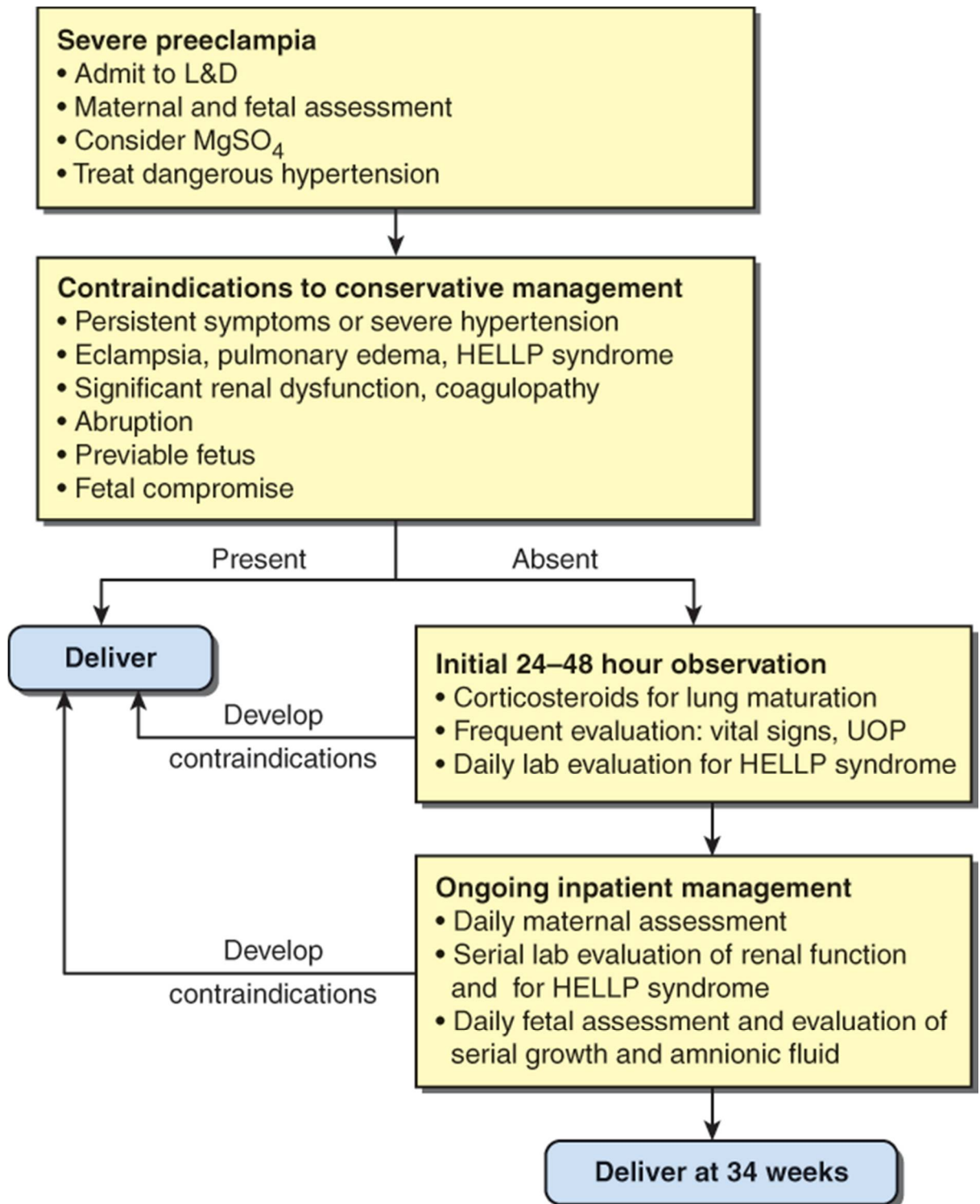
Severe preeclampia
- Admit to L&D
- Maternal and fetal assessment
- Consider $MgSO_4$
- Treat dangerous hypertension

Contraindications to conservative management
- Persistent symptoms or severe hypertension
- Eclampsia, pulmonary edema, HELLP syndrome
- Significant renal dysfunction, coagulopathy
- Abruption
- Previable fetus
- Fetal compromise

Present   Absent

Deliver

Develop contraindications

Initial 24–48 hour observation
- Corticosteroids for lung maturation
- Frequent evaluation: vital signs, UOP
- Daily lab evaluation for HELLP syndrome

Develop contraindications

Ongoing inpatient management
- Daily maternal assessment
- Serial lab evaluation of renal function and for HELLP syndrome
- Daily fetal assessment and evaluation of serial growth and amnionic fluid

Deliver at 34 weeks

LONG TERM MORBIDITY AND MORTALITY ASSOCIATED WITH PRE ECLAMPSIA SYNDROME:
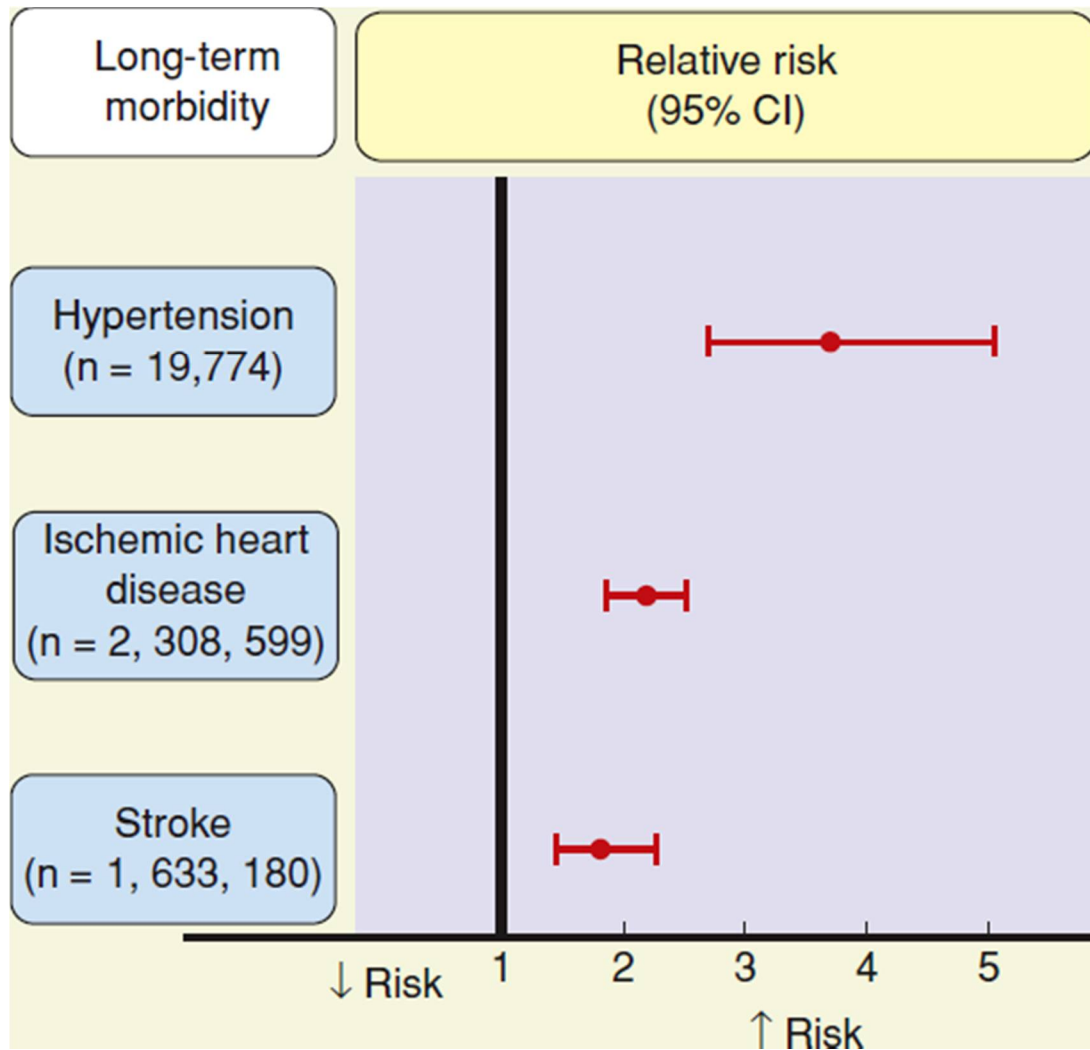
SOME LONG TERM CONSEQUENCES IN WOMEN WITH PRE ECLAMPSIA SYNDROME:

Cardiovascular:

Chronic hypertension

Ischemic heart disease

Artherosclerosis

Coronary artery calcification

Cardiomyopathy

Thromboembolism

Neurovascular:

Stroke

Retinal detachment

Diabetic retinopathy

Metabolic:

Type 2 diabetes

Metabolic syndrome

Dyslipidemia

Obesity

Renal:

Glomerular dysfunction

Proteinuria

Central nervous system:

White matter lesions

Cognitive dysfunction

Retinopathy

PREVENTION OF PRE ECLAMPSIA:

Some methods to prevent the development of pre eclampsia that have been evaluated in many randomized trials,

Dietary manipulation-

Low salt diet,

calcium or fish oil supplementation.

Exercise-

Physical activity and stretching.

Antioxidants-

Ascorbic acid(vitamin c),

alpha tocopherol(vitamin E),

vitamin D.

Antithrombotic agents-

Low dose aspirin,aspirin/dipyridamole,

Aspirin+heparin,

Aspirin +ketanserin

Cardiovascular drugs-

Diuretics,Antihypertensive drugs.

CALCIUM SUPPLEMENTATION:

Calcium supplementation in high doses (2gram /day) found useful in calcium deficient and high risk women.

Calcium supplementation has been studied in many trials,National Institute of child health and human development ,Levine 1997.

They included 4500 low risk nulliparous women ,conclude that calcium supplementation did not prevent pre eclampsia or pregnancy associated hypertension.

In one meta analysis by Patrelli,2012 concludes that increased calcium intake in high risk women ,lowered the risk of pre eclampsia.

However, in aggregate many trials shows calcium supplementation has no salutary effects ,unless women are calcium deficient.

LOW DOSE ASPIRIN:

Platelet aggregation and increase in platelet derived thromboxane implicated in the pathogenesis of pre eclampsia.

Aspirin at low doses 60-80 mg/day reduces thromboxane synthesis by platelets without affecting the prostacyclin production.

ACOG and NICE (National Institute for Health and Care Excellence):

Recommened the use of aspirin in doses of 75 mg/day started at 12 weeks and continued till delivery.

The indication are as follows-

- Women at high risk for pre eclampsia:

  - hypertensive disease during a previous pregnancy

  - chronic kidney disease

  - Autoimmune disease such as systemic lupus erythematosus

  - Antiphospholipid antibody syndrome

  - chronic hypertension

  - Type 1 or 2 diabetes mellitus

- Women with two or more of the following moderate risk factor for pre eclampsia:

  - first pregnancy

  - age more than 40 years

  - Pregnancy interval of more than 10 years

  - BMI of 35kg/m3 or more at first visit

  - Multiple pregnancy

ASPRE TRIAL:

Its a combined multimarker screening and randomized patient treatment with Aspirin for evidence based pre eclampsia prevention trial.

Rolnik DL, et al did a prospective first trimester randomized controlled study on screening for preterm pre eclampsia in 26941 singleton pregnancies ,by means of an algorithm that combines maternal factors,mean arterial pressure,uterine artery pulsatility index and maternal serum pregnancy associated plasma protein A and placental growth factor at 11-13 weeks Gestation.

Eligible women with an estimated risk for preterm pre eclampsia of more than 1 in 100 were invited to participate in a double -blind trial of aspirin (**150mg per day**) vs placebo from 11-14 until 36 weeks gestation ,which showed that ,in the aspirin group ,the incidence of preterm pre eclampsia was reduced by 62 percent..

In this ASPRE study ,combined screening detected 76.6% of cases of preterm pre-eclampsia and 38.3% of term pre-eclampsia at a false positive rate of 10%.(30)

Various predictors for pre-eclampsia have been proposed till date.

Examples:

GANT`S ROLL OVER TEST:

An elevation of 20mmhg or more in diastolic blood pressure when the women assumes supine postion from lateral decubitus position between 28-32 weeks of gestation predicts gestational hypertension.Positive predictive value -33%.

Positive roll over test indicates abnormal angiotensin II sensitivity.

SECOND TRIMESTER MEAN ARTERIAL PRESSURE TEST:

Average mean arterial pressure in second trimester of more than 90 mmhg predicts pre eclampsia.

MAP-DIASTOLIC BP+1/3 PULSE PRESSURE(systolic-diastolic)

(or)

MAP-SYSTOLIC BP+(2×DIASTOLIC BP)/3

MAP-Mean Arterial Pressure

BP-Blood Pressure

SERUM URIC ACID:

Elevated serum uric acid in pregnancy reflects the degree of placental cell destruction and with severity of pre eclampsia and perinatal outcome.Hyperuricemia in preeclampsia occurs due to decreased renal clearance and increased tubular reabsorption because of reduction in glomerular filtration rate.

ANGIOTENSIN SENSITIVITY TEST:

If pressor response with less than 8ng/kg/min of infused angiotensin between 26-30 weeks due to an alterations in vascular smooth muscle A II receptors are destined to develop pregnancy induced hypertension.

ISOMETRIC HAND GRIP TEST:

The patient compresses an inflated sphygmomanometer cuff for 3 minutes at maximal and then at 50% of maximal voluntary contraction.An increase in diastolic blood pressure of >20mmhg at 28-32 weeks of gestation associated with increased risk of GHT and pre eclampsia.

UTERINE ARETRY DOPPLER:

Presence of a diastolic notch in uterine artery waveform after 24 weeks is an prediction of pre eclampsia.

DOPPLER IMAGE OF UTERINE ARTERY
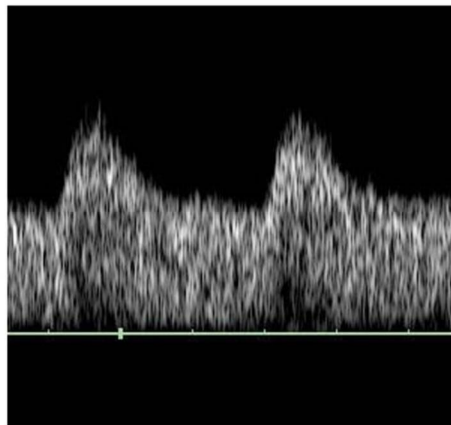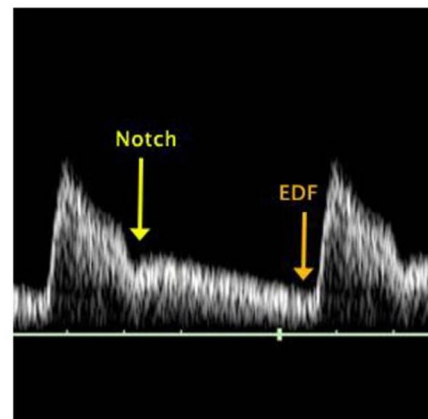
IN NORMAL WOMEN   IN PREECLAMPSIA WOMEN,

- Showing early diastolic NOTCH
- Decreased EDF(due to high resistance)

URINARY KALLIKREIN EXCRETION:

Ratio of less than 170 between 16 to 20 weeks of gestation predicts pre eclampsia.

PLATELET VOLUME:

Thrombocytopenia and platelet dysfunction are the integral features of pre eclampsia. Increased destruction causes the platelet volume to increase because of relatively younger and therefore larger platelets entering the circulation.Ahmed et al found high platelets volumes to be a marker of impending pre eclampsia but with a substantive overlap with normotensive women.

SERUM FIBRONECTIN:

It is released by placenta and is associated with endothelial damage and inflammation in pre eclampsia.Higher plasma level of fibronectin has been reported in pre eclampsia compared to uncomplicated pregnancies.

Though many other test predictors for pre eclampsia are available, but none of them proved ideal either because of high false positivity or complexity in study interpretation.

A Calcium creatinine ratio in a spot sample of urine may be considered as an useful tool for early diagnosis of pre eclampsia before 20 weeks of gestation.Therefore the study was done to determine the relationship between the hypocalciuria, calcium to creatinine ratio and pre eclampsia for an early predictor of pre eclampsia in a random urine sample.

1. Prediction of pre-eclampsia by calcium creatinine ratio in a spot urinary sample , a study conducted in Basaveshwara medical college hospital and research center,chitradurga,Karnataka by Gaurang et al.This study includes of 100 subjects consists of 50 pre eclamptic and 50 normal pregnant women.They concluded that urinary calcium in pre eclampsia is significantly reduced with p value of <0.01 as compared to normal pregnant women.(3).

2. David A et al conducted a study in OBG department ,Bangalore Baptist Hospital .116 patients were recruited in the study of which CCR <0.04 ,7 developed GHT,3 developed pre eclampsia and one remain Normotensive. With sensitivity of 80%,specificity of 98.04%,PPV 80%,NPV 98.04% with diagnostic ratio alone is taken as high risk factor for prediction of pre eclampsia.(11).

3.Rashmi Sinha,Indu Bhushan et al conducted a prospective study in Rama medical hospital and research center,Ghaziabad.A total 145 asymptomatic pregnant women between 20 to 28 weeks of gestation participated, Of which 32 developed pre eclampsia .It was found that CCR has a sensitivity of 81.2%,specificity 96.4%,positive predictive value 86.6%,negative predictive value 94.7% with statistical accuracy of 93.1% and a p value of <0.001(strongly significant).And found to be that CCR ratio in a spot sample of urine being a good test for prediction of pre eclampsia and can be recommended as a screening test.(12).

4. Patil et al conducted a clinical study of calcium creatinine ratio and Microalbuminuria in prediction of pre eclampsia in Indira Gandhi government medical college ,Maharashtra.In this prospective study comprising of 150 women between 20 and 34 weeks of gestation.

Among 150 women ,25 were test positive for CCR and 125 were test negative.on the other hand 20 were positive for test positive for microalbuminuria and 130 were negative for microalbuminuria.

CCR < 0.04 has a sensitivity of 64%,specificity 96.9%,PPV 80%,NPV 93.2% with p value of <0.001 which is strongly significant,where as microalbuminuria has less accurate with sensitivity of 26.31%,specificity of 92.2%,PPV of 33%,NPV of 87% with p value of <0.001.Ans it was found that CCR at <0.04 was a good test while

micro albuminuria was only a fair test for prediction of pre eclampsia.combined CCR and microalbuminuria seem to be effective as a screening test for pre eclampsia at present.(13)

5.Indu prasad et al did a case control study in patna medical college ,Bihar.Total number of 200 women of gestational age of 20-36 weeks was carried out for this study .They divided the sample into two groups ,study group consists of 100 patients of pre eclampsia and control group consists of normotensive pregnant patients for statistical significance and comparison.This study showed 89% of pre eclamptic women had CCR <0.004 with p value 0f <0.001.Therefore CCR in a spot sample of urine identifies the population at risk and may be an effective tool for the early diagnosis of pre eclampsia.So early therapeutic use of calcium significantly reduces morbidity and mortality of pre eclampsia.(14).

6. Study conducted by Kazerooni T et al in shiraz university ,Iran. CCR ratio was measured in spot urine sample of 102 normotensive pregnant women of 20-24 weeks gestation.Of about accuracy of 96.43%.with significant p value of <0.001.They concluded that CCR 94 women remain normotensive while 8 women developed pre eclampsia.mean CCR ratio also significantly lower in pre eclampsia womens.They concluded that CCR in a spot urine sample can be used as routine screening test for prediction of pre eclampsia.(8).

7. Ozcan T et al conducted a study in the maternity hospital,Turkey. 56 Antenatal women were tested for the CCR and calcium level,among 44 had normal CCR, while 8 developed hypertension.The mean CCR was estimated,which was significantly lower in pre eclamptic group than the normal asymptomatic pregnant women with significant p value.CCR was statistically analysed and had sensitivity of 75%,specificity of 86%,PPV of 55% and NPV of 95% and the results conclude that CCR can be used as screening test for prediction of pre eclampsia.(5).

8. Saudan PJ et al did a study in university of New south wales ,Australia.

81 Antenatal women with de novo hypertension in second half of pregnancy were included in the study.CCR ratio was determined during first visit in a random urine sample.

Patient was followed up until delivery and subsequently classified according to pre eclampsia.on follow up patient who had pre eclampsia had low calcium excretion antenatally than normotensives.on statistical analysis it showed sensitivity of 68% and specificity of 70%.

The renal involvement in pre eclampsia has been proved to occur before the establishment of symptoms.but this test doesn't have sufficient sensitivity to use as screening test for prediction of pre eclampsia.(6).

9. Calcium excretion in pre eclampsia was assessed by Sanchez Ramos L et al in ,Florida health science center,Florida.

They compared 24 hours urinary calcium data from 143 obstetrics patients,58 normotensive patients,52 patients with gestational hypertension, and 33 with pre eclampsia. The mean maternal age ,parity, and race didn't differ that much significantly.

When compared to patients with normal blood pressure ,pre eclampsia patients had significant hypocalciuria. The proteinuria and the blood pressure were significantly increased in pre eclampsia group on statistical analysis urinary calcium threshold 0f 12mg/dl was choosen as cuoff , with sensitivity and specificity of 85 % and 91% respectively for the prediction for pre eclampsia.(4).

10. A study by Rodriguez MH et al in Dept of OBG in southern California school of medicine ,Los Angels.

Around 88 normotensive pregnant women from 24 to 34 weeks of gestation were evaluvated for urinary calcium excretion and presence of microalbuminuria.

Pre eclampsia was developed in 83% of patients with low calcium creatinine ratio and high level of microalbuminuria (greater than or equal to 11 micrograms/ml).conversely 94% of women remains normotensive with low CCR and didn't have high microalbuminuria.

They concluded that microalbuminuria and spot CCR ratio can be used as assessment tool for early predictor of pre eclampsia.(9).

11. Izumi et al investigated around 1147 pregnant women in jichi medical college,tochigi,japan.They measured spot CCR ratio obtained at 12 weeks or less of gestation.71 had hypertension alone,39 developed proteinuria,9 developed super imposed pre eclampsia,13 developed pre eclampsia while 1015 remains normotensive.They conclude that spot CCR ratio in the first trimesteris is of only limited value for identifying women at risk for pre eclampsia.(7).

12. Nikita et al ,A Prospective study done in dept of OBG,SMS medical college,Jaipur. To evaluate the role of urinary calcium creatinine ratio in early prediction of pre eclampsia.Around 80 women over the period of one year between 16-20 weeks of gestation was included in this study.

On statistical analysis,sensitivity and specificity of this test was 92.8% and 95.45% respectively.The Positive predictive value was 81.25%, while the negative predictive value was 98.43%.

Therefore the above study has significant role as a screening test in the early prediction of pre eclampsia.(16).

13.Rodriquez et al evaluated the role of decreasing calcium to creatinine ratio and micro albuminuria in the prediction of pre eclampsia as early as in 1988 and have concluded that these tests may be useful screening tools in prediction of pre eclampsia.(9).

14.Karetal et al evaluating the predictive value of CCR at less than or equal to 0.04 between 20-34 weeks of gestation and had reported that as a satisfactory test for prediction of pre eclampsia and could be a effective screening test to predict pre eclampsia in a asymptomatic women.(10)

15.Patrick J saudan et al ,suggested primary or secondary disturbance in urinary calcium handling in pre eclampsia leads to hypocalciuria in urine.He found that decreased excretion of urinary calcium in pre eclampsia but lacked the sufficient sensitivity to use as tool for early diagnosis.(15).

16.Phuapradit W et al ,conducted a study in the obstetrics and gynaecology department,Mahidol University,Thailand.They assessed 190 primigravida at 28 to 32 weeks of gestation without any risk factors ,were involved in the study.

Pre eclampsia was noted in 6.8% of samples,patients with pre eclampsia did not demonstrate reduced excretion of calcium than normal population.(1)

17.Anai T et al ,conducted study in the department of obstetrics and gynaecology,Medical college of iota.Hypocalciuria im women with pre eclampsia.

To assess the significance of hypocalciuria in pregnant women,24-hours urinary calcium excretion and the CCR(mg/g) in random urine samples were measured in the following 4 groups :

3 mild pre eclamptic patients,

5 severe pre eclamptic patients,

4 patients with intrauterine growth retardation,

And 10 healthy pregnant women.

The mean 24-hour urinary calcium excretion in the 4 group was 44.3+/-21.3 mg/day,11.6+/-2.7 mg/day,161.4+/-80.4mg/day and 145.0+/-45.0 mg/day,respectively.calcium excretion was significantly lower in the mild and severe pre eclamptic patients than in the women with IUGR and the normal pregnant women.

There was also a sigmificant difference between the value in the mild and severe pre eclamptic patients.The mean calcium/creatinine ratioin random urine sample was 53+/-30 mg/g,18+/-5.6 mg/g,192+/-85mg/g and 169+/-70 mg/g,respectively.Also such significant as 24 hour urinary calcium excretion were found in the mean calcium/creatinine ratio.

They concluded saying that determination the CCR in random urine samples is a reliable index of pre eclampsia.(31).

MATERIALS AND METHODS

This study was conducted in the Department of obstetrics and gynaecology ,Coimbatore medical college hospital,Coimbatore.

STUDY DESIGN:

Prospective study

STUDY POPULATION:

Women of gestational age <20 weeks attending Antenatal clinic in the obstetrics and gynaecology in Coimbatore medical college hospital.

STUDY PERIOD:

January 2018 to January 2019.

SAMPLE SIZE:

200

SELECTION CRITERIA:

INCLUSION CRITERIA:

- Antenatal women of any age

- Singleton pregnancy

- Gestational age less than 20 weeks

- Any parity

- Normotensive patients

- Without proteinuria

EXCLUSION CRITERIA:

♣ Blood pressure of 140/90 mmhg or more

♣ Proteinuria -tested with dipstick >1+ in random urine sample

♣ History of PIH in past pregnancy

♣ History of chronic hypertension

♣ Multiple pregnancy

♣ Diabetes mellitus complicating pregnancy

♣ Renal disease

♣ Vascular disease

♣ Immunological disease .

METHODOLOGY

All antenatal women who attended the out patient department at the Department of Obstetrics and Gynaecology ,Coimbatore medical college hospital, Coimbatore based on selection criteria was enrolled in this study.

Women with history of chronic hypertension, diabetes mellitus ,renal disease were excluded from this study based on exclusion criteria.

Women who had baseline blood pressure of more than or equal to 140/90 mmhg and who had proteinuria by dipstick method at first visit were excluded from the study.

Blood pressure was measured in semi recumbent posture with lateral tilt in right arm at the level of heart and proteinuria was measured by dipstick method in a spot sample of urine for albumin.

MATERIALS

1. Informed written consent was obtained from all patients for spot urinary calcium creatinine ratio estimation.

2. Participation in the study was voluntary.

3. All subjects were informed about the aims and objectives of the study, the test to be done and the nature of their population.

4. A detailed history ,a complete physical general examination and obstetric examination was performed.

All women were examined in detail and history obtained in detail about the present and past medical and surgical illness.Anyone antenatal women with the history suggestive of illness ,mentioned in the exclusion criteria was not involved in the trail.And detailed obstetric examination was also done.

Blood pressure was measured, those women with higher blood pressure of more than 140/90 mmhg on two successive measurements of 4-6 hours apart.And preoteinuria of >1+ dipstick were excluded in this study.

5.A spot urine sample was collected for estimation for calcium and creatinine in the laboratory.

Calcium was determined by orthocresolphthalein complex method and urinary creatinine by Jafees method.

6.Calcium creatinine ratio was calculated those with ration of <0.04 were considered Positive, those with ratio of >0.04 were considered as test Negative.

7.Cutoff for CCR is taken as less than or equal to 0.04.

8.Patient are then followed every 4 weeks to predict how many of them developed pre eclampsia.

The doctors and patients were blinded from the CCR values,and they were observed and followed up regularly once in 4 weeks up to delivery.

Each and every patients involved in the study was closely observed for symptoms and signs of pre eclampsia,like headache, vomiting, epigastric pain, reduced urine output, pedal edema, increased weight pain, raised blood pressure and proteinuria.

The data was collected at the end of the study and entered in the excel spread sheet and statistical analysis was done.

STATISTICAL ANALYSIS:

The results obtained were further analysed for STANDARD DEVIATION ,t test, SEM and p value. The p value of <0.001 was considered significant comparative study was done using chi square test.

GESTATIONAL HYPERTENSION:

Defined as blood pressure of more than or equal to 140/90mmhg without proteinuria after 20 weeks of gestation.

PREECLAMPSIA:

Defined as blood pressure of more than or equal to 140/90 mmHg with associated proteinuria.

The women in the above definition were categorized as either normotensive or Hypertensive.

Calcium Creatinine Ratio were estimated and the value less than or equal to 0.04 were positive .(i.e low calcium excretion).

Those with calcium creatinine ratio more than 0.04 were considered Negative.(i.e normal calcium excretion).

The SD,t test,SEM and p value is determined by statistical analysis, chi square test is done for comparative study between the normal group and the group who developed pre eclampsia .

OUTCOME MEASURES:

The outcome of this study is measured based on

- Gestational age of collection of spot urine sample for CCR.

- Number of CCR positive women.

- Number of antenatal women with CCR positive developed Pre eclampsia.

- Gestational age of development of Pre eclampsia.

- Gestational age at delivery.

- Mode of delivery.

RESULTS

During the study period , a total of 200 antenatal asymptomatic low risk women were included in the study.

Spot urine samples were obtained for estimation of calcium creatinine ratio.

The result obtained are further analysed as follows,

Table 1: Number of positives and negatives

Test parameter	Test positive(n%)	Test negative (n%)	Total(n%)
CCR	19(9.5%)	181(90.5%)	200(100%)

CCR-Calcium Creatinine Ratio

Among 200 samples,

19 patient had abnormal CCR i.e CCR ratio less than or equal to 0.04 while 181 patients had normal CCR values i.e CCR ratio more than 0.05. i.e 19 were positives and 181 were negatives in this study.

Table 2: Age Distribution among study participants

Age Distribution	Frequency	Percentage (%)
17-20 YEARS	80	40.0
21-25 YEARS	81	40.5
26-30 YEARS	35	17.5
>31 YEARS	4	2.0
Total	200	100.0
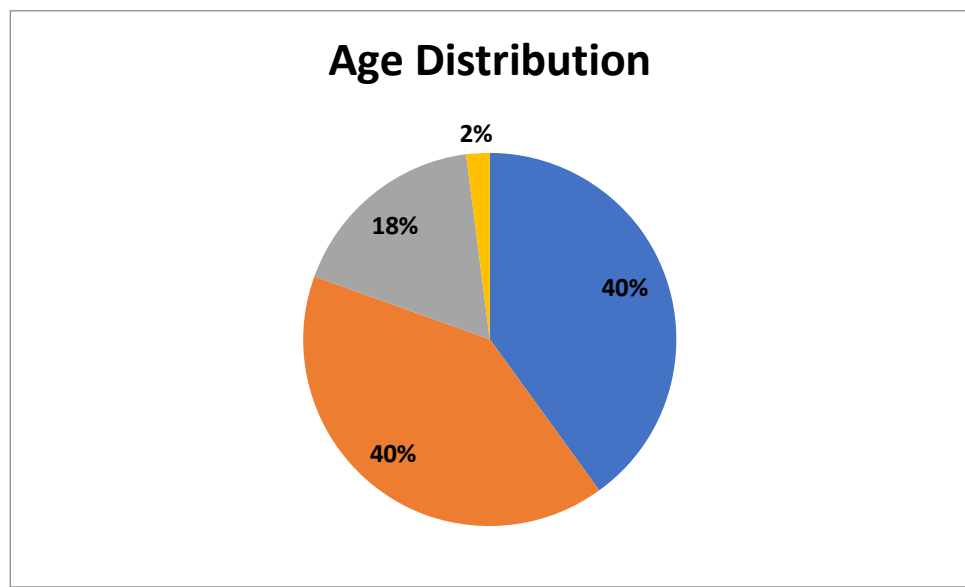
Among the age distribution in this study , 40% of women belongs to the age group between 17-20 years ,40.5% between 21-25 years ,17.5% between 26-30 years while remaining 2% of patients aged above 31 years.

Table 3: Mean age in association with CCR

	CCR	N	Mean	SD	P value
AGE	**POSITIVE<0.04**	19	23.16	5.480	**.416**
	NEGATIVE>0.05	181	22.46	3.304	

P value -0.416 and it is not statistically significant

CCR-Calcium Creatinine Ratio

N- Total number of patients

SD-Standard Deviation

Mean age in association with CCR
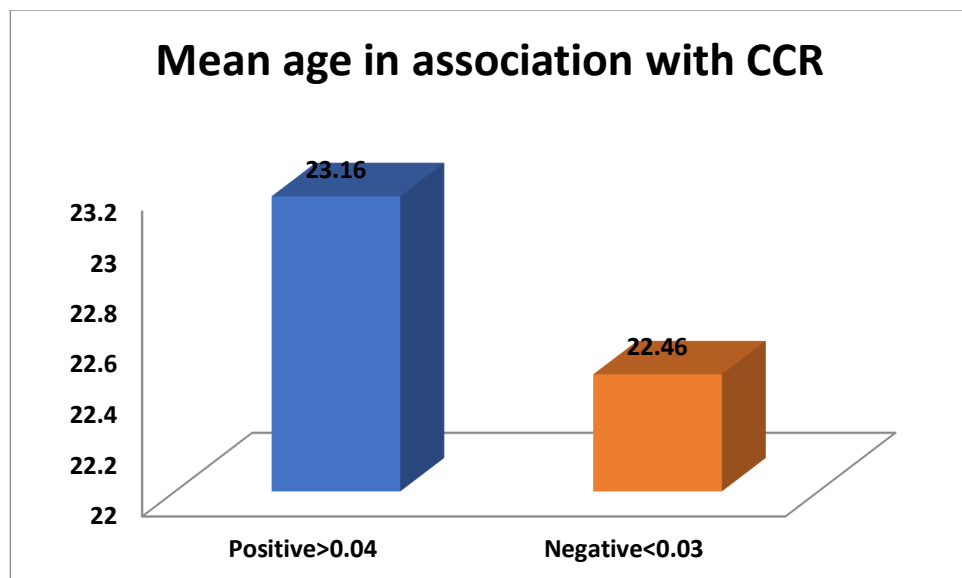
Table 4: Parity Distribution among study participants

Parity Distribution	Frequency	Percentage (%)
Primi gravida	127	63.5
Gravida 2	52	26.0
Gravida 3	21	10.5
Total	200	100.0

The total number of primi gravida involved in my study is 127,while multigravida is around 73. 63.5% patients of primi and 26.5% of multi gravida.
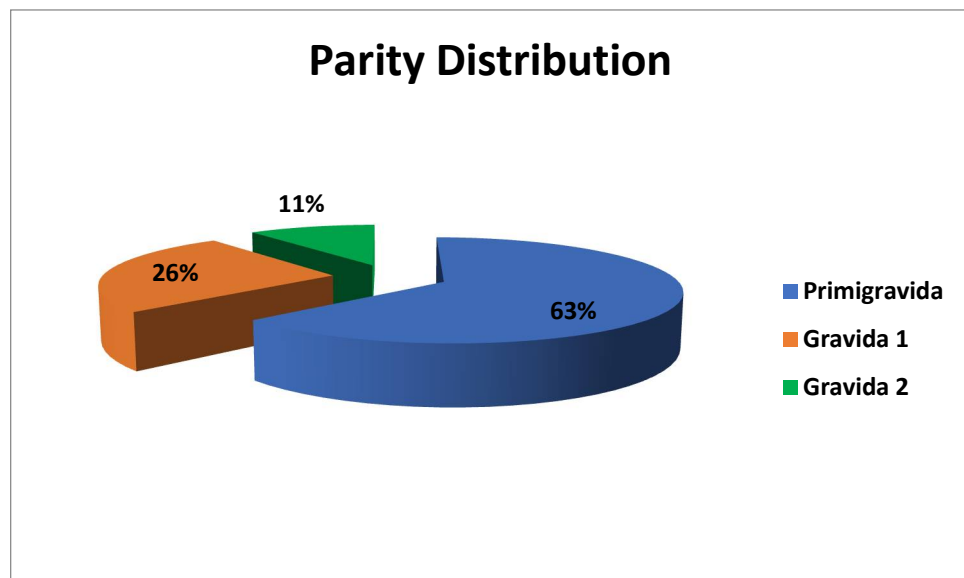
Table 5: Association of Parity with CCR

CCR	Parity		P Value
	PRIMI	**MULTIGRAVIDA**	
POSITIVE<0.04	15(78.9%)	4(21.1%)	.142
NEGATIVE>0.05	112(61.9%)	69(38.1%)	

P value-0.142 and it is not statistically significant

Among positive CCR, 15 belongs to primi and 4 women belongs to multigravida. While in Negative CCR,112 belongs to primi and 69 belongs to multigravida.
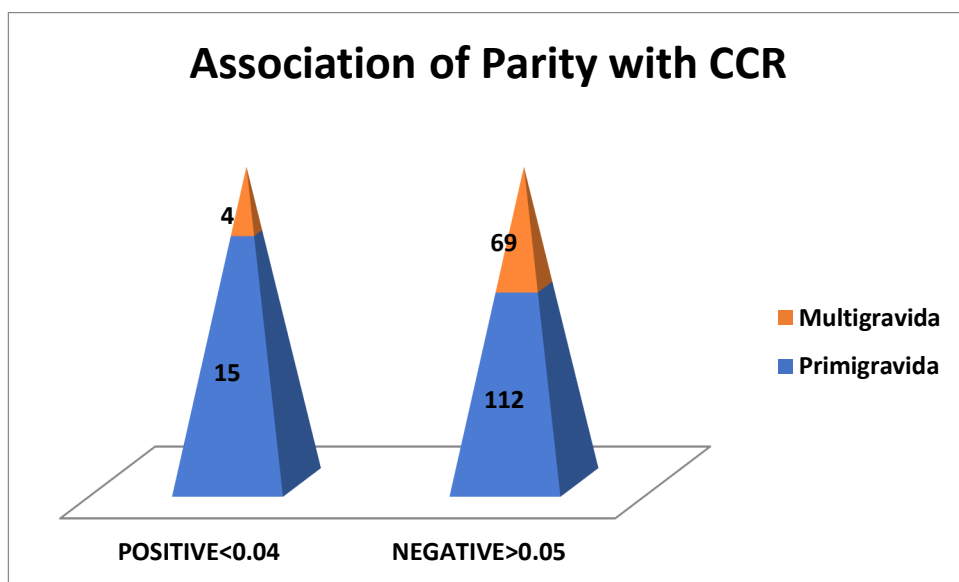
Table 6: Association of PIH with CCR

CCR	Pregnancy induced hypertension		P Value
	Yes	**No**	
POSITIVE<0.04	15(78.9%)	4(21.1%)	.000*
NEGATIVE>0.05	1(0.6%)	180(99.4%)	

*P- Value is <0.05 and it is statistically significant

Among 19 positive CCR,15 developed PIH while 4 remains normotensive.

Among 181 negative CCR,one developed PIH
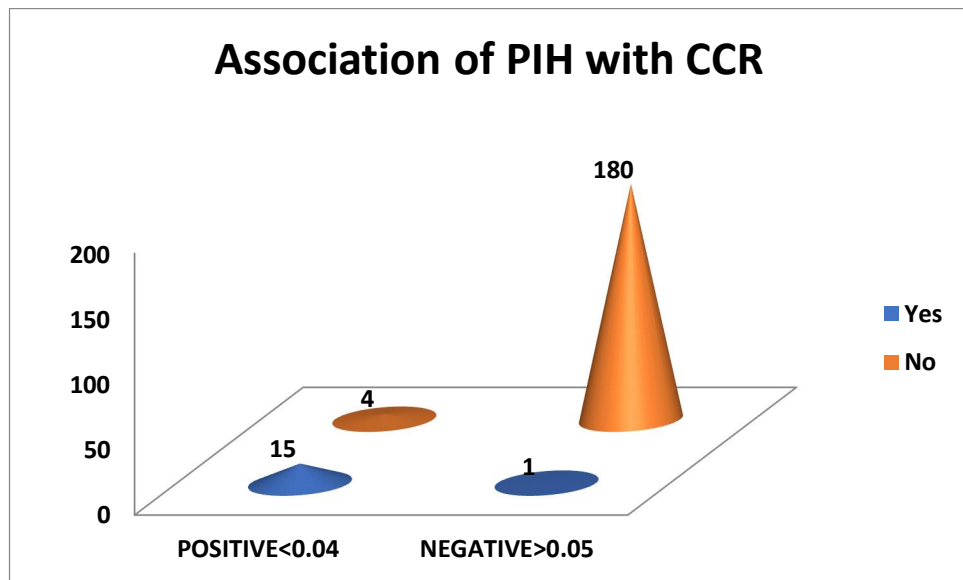
Table 7: Association of types of PIH with CCR

CCR	Pregnancy induced hypertension				P value
	SEVERE PREECLAMPSIA	NON SEVERE PREECLAMPSIA	GHT	Nil	
POSITIVE<0.04	6(31.6%)	5(26.3%)	4(21.1%)	4(21.1%)	
NEGATIVE>0.05	0(0.0%)	0(0.0%)	1(0.6%)	180(99.4%)	.814

Among 200 women involved in this study ,19 had positive CCR of which 6 developed severe pre eclampsia,5 developed non severe pre eclampsia and 4 developed GHT , remaining 4 didn't developed hypertension of pregnancy.

While 181 patients had negative CCR among that one patient developed GHT in spite of negative CCR and 180 patients didn't developed hypertension of pregnancy.

Association of PIH with CCR

Bar chart showing Association of PIH with CCR. Categories: SEVERE PREECLAMPSIA (POSITIVE<0.04 = 6, NEGATIVE>0.05 = 0), NON SEVERE PREECLAMPSIA (POSITIVE<0.04 = 5, NEGATIVE>0.05 = 0), GHT (POSITIVE<0.04 = 4, NEGATIVE>0.05 = 1), NIL (POSITIVE<0.04 = 4, NEGATIVE>0.05 = 1). Legend: POSITIVE<0.04, NEGATIVE>0.05.
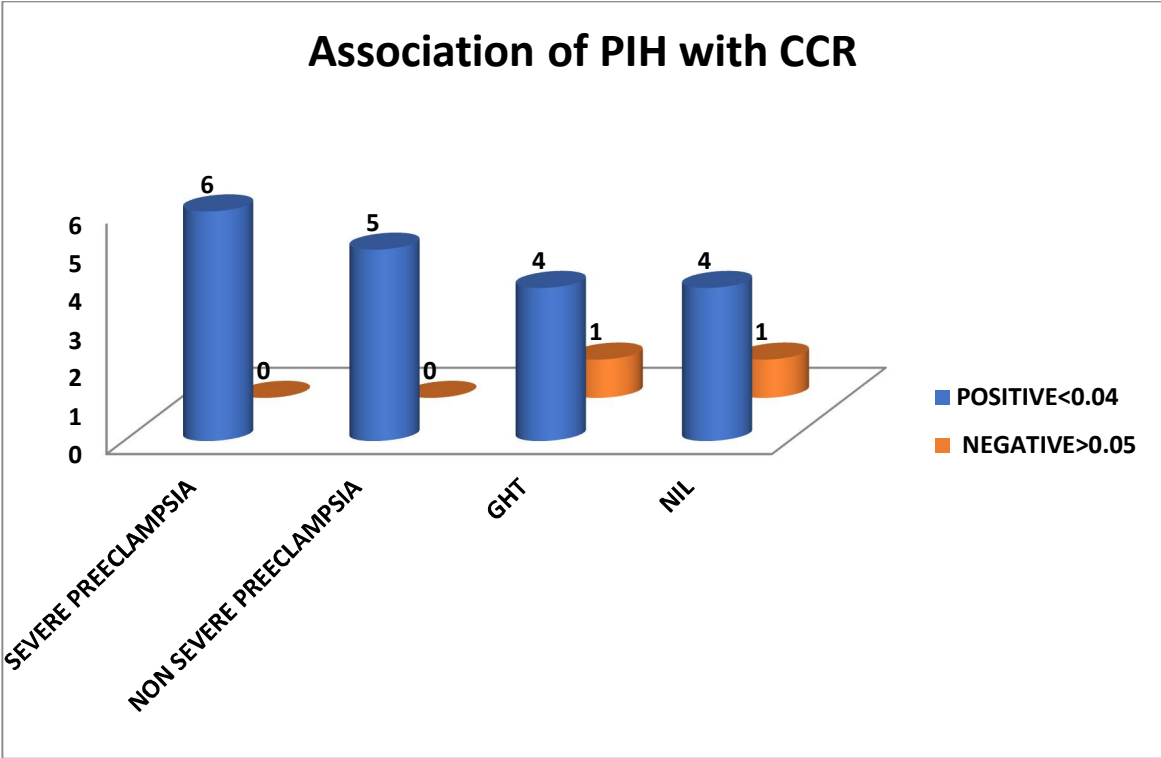
Table 8: Association of Gestational age at delivery with CCR

CCR	Gestational age		P Value
	PRETERM	TERM	
POSITIVE<0.04	5(26.3%)	14(73.7%)	
NEGATIVE>0.05	10(5.5%)	171(94.5%)	.000*

*P- Value is <0.05 and it is statistically significant

In among 19 positive CCR women,5 had preterm birth and 12 had term deliveries.

While in 181 negative CCR women,10 had preterm birth and 171 had term deliveries.

Association of Gestational age at delivery with CCR
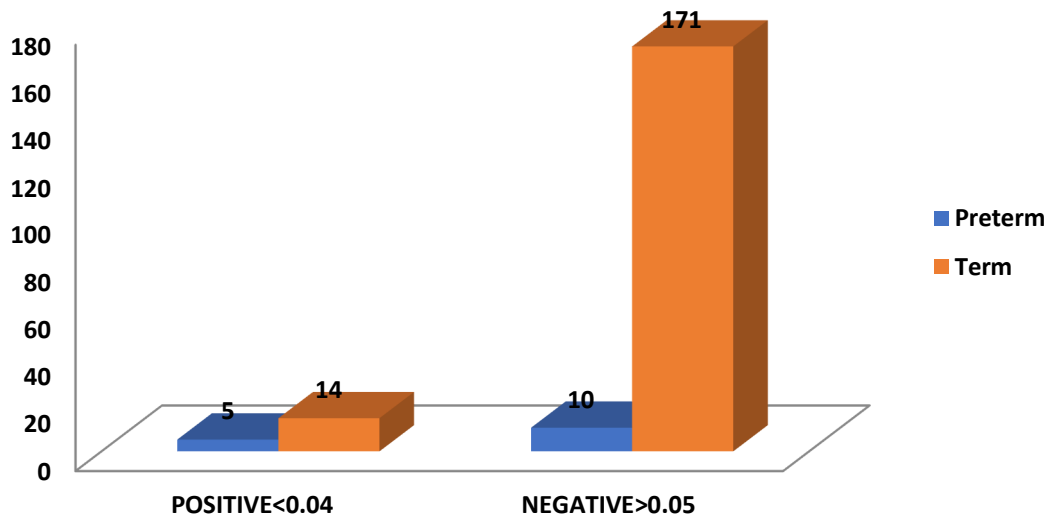
Table 9: Association of Gestational age of collection with CCR

CCR	Gestational age of collection		P Value
	1st trimester	2nd trimester	
POSITIVE<0.04	3(15.8%)	16(84.2%)	
NEGATIVE>0.05	69(38.1%)	112(61.9%)	.046*

*P- Value is <0.05 and it is statistically significant

Among the women with gestational age of less than 12 weeks ,69 women had negative CCR,3 had positive CCR while between 12-20 weeks ,16 women had positive CCR and 112 had negative CCR with significant p value of 0.046 .

And the estimation of CCR in second trimester is more ideal.

Association of Gestational age of collection with CCR

Legend:
- 2ndtrimester
- 1st trimester

	POSITIVE<0.04	NEGATIVE>0.05
2ndtrimester	16	112
1st trimester	3	69
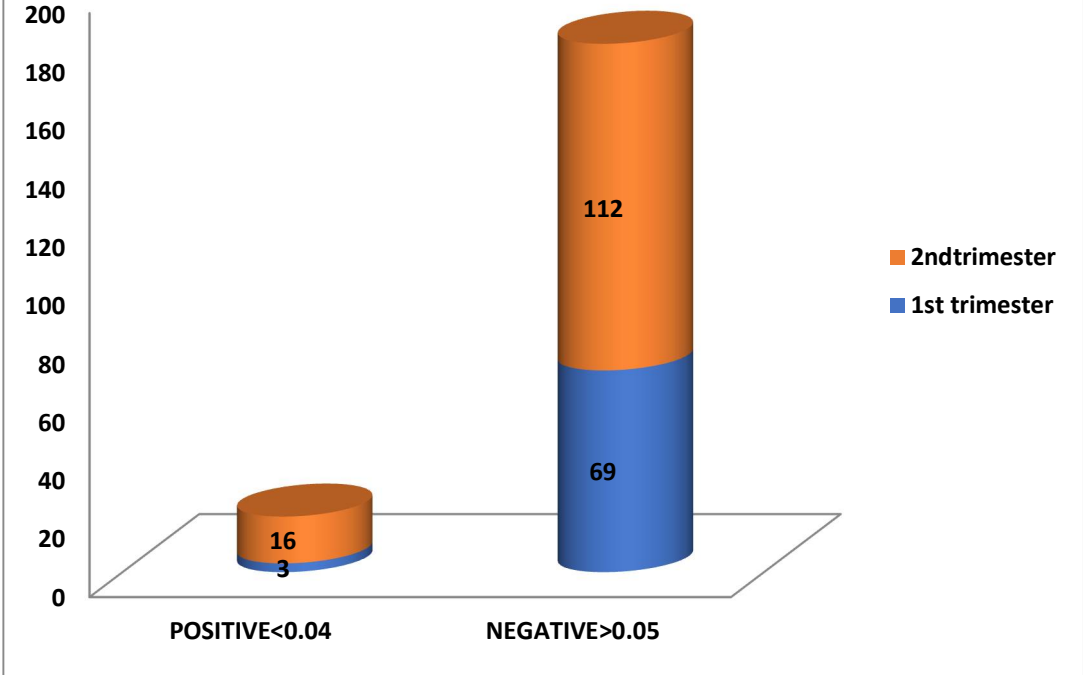
Table 10: Association of mode of delivery with CCR

CCR	MODE OF DELIVERY			P value
	LSCS	NVD	SPONTANEOUS ABORTION	
POSITIVE<0.04	6(31.6%)	13(68.4%)	0(0.0%)	.939
NEGATIVE>0.05	54(29.8%)	126(69.6%)	1(0.6%)	

LSCS-Lower Segment Caesaren Section.

NVD-Normal Vaginal Delivery.

Among 19 women with positive CCR , 6 had LSCS remaining 13 delivered vaginally.while among 181 women with negative CCR , 54 had LSCS and the remaining 126 patients had normal vaginal delivery with p-value of 0.939 and it is not statistically significant.

Association of mode of delivery with CCR
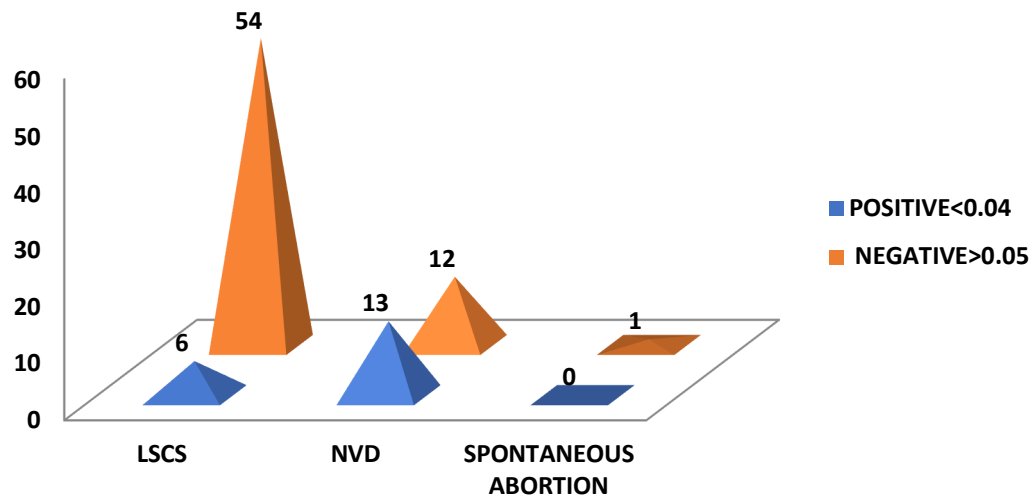
CCR-Calcium Creatinine Ratio

LSCS-Lower segment caesarean section

NVD-Normal Vaginal Delivery

Table 11 : Incidence of PIH in patients with Positive CCR

Parity	PIH
Primi gravida	15
Multi gravida	4
Total	19

Incidence of PIH in patients with Positive CCR
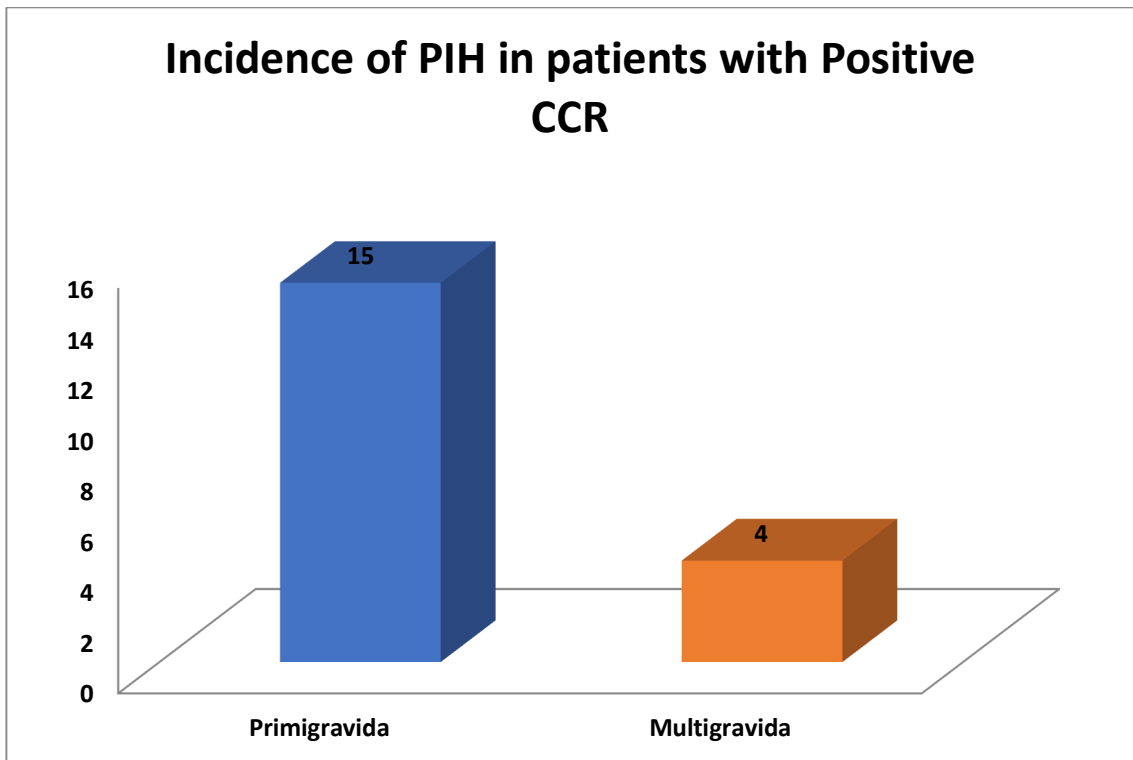
Table 12: Association of PIH with CCR in primigravida

CCR	Pregnancy induced hypertension (n=127)		P Value
	Yes	**No**	
POSITIVE<0.04	12(80.0%)	3(20.0%)	.000*
NEGATIVE>0.05	0(0.0%)	112(100.0%)	

*P- Value is <0.05 and it is statistically significant

Among 127 pirmigravida ,the incidence positive CCR in primi is about 11 % with p value of 0.000* and it is statistically significant.

Association of PIH with CCR in primigravida
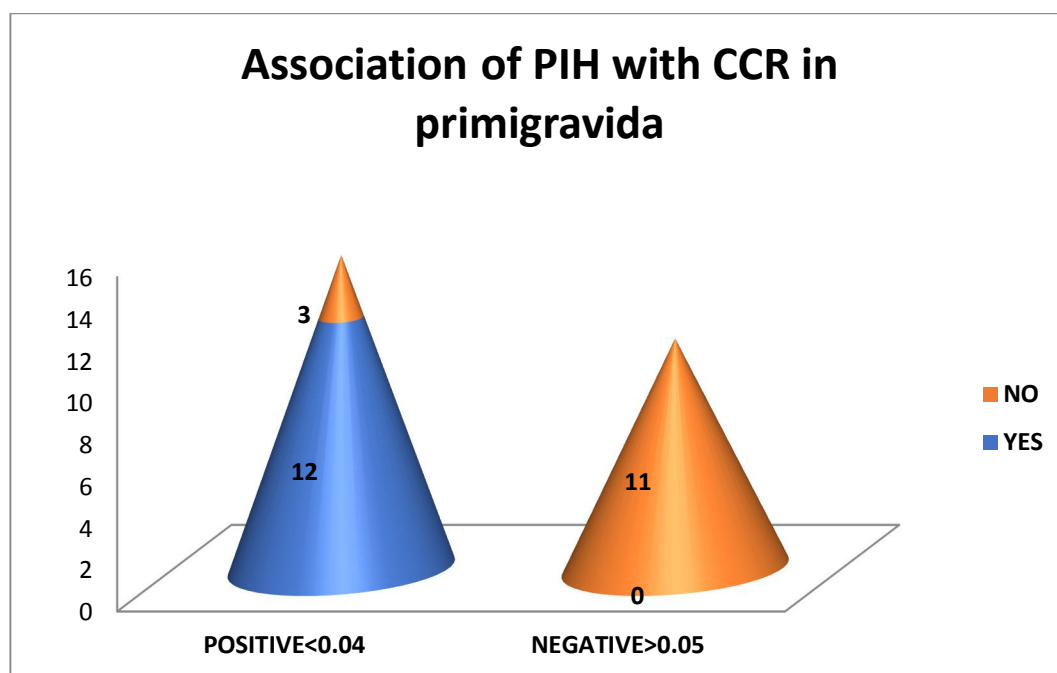
Table 13: Association of PIH with CCR in multigravida

CCR	Pregnancy induced hypertension		P Value
	Yes	No	
POSITIVE<0.04	3(75.0%)	1(25.0%)	
NEGATIVE>0.05	1(1.4%)	68(98.6%)	.000*

*P- Value is <0.05 and it is statistically significant

Among 73 multigravida, the positive CCR in multi is about 5% with significant p value 0.000* and it is statistically significant.

Association of PIH with CCR in multigravida
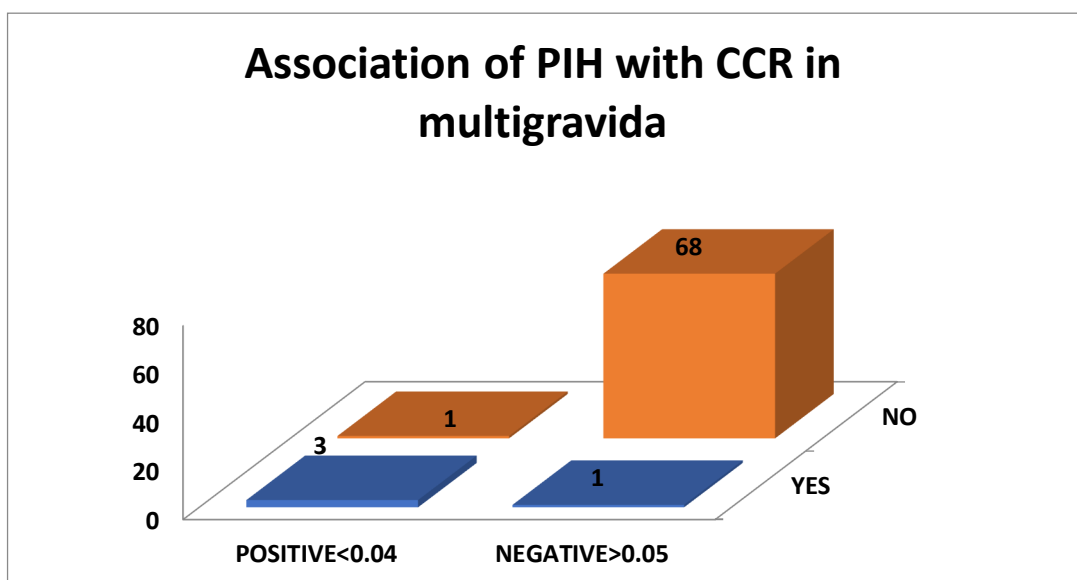
DISCUSSION

In the above study comprising of 200 low risk antenatal asymptomatic mothers with gestational age less than 20 weeks were enrolled in this study.They were assessed by determining the calcium to creatinine ratio in a spot sample of urine for the development of pre eclampsia.

CCR was calculated those with ratio less than or equal to 0.04 were considered positive and those with ratio of more than 0.04 were considered as test negative.

Cut off for positive CCR is taken as less than or equal to 0.04.

All 200 Patients were then followed till delivery once in four weeks to predict how many of them developed pre eclampsia.and the results obtained were analysed for statistical significance and if pre eclampsia developed managed as per local protocol.

Out of 200 samples,19 women had positive calcium creatinine ratio while 181 had negative calcium creatinine ratio.

Among the 19 positive CCR ratio-

- 15 developed hypertension i,e 6 developed severe pre eclampsia,5 developed non severe pre eclampsia and 4 developed gestational induced hypertension, while the remaining 4 women remains normotensive and No one developed eclampsia.

While among 181 negative CCR ratio ,one women developed gestational induced hypertension.

In our study we estimated the association between the CCR ratio and the development of hypertension in pregnancy and the p value obtained is 0.000* and it is considered as statistically significant.

Narendra Patil et al, government medical college and cancer hospital ,Aurangabad ,Maharashtra conducted a study ,calcium to creatinine ratio and microalbuminuira in prediction of pre eclampsia in a spot sample of urine between 20 and 34 weeks of gestation. They concluded that CCR ratio less than or equal to 0.04 is a good test for prediction of pre eclampsia and can be recommended as screening test in asymptomatic low risk antenatal women.while microalbuminuria on the other hand is a weak test for prediction of pre eclampsia .(4).

Whereas in our study we estimated only CCR ratio with less than 20 weeks of gestation with significant p value.

Ozcan conducted a trial, for determining the efficacy of hypocalciuria in urine sample for prediction of pre eclampsia as early as 1990s and concluded hypocalciuria can be used as prediction of pre eclampsia.(5).

And therefore from the above study shows that it can be used as screening test in low risk aymptomatic women for prediction of pre eclampsia with p value 0f <0.001.

In our study we also compared the association of types of PIH with CCR ratio.Among the 19 positive CCR ratio patients, 6 developed severe pre eclampsia,5 developed non severe pre eclampsia ,4 developed gestational hypertension and 4 remains normotensive. And one women developed Gestational hypertension even though CCR ratio is more than 0.04.

On statistical analysis ,the association of types of PIH with CCR ratio had p value of 0.814 and it is statistically not significant.so in our study the CCR ratio has no influence on the types of PIH.

In our study we also the compared the mean age association with CCR.on analysis (table 2),

- 40%-belongs to age group 17-20 years

- 40.5%-belongs to age group 21-25 years

- 17%-belongs t0 age group 26-30 years

- 25-aged above 31 years

On statistical analysis , the association of types of PIH with CCR shows p value of 0.416 and it is not statistically significant.

In comparing the association of parity with CCR,the incidence of positive CCR in primi is 78.9%,while in multi it is 21.1%. Among which 12 cases of primi and 4 cases of multi developed hypertension during pregnancy.The incidence of hypertension in pregnancy is 10% in primi and 5 % in multigravida.so in my study also interprets the incidence of PIH is more in primi than multi gravida.

On statistical analysis ,the association of parity with CCR shows p value of 0.142 and it is not statistically significant..

The incidence of preterm birth is more common than term birth in hypertension of pregnancy and it is about more than 40%. In our study also when comparing the association of gestational age at delivery with CCR, premature deliveries is more than term deliveries in women those who developed hypertension during pregnancy and it showed p value of 0.000* and it is statistically significant.

So there is more number of premature deliveries in hypertension of pregnancy than normotensive women might be due to early intervention and termination of pregnancy to prevent maternal mortality and morbidity.

Izumi had reported that CCR had reduced value as a screening method for pre eclampsia , but the screening was done during initial period of pregnancy at equal or less than 12 weeks of gestation ,where as in above study the gestational age of less than 20 weeks is taken ,giving a wider range of prediction.(7).

In our study we compared the association of gestational age of collection with CCR ,

- First trimester (14 weeks)-69 had negative CCR and 3 of them had positive CCR.

- Second trimester(14-20 weeks)-112 had negative CCR and 16 had positive CCR.

  While comparing the association of gestational age of collection with CCR had p value of 0.046 and it is statistically aignificant. And the second trimester CCR(84%) is more ideal than first trimester(15%).

On comparing the association of mode of delivery with CCR ratio, Among 19 positive CCR,6 delivered by LSCS and 13 delivered by NVD. While among 181 negative CCR,54 delivered by LSCS and 126 delivered by NVD.

On statistical analysis, the association of mode of delivery with CCR had p value of 0.939 and it is not statistically significant.

On comparing the association of PIH with CCR in primigravida, among 127 women,15 had positive CCR with incidence of 15%,with significant P value of 0.000* and it is statistically significant.

While comparing the association of PIH with CCR in multigravida ,among 73 women 4 had positive CCR with incidence of 5% with significant p value and it is statistically significant .so there is similarity noted between the incidence of PIH and association of PIH with CCR in this study.

CONCLUSION

From this study ,the following conclusion have been arrived,

The estimation of Calcium Creatinine Ratio in a spot sample of urine for prediction of pre eclampsia had p value of < 0.001 and it is statistically significant and it can be used as a screening test for low risk asymptomatic antenatal women with less than 20 weeks of gestation for prediction of pre eclampsia.

And the association of gestational age at delivery with CCR,the premature deliveries is more common than term deliveries in those who developed hypertension during pregnancy with significant p value of 0.001 and it is statistically significant.

Also the association of gestational age of collection less than 20 weeks with CCR,has a significance p value and it is also statistically significant and while comparing second trimester CCR is more ideal than first trimester.

The association of PIH with CCR in primigravida and multigravida is also statistically significant with significant p value of 0.000*.

The incidence of positive CCR in primi and multi in our study is about 11% and 5% respectively, which is as similar as incidence of PIH in primi and multi and its about 10-15% and 5% respectively.

While comparing the association of CCR with mean age, parity, types of PIH, and mode of delivery doesn't have significant p value and it is not statistically significant.

Estimation of Calcium Creatinine Ratio in a spot sample of urine is easy to perform ,feasible test and hence it has high patient acquiescence.

It can therefore be suggested as a screening test for low risk antenatal women with less than 20 weeks of gestation for prediction of pre eclampsia,especially when the government encouragesin booking visit.

As PICME (Pregnancy and Infant Cohort Monitoring and Evaluation) entry should be made before 12 weeks as per government norms,so we can have the opportunity to screen the mother with this CCR ratio at earlier period to predict pre-eclampsia during this booking visit.

And also PMSMA-The Pradhan Mantri Surakshit Matritva Abhiyan under ministry of health and family welfare guarantees a antenatal care free of cost universally to all pregnant women in their second and third trimesters of pregnancy on the 9th of every month.

We can also screen the mother with this CCR ratio to predict the pre eclampsia as a part of this government schemes.

Pre eclampsia is a chief cause for maternal morbidity and mortality in worldwide, especially in developing countries. Many research work are going on for a better predictor for pre eclampsia and therefore to prevent the maternal mortality and mortality associated with that.

An accessibility of a good screening test would pledge and encourage more exploration work in the direction of secondary prevention of early diagnosis and treatment.

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PRO FORMA

NAME: DATE:

AGE:

SERIAL NUMBER:

OUT PATIENT NUMBER:

UNIT:

ADDRESS:

SOCIO ECONOMIC STATUS:

PARITY:

LMP: EDD:

LCB:

MODE OF DEIVERY IN PREVIOUS PREGNANCY:

GESTATIONAL AGE(PRESENT PREGNANCY):

HISTORY OF PRESENT ILLNESS:

MENSTURAL HISTORY:

MARITAL HISTORY:

OBSTETRIC HISTORY:

SIGNIFICANT PAST MEDICAL ILLNESS:

DIABETES   -YES/NO

CHRONIC HYPERTENSON   -YES/NO

HISTORY OF PIH IN PAST PREGNANCY-YES/NO

RENAL DISEASE   -YES/NO

VASCULAR DISEASE   -YES/NO

IMMUNOLOGICAL DISEASE   -YES/NO

ANY SURGICAL HISTORY:

VITALS:

PR: BLOOD PRESSURE: URINE ALBUMIN:

HEIGHT: WEIGHT: BMI:

EXAMINATION:

PALLOR-   PEDAL EDEMA-

ICTERUS-

SYSTEMIC EXAMINATION:

CVS-

RS-

CNS-

PER ABDOMEN EXAMINATION-

CALCIUM CREATININE RATIO-

GESTATIONAL AGE OF COLLECTION-

FOLLOW UP-

GA OF DEVELOPMENT OF PRE ECLAMPSIA:

COMPLICATIONS:

MODE OF DELIVERY:

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி:

கோவை அரசு மருத்துவக்கல்லூரி மருத்துவமனையில் மருத்துவர் **கோ.நித்யா** தலைமையில் நடைபெறும் இந்த ஆய்வில் முழு சம்மதத்துடன் கலந்துகொள்ள சம்மதிக்கிறேன். இந்த ஆய்வில் என்னை பற்றி விவரங்களை பாதுகாப்புடன் இந்த ஆய்வில் வெளியிட ஆட்சேபணை இல்லை என்று தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் ஆய்வில் இருந்து எந்த நேரத்திலும் விலக்கிக்கொள்ளும் உரிமை உண்டு என்று அறிவேன்.

இடம் :

தேதி:

S.NO	AGE	OP:NO	PARITY	SPOT CCR	GA OF COLLECTION	PIH DEVELOPED-YES/NO	GA OF PIH IN WEEKS	TYPE OF PIH	GA OF DELIVERYIN WEEKS	MODE OF DELIVERY
1	26	1826760	PRIMI	0.18	16 WEEKS	NO			39WEEKS+2 DAYS	NVD
2	19	1760935	G2P1L1	0.16	12 WEEKS	NO			39 WEEKS	NVD
3	23	1890356	G2P1P1	0.09	10WEEKS+3DAYS	NO			38 WEEKS+6 DAYS	LSCS
4	23	1760903	G3P1L1A1	0.07	17WEEKS	NO			37WEEKS	NVD
5	19	1723987	PRIMI	0.18	8WEEKS+6DAYS	NO			38WEEKS	LSCS
6	19	1830756	G2A1	0.01	17WEEKS+2 DAYS	YES	34 WEEKS	SEVERE PREECLAMPSIA	38WEEKS	NVD
7	18	1899235	G2P1L1	0.17	15WEEKS	NO			39WEEKS+2 DAYS	LSCS
8	28	1635876	G3P2L2	0.02	19 WEEKS	NO			38WEEKS	NVD
9	26	1836450	G2P1L1	0.05	20 WEEKS	NO			38WEEKS+6 DAYS	LSCS
10	25	1765901	PRIMI	0.08	17WEEKS	NO			37WEEKS+6DAYS	NVD
11	33	1876501	PRIMI	0.02	19 WEEKS	YES	32WEEKS	GHT	39WEEKS	NVD

12	30	1765489	G2A1	0.06	15 WEEKS	NO			36WEEKS+6DAYS	NVD
13	17	1865237	G2P1L0	0.18	17WEEKS	NO			39WEEKS	NVD
14	19	1534564	G2P1L1	0.06	10WEEKS+3DAYS	NO			40WEEKS	LSCS
15	21	1846521	PRIMI	0.07	14WEEKS	NO			38WEEKS+5DAYS	NVD
16	25	1286403	G3P1L1A1	0.05	17WEEKS	NO			39WEEKS	LSCS
17	20	1389605	PRIMI	0.23	16WEEKS	NO			39WEEKS+3DAYS	NVD
18	20	1547831	G2P1L1	0.2	18WEEKS	NO			39WEEKS	LSCS
19	31	1754390	G3P1L1A1	0.31	15WEEKS	NO			39WEEKS+3DAYS	LSCS
20	24	1834567	PRIMI	0.24	15WEEKS+4DAYS	NO			38WEEKS	NVD
21	20	1880213	PRIMI	0.41	18WEEKS	NO			39WEEKS	LSCS
22	26	1870932	G2P1L1	0.25	18WEEKS+2DAYS	NO			39WEEKS+5DAYS	NVD
23	19	1876409	PRIMI	0.08	17WEEKS	NO			38WEEKS+4DAYS	NVD
24	21	1635709	PRIMI	0.31	10WEEKS+5DAYS	NO			39WEEKS	NVD
25	23	1746908	PRIMI	0.07	16WEEKS	NO			38WEEKS	NVD

26	18	1877554	PRIMI	0.01	16WEEKS+5DAYS	YES	34WEEKS+4DAYS	SEVERE PREECLAMPSIA	36WEEKS+2DAYS	LSCS
27	21	1754564	PRIMI	0.24	13WEEKS	NO			38WEEKS+4DAYS	NVD
28	26	1648709	G2P1L1	0.15	14WEEKS	NO			37WEEKS+5DAYS	LSCS
29	30	1677834	PRIMI	0.17	16WEEKS	NO			39WEEKS+1DAY	NVD
30	22	1734567	PRIMI	0.02	20WEEKS	YES	32WEEKS	NON SEVERE PREECLAMPSIA	38 WEEKS	NVD
31	20	1845690	G2A1	0.15	19WEEKS+3DAYS	NO			38WEEKS=6DAYS	NVD
32	21	1654300	G2P1L1	0.16	18WEEKS	NO			39WEEKS	LSCS
33	28	1765489	PRIMI	0.02	17WEEKS	NO			39WEEKS	NVD
34	29	1845688	PRIMI	0.01	19WEEKS+3DAYS	YES	35WEEKS	NON SEVERE PREECLAMPSIA	37WEEKS	LSCS
35	18	1923450	PRIMI	0.21	18WEEKS	NO			39WEEKS	NVD
36	20	1534709	G3P1L1A1	0.29	17WEEKS+5DAYS	NO			39WEEKS+3DAYS	NVD
37	25	1233450	G2P1P1	0.23	10WEEKS	NO			40WEEKS+2DAYS	NVD

38	26	1645899	PRIMI	0.18	13WEEKS	NO			38WEEKS+6DAYS	NVD
39	19	1543876	PRIMI	0.22	18WEEKS	NO			36WEEKS+6DAYS	NVD
40	20	1645600	PRIMI	0.18	19WEEKS+4DAYS	NO			38WEEKS	LSCS
41	25	1467840	PRIMI	0.11	15WEEKS	NO			39WEEKS	NVD
42	27	1794236	G2A1	0.18	17WEEKS	NO			39WEEKS	NVD
43	23	1845370	G3P1L2	0.15	18WEEKS	NO			40WEEKS	NVD
44	25	1753480	G2P1L1	0.2	11WEEKS+3DAYS	NO			39WEEKS+4DAYS	NVD
45	18	1834700	PRIMI	0.13	14WEEKS	NO			37WEEKS	LSCS
46	20	1639487	PRIMI	0.03	15WEEKS	NO			39WEEKS	NVD
47	25	1745740	PRIMI	0.09	8WEEKS+6DAYS	NO			39WEEKS+3DAYS	NVD
48	34	1834555	G2P1L1	0.12	15WEEKS	NO			39WEEKS	NVD
49	27	1764539	PRIMI	0.23	16WEEKS	NO			38WEEKS+6DAYS	NVD
50	18	1730059	G2P1L1	0.06	12WEEKS	NO			37WEEKS	NVD
51	20	1846570	PRIMI	0.17	17WEEKS+1DAY	NO			39WEEKS	LSCS

52	23	1745371	PRIMI	0.18	16WEEKS	NO			38WEEKS+3DAYS	LSCS
53	21	1543723	PRIMI	0.22	13WEEKS	NO			39WEEKS	NVD
54	28	1325467	PRIMI	0.15	16WEEKS	NO			39WEEKS+1DAY	NVD
55	24	1548762	G3P2L2	0.27	14WEEKS	NO			39WEEKS+5DAYS	NVD
56	23	1754300	PRIMI	0.18	15WEEKS	NO			37WEEKS+6DAYS	NVD
57	20	1834076	G2P1P1	0.23	10WEEKS+2DAYS	NO			39 WEEKS	NVD
58	17	1835678	PRIMI	0.01	14 WEEKS	YES	34 WEEKS	NON SEVERE PREECLAMPSIA	37WEEKS+3DAYS	LSCS
59	24	1645309	G2P1L1	0.21	13WEEKS	NO			39WEEKS	NVD
60	25	1735648	PRIMI	0.26	15WEEKS	NO			39WEEKS+3DAYS	NVD
61	20	1834537	PRIMI	0.15	16WEEKS	NO			39WEEKS	NVD
62	19	1820935	PRIMI	0.03	14 WEEKS	NO			38 WEEKS+6 DAYS	LSCS
63	30	1635421	PRIMI	0.21	9WEEKS	NO			37WEEKS+5DAYS	NVD
64	21	1736540	G3P2L1	0.07	11WEEKS+4	NO			38WEEKS	NVD

					DAYS					
65	18	1836540	PRIMI	0.09	13WEEKS+2 DAYS	NO			38WEEKS+4DAYS	NVD
66	25	1730654	PRIMI	0.1	20WEEKS	NO			39WEEKS+1DAY	NVD
67	22	1834652	G2P1L1	0.25	17WEEKS	NO			36WEEKS+6DAYS	LSCS
68	24	1549056	PRIMI	0.3	10WEEKS	NO			12WEEKS	SPONTANEOUS ABORTION
69	29	1653987	PRIMI	0.22	15WEEKS	NO			38WEEKS	NVD
70	23	1746531	PRIMI	0.11	16WEEKS	NO			39WEEKS+3DAYS	LSCS
71	19	1834129	G2P1L1	0.24	17WEEKS+3DAYS	NO			39WEEKS	NVD
72	26	1734609	PRIMI	0.18	10WEEKS+2DAYS	NO			39WEEKS+3DAYS	NVD
73	33	1836534	PRIMI	0.02	19WEEKS+6DAYS	YES	28WEEKS	SEVERE PREECLAMPSIA	32WEEKS+2DAYS	NVD
74	21	1245630	G3P1L1A1	0.17	14WEEKS	NO			38WEEKS+5DAYS	NVD
75	20	1548769	PRIMI	0.3	13WEEKS+2DAYS	NO			39WEEKS+4DAYS	NVD

76	19	1635490	PRIMI	0.26	16WEEKS	NO			39WEEKS+1DAY	LSCS
77	25	1653785	G2P1L1	0.15	20WEEKS	NO			40WEEKS+4DAYS	NVD
78	22	1763865	PRIMI	0.26	12WEEKS	NO			39WEEKS	NVD
79	26	1863467	PRIMI	0.18	14WEEKS	NO			38WEEKS+5DAYS	NVD
80	18	1635865	PRIMI	0.2	16WEEKS+1DAY	NO			37WEEKS+5DAYS	LSCS
81	19	1538658	G2P1L1	0.15	17WEEKS	NO			39WEEKS	LSCS
82	28	1643676	G3P1L1A1	0.01	14WEEKS	YES	31WEEKS+2 DAYS	GHT	37WEEKS	NVD
83	20	1835467	PRIMI	0.2	15WEEKS	NO			39WEEKS+3DAYS	NVD
84	22	1637338	PRIMI	0.16	10WEEKS+2DAYS	NO			38WEEKS+5DAYS	NVD
85	20	1320456	G2P1L1	0.21	18WEEKS	YES	37WEEKS	GHT	38WEEKS	NVD
86	17	1586362	PRIMI	0.22	16WEEKS	NO			39WEEKS	LSCS
87	19	1630986	PRIMI	0.15	14WEEKS+1DAY	NO			39WEEKS+3DAYS	NVD
88	18	1734201	PRIMI	0.18	17WEEKS	NO			38WEEKS+3DAYS	NVD

89	25	1824543	G2P1L1	0.26	8WEEKS+4DAYS	NO			39WEEKS	LSCS
90	19	1637620	PRIMI	0.25	11WEEKS+4DAYS	NO			40WEEKS	NVD
91	18	1537552	PRIMI	0.26	18WEEKS	NO			39WEEKS+1DAY	LSCS
92	27	1735749	PRIMI	0.2	17WEEKS	NO			38WEEKS+4DAYS	NVD
93	26	1836536	G3P1L1A1	0.17	16WEEKS	NO			38WEEKS	NVD
94	23	1327934	PRIMI	0.16	13WEEKS	NO			39WEEKS+2DAYS	NVD
95	22	1528376	G2P1L1	0.1	14WEEKS+3DAYS	NO			39WEEKS	NVD
96	21	1450838	PRIMI	0.26	16WEEKS	NO			38WEEKS+3DAYS	LSCS
97	18	1639207	PRIMI	0.08	10WEEKS+2DAYS	NO			39WEEKS	LSCS
98	20	1734509	PRIMI	0.18	14WEEKS	NO			38WEEKS+6DAYS	NVD
99	27	1473687	G2P1L1	0.2	17WEEKS	NO			39WEEKS+3DAYS	NVD
100	20	1635278	PRIMI	0.26	11WEEKS+5DAYS	NO			39WEEKS	NVD
101	26	1723609	PRIMI	0.18	13WEEKS	NO			38WEEKS+4DAYS	LSCS
102	17	1538650	PRIMI	0.06	16WEEKS	NO			39WEEKS+6DAYS	NVD

103	22	1637627	G2P1L1	0.2	10WEEKS+4DAYS	NO			38WEEKS+5DAYS	LSCS
104	19	1392678	PRIMI	0.15	13WEEKS	NO			35WEEKS+6DAYS	NVD
105	23	1435783	PRIMI	0.26	15WEEKS	NO			39WEEKS	NVD
106	20	1547282	PRIMI	0.22	17WEEKS	NO			38WEEKS+4DAYS	NVD
107	25	1648233	G2P1L1	0.18	15WEEKS+4DAYS	NO			37WEEKS	LSCS
108	26	1534708	G2P1L1	0.24	20WEEKS	NO			39WEEKS	NVD
109	20	1638268	G3P1L1A1	0.17	18WEEKS	NO			38WEEKS+3DAYS	LSCS
110	24	1620087	PRIMI	0.15	19WEEKS	NO			39WEEKS+3DAYS	NVD
111	19	1723056	PRIMI	0.02	19WEEKS+2 DAYS	YES	34WEEKS	NON SEVERE PREECLAMPSIA	38WEEKS	NVD
112	23	1423856	G2P1L1	0.17	11WEEKS	NO			39WEEKS	NVD
113	25	1538761	PRIMI	0.09	18WEEKS	NO			38WEEKS+5DAYS	LSCS
114	24	1639746	PRIMI	0.05	19WEEKS	NO			39WEEKS	NVD
115	28	1834856	PRIMI	0.26	10WEEKS	NO			38WEEKS+3DAYS	NVD

116	18	1746284	PRIMI	0.18	15WEEKS	NO			39WEEKS+1DAYS	LSCS
117	20	1426467	G2P1L1	0.24	16WEEKS+2DAYS	NO			38WEEKS+4DAYS	NVD
118	24	1452848	PRIMI	0.2	17WEEKS	NO			39WEEKS	NVD
119	25	1239481	G2P1L1	0.16	13WEEKS	NO			36WEEKS+6DAYS	NVD
120	22	1453827	PRIMI	0.07	15WEEKS+6DAYS	NO			38WEEKS+4DAYS	LSCS
121	18	1563882	G2A1	0.23	18WEEKS	NO			37WEEKS+5DAYS	NVD
122	20	1638568	PRIMI	0.19	16WEEKS+3DAYS	NO			39WEEKS	NVD
123	23	1743785	PRIMI	0.17	13WEEKS+3DAYS	NO			38WEEKS	LSCS
124	25	1846237	PRIMI	0.18	14WEEKS	NO			38WEEKS+5DAYS	LSCS
125	20	1894748	G2P1L1	0.26	15WEEKS	NO			38WEEKS	NVD
126	23	1974372	PRIMI	0.18	15WEEKS+5DAYS	NO			38WEEKS+3DAYS	NVD
127	30	1358584	PRIMI	0.07	20WEEKS	NO			39WEEKS	NVD
128	27	1736458	PRIMI	0.08	17WEEKS	NO			38WEEKS+6DAYS	NVD
129	23	1358678	G3P1L1A1	0.16	20WEEKS	NO			39WEEKS	LSCS

130	24	1548561	PRIMI	0.27	18WEEKS	NO			38WEEKS+5DAYS	NVD
131	20	1648647	PRIMI	0.15	11WEEKS+5DAYS	NO			37WEEKS+5DAYS	NVD
132	19	1657653	PRIMI	0.26	14WEEKS	NO			39WEEKS+2DAYS	NVD
133	26	1436474	G2P1L1	0.16	15WEEKS	NO			37WEEKS+6DAYS	NVD
134	23	1556781	G3P1L1A1	0.25	13WEEKS	NO			40WEEKS+3DAYS	LSCS
135	17	1658968	PRIMI	0.03	20WEEKS	YES	30WEEKS	SEVERE PREECLAMPSIA	34WEEKS+4DAYS	NVD
136	23	1748699	PRIMI	0.13	15WEEKS+2DAYS	NO			39WEEKS	NVD
137	19	1864578	PRIMI	0.24	16WEEKS	NO			38WEEKS+4DAYS	LSCS
138	20	1755275	G2P1L1	0.2	13WEEKS+4DAYS	NO			39WEEKS+1DAY	NVD
139	24	1435673	PRIMI	0.17	16WEEKS+4DAYS	NO			39WEEKS+3DAYS	NVD
140	25	1545876	PRIMI	0.18	17WEEKS+2DAYS	NO			37WEEKS+5DAYS	LSCS
141	17	1335467	PRIMI	0.09	13WEEKS	NO			38WEEKS	NVD
142	23	1565778	G2P1L1	0.07	15WEEKS+4DAYS	NO			36WEEKS+5DAYS	NVD

143	19	1638762	PRIMI	0.12	18WEEKS	NO			39WEEKS	NVD
144	26	1732465	PRIMI	0.26	14WEEKS	NO			38WEEKS+5DAYS	LSCS
145	26	1845787	PRIMI	0.18	20WEEKS	NO			39WEEKS	NVD
146	23	1455784	PRIMI	0.15	17WEEKS	NO			38WEEKS+6DAYS	LSCS
147	20	1246688	G2P1L1	0.19	13WEEKS	NO			39WEEKS	NVD
148	25	1545376	G2P1L1	0.2	16WEEKS	NO			38WEEKS+4DAYS	LSCS
149	23	1465784	G2A1	0.18	10WEEKS+4DAYS	NO			40WEEKS+1DAY	NVD
150	26	1836455	PRIMI	0.08	14WEEKS+5DAYS	NO			39WEEKS+3DAYS	LSCS
151	19	1743756	PRIMI	0.25	16WEEKS	NO			38WEEKS+5DAYS	NVD
152	24	1546577	G2P1L1	0.19	17WEEKS	NO			39WEEKS	NVD
153	25	1431257	PRIMI	0.07	13WEEKS	NO			38WEEKS	NVD
154	23	1347676	PRIMI	0.06	15WEEKS	NO			39WEEKS+3DAYS	NVD
155	29	1544337	G3P1L1A1	0.09	13WEEKS+4DAYS	NO			39WEEKS	LSCS
156	20	1675848	G2P1L1	0.17	12WEEKS	NO			39WEEKS+1DAY	NVD

157	18	1546477	PRIMI	0.24	17WEEKS	NO			37WEEKS	NVD
158	28	1354656	PRIMI	0.12	20WEEKS	NO			36WEEKS	NVD
159	22	1456756	G2P1L1	0.05	19WEEKS+5DAYS	NO			39WEEKS	LSCS
160	20	1557474	PRIMI	0.23	16WEEKS	NO			37WEEKS+5DAYS	NVD
161	25	1437188	G3P1L1A1	0.18	20WEEKS	NO			35WEEKS+5DAYS	LSCS
162	20	1354578	PRIMI	0.16	11WEEKS+3DAYS	NO			38WEEKS+6DAYS	NVD
163	18	1743573	PRIMI	0.02	17WEEKS	YES	36WEEKS	GHT	38WEEKS	NVD
164	18	1835645	PRIMI	0.25	16WEEKS	NO			39WEEKS	NVD
165	23	1534543	G2P1L1	0.17	13WEEKS	NO			38WEEKS+4DAYS	NVD
166	20	1434657	G3P1L1A1	0.23	15WEEKS	NO			39WEEKS	NVD
167	25	1845536	PRIMI	0.12	20WEEKS	NO			38WEEKS+5DAYS	LSCS
168	19	1534467	PRIMI	0.08	10WEEKS+4DAYS	NO			38WEEKS+1DAY	NVD
169	26	1745473	G3P2L2	0.14	17WEEKS+2DAYS	NO			37WEEKS	LSCS
170	23	1734677	G2P1L1	0.19	18WEEKS	NO			35WEEKS+6DAYS	NVD

171	20	1543658	PRIMI	0.25	20WEEKS	NO			39WEEKS	NVD
172	23	1645677	PRIMI	0.15	16WEEKS	NO			38WEEKS	NVD
173	25	1745473	G2P1L1	0.08	17WEEKS	NO			38WEEKS	LSCS
174	19	1846572	PRIMI	0.05	18WEEKS	NO			38WEEKS+5DAYS	NVD
175	22	1943857	PRIMI	0.12	14WEEKS	NO			37WEEKS+4DAYS	NVD
176	20	1635578	PRIMI	0.03	15WEEKS	YES	30WEEKS	NON SEVERE PREECLAMPSIA	37WEEKS	NVD
177	25	1335793	G2P1L1	0.13	10WEEKS+4DAYS	NO			39WEEKS	LSCS
178	18	1456783	PRIMI	0.2	13WEEKS	NO			38WEEKS+2DAYS	LSCS
179	19	1756488	G3P1L1A1	0.24	15WEEKS	NO			37WEEKS+4DAYS	NVD
180	24	1356437	PRIMI	0.26	16WEEKS	NO			39WEEKS	NVD
181	25	1547324	PRIMI	0.16	9WEEKS+2DAYS	NO			38WEEKS	LSCS
182	18	1465678	PRIMI	0.18	11WEEKS+4DAYS	NO			38WEEKS+4DAYS	NVD
183	20	1643758	G2P1L1	0.23	17WEEKS	NO			39WEEKS	NVD

184	23	1745231	PRIMI	0.16	20WEEKS	NO			38WEEKS+3DAYS	LSCS
185	25	1245772	PRIMI	0.2	13WEEKS	NO			37WEEKS+3DAYS	NVD
186	20	1542748	PRIMI	0.15	14WEEKS+2DAYS	NO			38WEEKS	NVD
187	27	1547674	PRIMI	0.01	19WEEKS	YES	29WEEKS+2DAYS	SEVERE PREECLAMPSIA	35WEEKS	LSCS
188	19	1356745	G3P1L1A1	0.24	12WEEKS+1DAY	NO			39WEEKS	NVD
189	20	1743534	PRIMI	0.13	16WEEKS	NO			38WEEKS+4DAYS	NVD
190	26	1834354	G2P1L1	0.03	17WEEKS+2DAYS	YES	27WEEKS	SEVERE PREECLAMPSIA	31WEEKS	NVD
191	25	1535647	PRIMI	0.16	15WEEKS	NO			38WEEKS	LSCS
192	23	1364677	PRIMI	0.17	14WEEKS	NO			37WEEKS+4DAYS	NVD
193	19	1645477	PRIMI	0.12	15WEEKS+5DAYS	NO			38WEEKS+5DAYS	NVD
194	25	1584345	G2P1L1	0.24	16WEEKS	NO			38WEEKS	NVD
195	23	1735377	PRIMI	0.25	17WEEKS	NO			37WEEKS+6DAYS	NVD

196	21	1835462	PRIMI	0.26	13WEEKS+3DAYS	NO			38WEEKS	NVD
197	22	1454667	G3P1L1A1	0.38	18WEEKS	NO			38WEEKS+4DAYS	NVD
198	24	1567882	PRIMI	0.21	16WEEKS	NO			40WEEKS+2DAYS	NVD
199	20	1746329	PRIMI	0.19	15WEEKS	NO			39WEEKS	LSCS
200	19	1658378	PRIMI	0.02	19WEEKS+5DAYS	YES	31WEEKS+5DAYS	GHT	37WEEKS	LSCS