“FIRST TRIMESTER AND MIDTRIMESTER UTERINE ARTERY DOPPLER SONOGRAPHY IN PREDICTING PREECLAMPSIA AND IUGR”

Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical University

In partial fulfilment of the requirement for the award of the Degree of

M.S. OBSTETRICS AND GYNAECOLOGY

BRANCH II

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

INSTITUTE OF OBSTETRICS AND GYNAECOLOGY,

GOVERNMENT HOSPITAL FOR WOMEN & CHILDREN,

MADRAS MEDICAL COLLEGE.

APRIL - 2018

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"FIRST TRIMESTER AND MIDTRIMESTER UTERINE ARTERY DOPPLER SONOGRAPHY IN PREDICTING PREECLAMPSIA AND IUGR"** is the bonafide original work done by **Dr.PRIEYADHARSHINI.J**, post graduate in the Department of Obstetrics and Gynaecology, under the guidance of **Dr.S.VIJAYA, MD, DGO.,** Professor, Institute of Social Obstetrics and Gynaecology, Kasturba Gandhi Hospital, Madras Medical College, Chennai, towards partial fulfillment of the requirement of the Tamil Nadu Dr. M.G.R Medical University for the award of M.S Degree in Obstetrics and Gynaecology, April 2018. The period of post graduate study is from June 2015 to June 2018.

GUIDE **DIRECTOR**

Prof. Dr. S. VIJAYA, MD, DGO
Professor,
ISO-KGH

Prof Dr. T.K.SHAANTHY GUNASINGH, MD, DGO
Professor, Director and Superindent,
IOG

Prof R.NARAYANABABU MD, DCH
Dean
Madras Medical College.

DECLARATION

I solemnly declare that this dissertation **"FIRST TRIMESTER AND MIDTRIMESTER UTERINE ARTERY DOPPLER SONOGRAPHY IN PREDICTING PREECLAMPSIA AND IUGR"** was prepared by me under the guidance and supervision of **Dr.S.VIJAYA, MD, DGO.,** Professor, Institute of Social Obstetrics and Gynaecology, Kasturba Gandhi Hospital, Madras Medical College, Triplicane, Chennai.

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

Place: Chennai

Date: **DR.PRIEYADHARSHINI.J**

ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank **Dr.R.Narayana Babu, MD, DCH.,** Dean, Madras Medical College, for allowing me to use the facilities and clinical materials available in the hospital.

I extend my sincere thanks and gratitude to **Dr.T.K.Shaanthy Gunasingh, MD, DGO.,** Director and Superintendent, IOG, for granting me permission to utilize the facilities of the institute for my study.

I am extremely grateful to our beloved Professor, **Dr.S.Vijaya, MD, DGO.,** Professor of Obstetrics & Gynaecology, ISO-KGH, for her valuable guidance, motivation and encouragement given during the study.

I humbly thank all the Professors and Assistant Professors of Government Kasturba Gandhi Hospital, Triplicane and IOG, Egmore, for all their help during the course of the study.

My sincere thanks to my statistician **Mrs.Rebecca,** who patiently helped me in analysing the results of this study.

My special thanks to my husband **Dr.N.S.JEYARAM** and my friend **Dr.Aravindh Rajha**, for their physical help and moral support without which nothing would have been possible.

I am immensely grateful to all the patients who took part in the study.

TABLE OF CONTENTS

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Prieyadharshini.J.
Post Graduate in MS O & G
Institute of Social Obstetrics & Gynaecology
Madras Medical College
Chennai 600 005

Dear Dr. Prieyadharshini.J.,

The Institutional Ethics Committee has considered your request and approved your study titled **"FIRST TRIMESTER AND MIDTRIMESTER UTERINE ARTERY DOPPLER SONOGRAPHY IN PREDICTING PREECLAMPSIA AND IUGR" - NO.29122016 (II).**

The following members of Ethics Committee were present in the meeting hold on **19.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

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

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

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

URKUND

Urkund Analysis Result

Analysed Document: THESIS revised.docx (D31516202)
Submitted: 10/20/2017 10:52:00 PM
Submitted By: prieyadharshini@gmail.com
Significance: 0 %

Sources included in the report:

Instances where selected sources appear:

0

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"FIRST TRIMESTER AND MIDTRIMESTER UTERINE ARTERY DOPPLER SONOGRAPHY IN PREDICTING PREECLAMPSIA AND IUGR"** of the candidate **Dr.PRIEYADHARSHINI.J**, with Registration Number **221516016** for the award of **MS Branch-II,** in **Obstetrics & Gynaecology.** I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the upload thesis file contains from introduction to conclusion pages and result shows **0% (Zero percentage)** of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

INTRODUCTION

Hypertensive disorders complicate 5 to 10% of all pregnancies and together it forms one member of the deadly triad, along with haemorrhage and infection, which contribute greatly to maternal morbidity and mortality rates[1]. Preeclampsia is a multisystem disorder and represents a major threat to foetus and mother when it emerges[2]. Apart from its most dreaded complication of progressing into eclampsia, preeclampsia by itself can result in substantial perinatal and maternal morbidity.

It has been reported that the major cause of both maternal and fetal morbidity and mortality is preeclampsia (Bringman et al., 2006). It has been estimated that more than 14% (58,000) of maternal deaths/year worldwide are due to eclampsia and preeclampsia, but in developed countries, it mainly affects fetus[3]. The incidence of preterm birth due to preeclampsia is around 15%[4].

The trophoblast normally invades the decidual portion of the spiral arteries beginning by eighth week and this invasion is usually complete by the thirteenth week. After this time the second stage of spiral artery invasion starts in, whereby the myometrial portion of the spiral arteries are similarly invaded by the trophoblast. This is usually completed by 18 to 19 weeks but may be delayed upto 22 to 24 weeks. In an overwhelming majority of preeclamptics, this transformation does not occur in the spiral artery bed leading to increased resistance to flow into the intervillous space. The method of choice to indirectly monitor the status of spiral artery bed is by uterine artery waveform[4]. Increased uterine artery velocimetry determined by Doppler ultrasound in the first and middle trimester should provide indirect evidence of this process and thus serve as a predictive test for preeclampsia. Performing uterine artery

Doppler studies at 23- 26 weeks' gestation instead of 19- 22 weeks' gestation increases the predictive value for adverse pregnancy outcomes[6].

In the non-pregnant state uterine artery Doppler shows low peak flow velocity and early diastolic notch. At 18 to 20 weeks, there is high flow with no diastolic notch. Impaired uterine artery flow is considered when there are high resistance uteroplacental waveforms and the presence of diastolic notch which is the manifestation of arterial vessel tone and represents elasticity of the vessel and vasospasm. It disappears in the second trimester. A high resistance pattern is associated with higher rate of pregnancy complication with a 70% chance of developing protienuric hypertension and a 30% chance of a coexisting small for gestational age fetus[7]. Although several studies have used uterine artery doppler as a screening tool for preeclampsia and fetal growth restriction in unselected population, a debate continues as to its value. Varying sensitivities are obtained depending on the type of Doppler used, the sampling site, the definition of abnormal uterine artery resistance, gestational age of assessment and different end points[7].This study helps to evaluate the usefulness of first and midtrimester uterine artery Doppler study in both high risk and low risk women to predict preeclampsia.

AIMS AND OBJECTIVES OF THE STUDY

- To evaluate the usefulness of uterine artery doppler screening in first and mid trimester to predict the risk for preeclampsia and IUGR.
- To know the sensitivity and specificity of uterine artery Doppler indices(Pulsatility index and diastolic notching) in prediction of preeclampsia in pregnant women
- To know the outcome of pregnancy and its relation with the uterine artery Doppler indices.

REVIEW OF LITERATURE

History

The interesting history of hypertensive disorders in pregnancy is probably as old as human existence. From ancient times, convulsions were found in pregnancy towards term, during labour and postpartum. Indian Atharvaveda and Sushruta both mention about preeclampsia and eclampsia. Hippocrates had also recognised the grave prognosis of convulsions occurring during childbirth and differentiated it from epilepsy.

The disorder was first recognised almost 2000 years ago. Celsus described pregnant women with seizures that abated with delivery. This disorder was termed eclampsia and for two thousand years was considered a pregnancy specific seizure disorder.

In the late 17^{th} century, obstetrician Francis Mauericeua identified preeclampsia as a specific disorder related to pregnancy. He observed that the convulsions often cease after delivery and recommended prompt termination of pregnancy as the best treatment.

In the late 1800s the association of initial protienuria and later increased blood pressure with eclampsia was recognised. It was also noted that women with increased blood pressure and urinary protein antedated the seizures. From this came the term preeclampsia..

Later Young in 1974 attributed preeclampsia to the placental toxin that was elaborated in the area of red infarct in the placenta and termed preeclampsia as ‘Toxemia of pregnancy’. JCM Browne and Veale in 1953 showed the presence of

placental ischemia in pregnancy induced hypertension. About 10 years ago, Roberts et al formerly proposed that maternal endothelial dysfunction is the key event resulting in the diverse clinical manifestations of preeclampsia[9].

The first pulsed wave Doppler equipment was developed by Seattle research team in 1966. Outstanding contribution was made by Donand Baker, Dennis Watkins and John Reid. Duplex Doppler techniques allowed the ultrasound operator to determine deep fetal and maternal circulation could be studied.

Campbell, a pioneer and consistent leading light in obstetric sonography, was the first to explore the potential of uterine artery waveforms in predicting preeclampsia. Initially, he and his colleagues used a handheld continuous wave Doppler device to find the characteristic waveform at about 18weeks. Although his initial results were encouraging with regard to its predictive ability for preeclampsia, others initially could not repeat his results. However, it became clear that the continuous wave Doppler did not allow an ability to pinpoint the sampling site (as with pulse wave Doppler), and, most importantly, a good 25% of patients who initially have abnormal Doppler at 18weeks' do convert over to a normal waveform by 24weeks'. These late converters do not have the same predilection for preeclampsia as those whose waveforms remain abnormal at 24weeks[10].

HYPERTENSIVE DISORDERS IN PREGNANGY

The term ‘Hypertension in Pregnancy is commonly used to describe a wide spectrum of patients who may have only mild elevations in blood pressure (BP)or severe hypertension with various organ dysfunctions.

Incidence

Hypertensive disorders complicate 5 - 10 percent of all pregnancies. In India, incidence is 5-15%[11], incidence being more in nullipara, around 15% and in multiparas around 10%[9,11]. The incidences of the various types of hypertensive disorders in pregnancy are given in Table 1.

TABLE-1 . Incidence of Hypertensive disorders in Pregnancy.

Gestational hypertension	**5%**
Preeclampsia	5-7%
Eclampsia	0.5-2%
Preeclampsia superimposed on chronic hypertension	25%
Chronic hypertension	1-2%

Classification of hypertensive disorders in pregnancy

The working group classification of hypertensive disorders complicating pregnancy describes four types of hypertensive disease[1].

- Gestational hypertension—formerly termed Pregnancy-induced Hypertension.
- Preeclampsia and Eclampsia syndrome
- Preeclampsia syndrome superimposed on chronic hypertension
- Chronic hypertension

Definitions(National high blood pressure education program working group report on high blood pressure in pregnancy 2000)[1].

Gestational hypertension:

- Systolic BP 140 or diastolic BP 90 mm Hg for the first time during pregnancy
- No proteinuria
- Blood pressure returns to normal before 12 weeks postpartum
- Final diagnosis made only postpartum
- May have other signs or symptoms of preeclampsia. For example, epigastric discomfort or thrombocytopenia

Preeclampsia:

- **Minimum criteria:**

Blood pressure 140/90 mm Hg after 20 weeks' gestation

Proteinuria 300 mg/24 hours or 1+ dipstick

- **Increased certainty of preeclampsia:**

Blood pressure 160/110 mm Hg

Proteinuria 2.0 g/24 hours or 2+ dipstick

Serum creatinine >1.20 mg/dl unless known to be previously elevated

Microangiopathichemolysis—increased LDH

Platelets < 1,00,000/l

Elevated serum transaminase levels—ALT or AST

Persistent headache or other cerebral or visual disturbance

Persistent epigastric pain

Eclampsia:

- Seizures that cannot be attributed to other causes in a woman with preeclampsia

Superimposed preeclampsia on chronic hypertension:

- New-onset proteinuria of 300 mg/24 hours in hypertensive women but no proteinuria before 20 weeks' gestation
- A sudden increase in proteinuria or blood pressure or platelet count < 100,000/l in women with hypertension and proteinuria before 20 weeks' gestation

Chronic hypertension:

- Blood pressure 140/90 mm Hg before pregnancy or diagnosed before 20 weeks' gestation not attributable to gestational trophoblastic disease or

- Hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks postpartum

Risk factors for preeclampsia[13, 14]

- **Pregnancy associated factors**
  - Chromosomal abnormalities
  - Hydatidiform mole
  - Hydropsfetalis
  - Multifetal pregnancy
  - Structural congenital anomalies
- **Maternal specific factors**
  - Age less than 20 years
  - Age greater than 35 years
  - Nulliparity
  - Preeclampsia in a previous pregnancy
  - Family history of preeclampsia
  - Specific medical conditions: gestational diabetes, type 1 diabetes, obesity, chronic hypertension, renal disease, thrombophilias

FETAL FEATURES OF PRE-ECLAMPSIA

Ultrasound features of pre-eclampsia demonstrated in the fetus include:

- Fetal growth restriction
- Changes in amniotic fluid volume (oligohydramnios)
- Abnormal Doppler waveforms

Severe growth restriction results in premature delivery, with the related risk of long term respiratory and neuro developmental problems. There is an increased

perinatal mortality, particularly in very low birth weight infants. Intrauterine hypoxia which can occur in FGR may contribute to the risk for cerebral palsy. If central redistribution of blood flow in the fetus occurs, there can be ischemia of the gut leading to necrotizing enterocolitis (Loughna 2006:266).

MATERNALCOMPLICATIONS

Maternal complications of pre-eclampsia include:

- Placental abruption (1-4%)
- HELLP syndrome (10-20%)
- Pulmonary oedema (2-5%)
- Acute renal failure (1-5%)
- Eclampsia (<1%)
- Death

Death associated with pre-eclampsia-eclampsia may be due to cerebrovascular events, renal or hepatic failure or HELLP syndrome.

NEONATALCOMPLICATIONS

Evidence suggests that pre-eclampsia often coexists with FGR (Papageorghiou*etal.*,2008: 367). The report on Confidential Enquiry into Stillbirths and Deaths in Infancy cites one in six stillbirths that occur in pregnancies complicated by maternal hypertension.

Fetal complications of preeclampsia include:

- Preterm delivery (15-67%)
- FGR (10-25%)
- Hypoxia-neurologic injury (<1%)
- Perinatal death (1-2%)

Theories for causation of preeclampsia

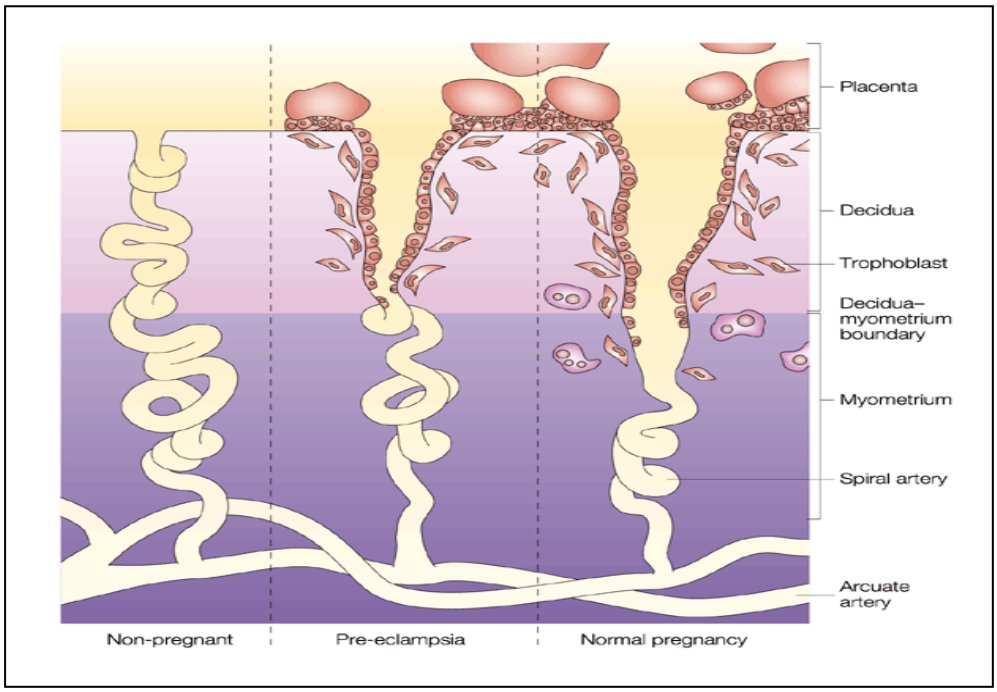
DISEASE OF THEORIES WITHOUT ANY CAUSE[15]. Writings describing eclampsia have been traced as far back as 2200 BC (Lindheimer and colleagues, 1999).It is not surprising that a number of mechanisms have been proposed to explain its causes. Many of the absurd and especially the dangerous thankfully have been discarded. According to Sibai (2003), currently plausible potential causes include the following[1].

- Abnormal trophoblastic invasion of uterine vessels
- Immunological factors
- Endothelial cell activation
- Genetic influences
- Dietary deficiencies

Abnormal trophoblastic invasion of uterine vessels

Preeclampsia is characterised by incomplete trophoblastic invasion[1, 15]. With shallow invasion, only the decidual vessels that become lined with endovascular trophoblasts. As a result of which the deeper myometrial arterioles do not lose their endothelial lining and musculoelastic tissue, and their external diameter is only half that of vessels in normal placenta. In the process of pseudovasculogenesis or vascular mimicry, the cytotrophoblast differentiates from an epithelial phenotype to an endothelial phenotype, as shown in Figure1.

FIGURE-1.Normal and abnormal trophoblastic invasion of uterine vessels.



De wolf and co-workers (1980) observed that early preeclamptic changes included endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells, medial necrosis and lipid accumulation first in myointimal cells and later in macrophages. Such lipid laden cells and associated findings have been termed Atherosis. Aneurismal dilatations develop in the vessels affected by atherosis and are frequently found in spiral arterioles which have failed to undergo normal adaptation. Luminal narrowing in the spiral arteriolar by atherosis causes diminished which eventually leads to the preeclampsia syndrome[1, 16].

IMMUNOLOGICAL FACTORS

This can be explained by

- **Immune dysregulation:** During pregnancy, there is immune tolerance to paternal derived placental and fetal antigens. Loss of this tolerance or probably its dysregulation is another theory cited for preeclampsia. The microscopic changes at the maternal placental interface are suggestive of acute graft rejection. The risk

of preeclampsia is enhanced in circumstances where formation of blocking antibodies to placental antigenic sites provided by the placenta is unusually great compared with the amount of antibody, as with multiple fetuses.

- **Immune maladaptation:** Dekker and Sibai (1998) have reviewed the possible role of immune maladaptation in the pathophysiology of preeclampsia. In women destined to develop preeclampsia at early second trimester, have a lower proportion of helper T cells compared with that of women who remain normotensive. This th2 dominance with th1/th2 imbalance may be mediated by adenosine which is found in higher serum levels in preeclamptic compared with normotensive women. These helper t lymphocytes secrete specific cytokines that promote implantation, and their dysfunction may favour preeclampsia[1, 16].

Endothelial cell activation

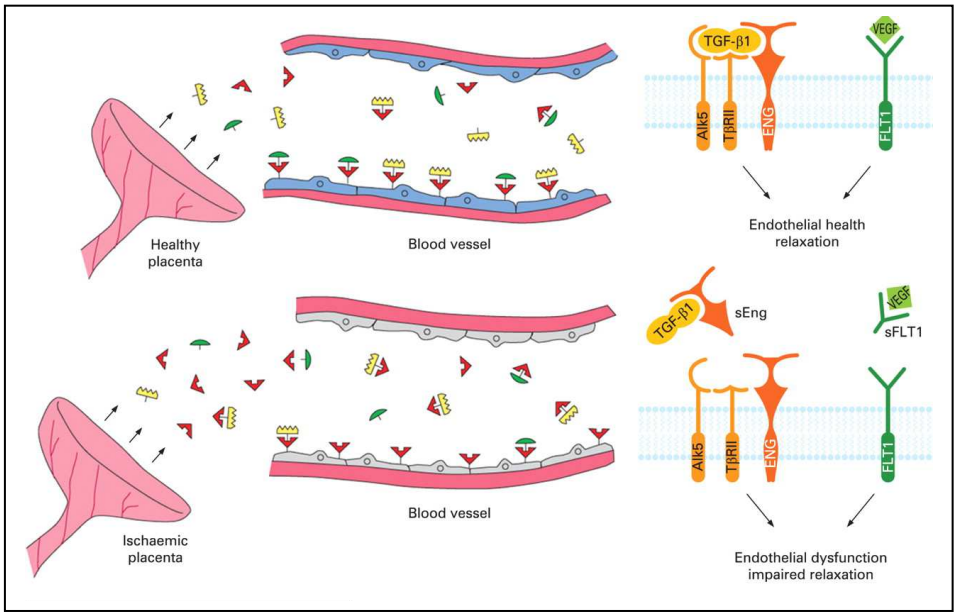
Inflammatory changes are thought to bea continuation of stage 1 changes caused by defective placentation. In response to ischemic changes certain placental factors released which causes, a cascade of events in which antiangiogenic factors and other inflammatory mediators provoke endothelial cell injury.

Cytokines such as tumor necrosis factor and the interleukins contribute to the oxidative stress associated with preeclampsia. Oxidative stress leads to formation of free radicals which lead to formation of self-propagating lipid peroxides which in turn generate highly toxic radicals that injure endothelial cells, modify their nitric oxide production and interfere with prostaglandin balance.

Angiogenic imbalance is due to the excessive amount of anti angiogenic factors like soluble endoglin(seng) and placental soluble fms like tyrosine kinase 1(sflt-1). The production of these factors is stimulated by the hypoxia at the uteroplacental interface.

Sflt-1 antagonises vascular endothelial growth factor (vegf) and placental growth factor (plgf), blocking the induction of nitric oxide and vasodilator prostacyclins in the endothelial cells as shown in Figure2.

FIGURE- 2.Endothelial dysfunction in preeclampsia.



A rise in sflt-1 levels and a corresponding drop in vegf and plgf levels can be measured 5 to 6 weeks before the onset of clinical preeclampsia and have been established as predictors for the subsequent development of preeclampsia[1, 17].

Genetic factors

Preeclampsia is a multifactorial, polygenic disorder. Ward and Lindheimer (2009) cite an increased risk for preeclampsia in a patient with family history of preeclampsia in a first degree relative[1]. The below Table 2 represents the incidence of preeclampsia in a given patient if the family history of preeclampsia is found to be positive.

TABLE - 2.Incident risk if patient's first degree relative is preeclamptic.

Relatives with history of preeclampsia	Incident risk in the patient
Mother	20-40%
Sisters	11-37%
Twin sister **Heterozygous** **Monozygous**	 22-47% 60%

This hereditary predisposition a result of inherited gene which control enzymatic and metabolic functions throughout every organ system. Thus the clinical manifestation in any given woman with the preeclamptic syndrome will occupy a spectrum as discussed under the two stage concept. Around 70 genes have been identified for their probable association. Polymorphisms of the genes for tnf, lymphotoxin and interleukin-1 have been studied with varying results.

Because of heterogeneity of preeclampsia syndrome, and other genetic and environmental factors that interact with its complex phenotypic expression, it is doubtful that any one gene will be found responsible[1].

Genes with Possible Associations with Preeclampsia Syndrome are

- F5(leiden) Factor VLeiden
- AGT (M235T) Angiotensinogen
- NOS3 (Glu 298 Asp) Endothelial nitric oxide
- F2 (G20210A) Prothrombin (factor II)
- ACE (I/DatIntron 16) Angiotensin-converting enzyme

Nutritional factors

First it was postulated that lowered serum magnesium levels during pregnancy might predispose to seizures during pregnancy in susceptible women, such as those with a tendency toward epilepsy (Suter and Klingman, 1957)[8].

An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980. Epidemiological and clinical studies led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high blood pressure and preeclampsia among women with low dietary calcium. An association has been found between preeclampsia and hypocalciuria, low urine calcium to creatinine ratio, hypocalcaemia, low plasma and high membranous calcium, low dietary milk intake. The lowering of serum calcium and the increase of intracellular calcium may cause an elevation of blood pressure in preeclamptic mothers.

PATHOGENESIS

Vasospasm: The concept of vasospasm was advanced by Volhard (1918) based on direct observations of small blood vessels in the nail beds, ocular fundi, and bulbar conjunctivae. It was also proved from histological changes seen in various affected organs. Vascular constriction causes resistance and subsequent hypertension. At the same time, endothelial cell damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen, are deposited subendothelially. With diminished blood flow because of maldistribution, ischemia of surrounding tissues would lead to necrosis, haemorrhage and other end organ disturbances characteristic of the syndrome. Ironically, vasospasm may be worse in women with preeclampsia than in those with the hellp syndrome[1, 16, and 17].

Endothelial cell activation: Over the past two decades, endothelial cell activation has become the centrepiece in the contemporary understanding of the pathogenesis of preeclampsia. Unknown factors, likely from the placenta are secreted into the maternal circulation and provoke activation and dysfunction of the vascular endothelium. The clinical syndrome of preeclampsia is thought to result from this widespread endothelial cell changes. In addition to micro particles, Grundmann and associates have reported that circulating endothelial cell (CEG) levels are significantly elevated four fold in the peripheral blood of preeclamptic women[1, 16, and 17].

The function of intact endothelium

- It primarily takes part in hemostasis and blunts the response of the vascular smooth muscle to vasospasm.
- It also blunts the response of vascular smooth muscle to agonists by releasing nitric oxide.
- The anticoagulant property is exerted by preventing blood clot formation.
- It causes fibrinolysis which is mediated through plasminogen activators.

Damaged or activated endothelial cells secrete substances that promote coagulation and increase the sensitivity to vasopressors. Further evidence of endothelial activation includes the characteristic changes in glomerular capillary endothelial morphology, increased capillary permeability, and elevated blood concentrations of substances associated with such activation[17].

Role of vasoactive agents: Normally pregnant women have refractoriness to vasopressor substances viz., angiotensin II, norepinephrine, and vasopressin. In preeclampsia this refractoriness is lost and there is increased vascular reactivity[1].

The vasoactive substances which bring about these changes are

- **Prostaglandins**: A number of prostaglandins are central to the pathophysiology of the preeclampsia syndrome. Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to decreased vascular responsiveness mediated by vascular endothelial prostaglandin synthesis. When compared with normal pregnancy, endothelial prostacyclin (pgi2) production is decreased in preeclampsia.
- **Endothelins**: These are potent vasoconstrictors with 21 amino acid peptides and endothelin 1 is the primary isoform produced by human endothelium. Plasma ET1 is the primary isoform produced by human endothelium. Plasma ET1 is increased in normotensive pregnant women, but women with preeclampsia have even higher levels. Interestingly treatment of preeclamptic women with magnesium sulphate lowers ET1 concentration[1, 17].

Angiogenic factors: Placental vasculogenesis is evident by 21days after conception. Angiogenic imbalance is used to describe excessive amounts of antiangiogenic factors that are hypothesised to be stimulated by worsening hypoxia at the uteroplacental interface.

Trophoblastic tissue of women destined to develop preeclampsia overproduces at least two angiogenic peptides that enter the maternal circulation.

- **Soluble fms like tyrosine kinase 1**(sFlt-1): it is a variant of the sflt 1 receptor for placental growth factor and vascular endothelial growth factor. Increased maternal sflt 1 levels inactivate and decrease circulating free plgf and vegf concentrations leading to endothelial dysfunction. Sflt 1 level begins to increase in maternal serum months before preeclampsia is evident[1, 16].

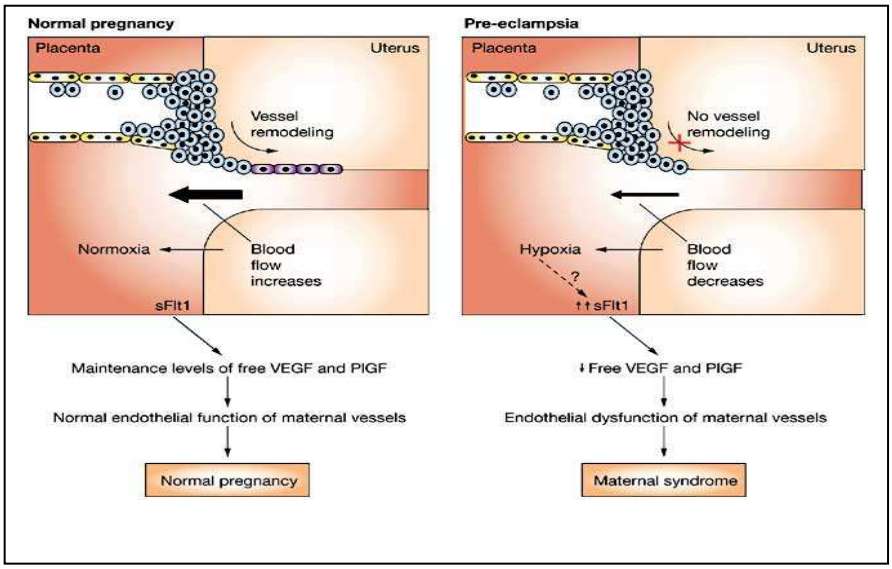
- **Soluble endoglin** (seng): it is a placental derived 65 Kda molecule that blocks endoglin, also called cd105, which is a co receptor for the tgf b family. This soluble form of endoglin inhibits various tgf b isotopes from binding to endothelial receptors and result in decreased endothelial nitric oxide dependent vasodilation[1, 16].

The cause of placental overproduction of antiangiogenic proteins remains an enigma. The soluble forms are not increased in the fetal circulation or amniotic fluid, and their levels in maternal blood dissipate after delivery. Widmer and associate concluded that retrospective studies shows that third trimester elevation of sflt 1 levels and decreased plgf concentration correlate with preeclampsia development after 25 weeks as shown in Figure 3.

Role of nitric oxide: This is a potent vasodilator which is synthesised from L arginine by endothelial cells of blood vessels of the mother and also fetus. It maintains the normal low pressure vasodilated state which is characteristic of fetoplacental perfusion.

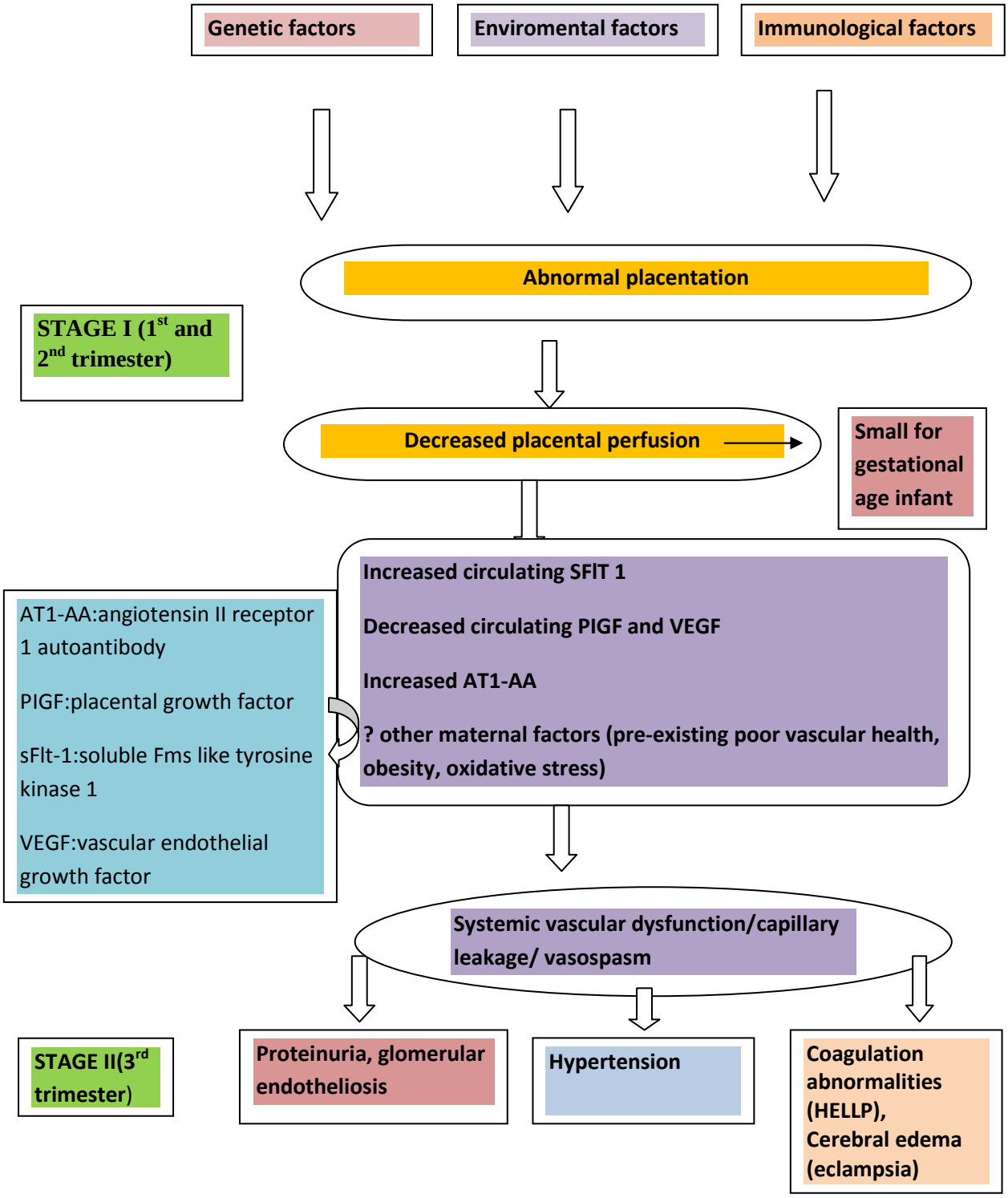
The effect of nitric oxide production in preeclampsia is unclear. It appears that the syndrome is associated with decreased endothelial nitric oxide synthetase expression thus increasing nitric oxide inactivation. These responses may be race related, with African American women producing more nitric oxide[1, 17].

FIGURE-3[45].Angiogenic factors in pathogenesis of preeclampsia.



In summary the cause of preeclampsia remains obscure, although more and more evidence is accruing to support the hypothesis that placenta plays a crucial role. Some describe aetiology as a two-step process. The first as asymptomatic stage (placental) involves abnormal placentation which is then followed by placental elaboration of soluble factors that enters the maternal circulation and causes widespread endothelial dysfunction as shown in Figure 4.

FIGURE- 4[15]. Pathogenesis of preeclampsia



SCREENING FOR HYPERTENSIVE DISORDERS OF PREGNANCY

Preeclampsia and intrauterine growth restriction remain important causes of maternal and perinatal morbidity and mortality[30, 31, 32]. Maternal complications of preeclampsia include coagulopathy, renal and liver failure and stroke[32]. Adults who were affected by intrauterine growth restriction in utero are at increased risk for cardiovascular disease, hypertension and type 2 diabetes[33, 34].The substantial loss of life as well as serious long term sequel of preeclampsia could be largely eliminated if we could accurately predict, prevent and better manage preeclampsia. It is evident at the present time that there is no clinically useful test to accurately predict preeclampsia.

Delineation of a reliable and safe screening test for preeclampsia has been an investigators dream for many decades and an extensive systematic review of most of these tests was published in 2004. 87 out of 7,191 potentially relevant articles that described a variety of biophysical and biochemical tests assessing their usefulness in predicting preeclampsia were analysed. The conclusion was that there were no clinically useful screening tests to predict the development of preeclampsia[18].

Attempts have been made to identify early markers of faulty placentation, impaired placental perfusion, endothelial cell activation and dysfunction, and activation of coagulation.

The list of predictive factors evaluated during the past three decades is legion. Although most have been evaluated in the first half of pregnancy, some have been tested as predictors of severity in the third trimester. Others have been used to forecast recurrent preeclampsia. Table 3 shows the list of markers studied since 1980s for the prediction of development of preeclampsia[20].

TABLE-3.List of markers for prediction of preeclampsia.

Placental perfusion and vascular resistance dysfunction related tests:
Mean blood pressure in second trimester
Roll over test
Isometric exercise test
Platelet angiotensin II binding
24 hr ambulatory blood pressure monitoring
Doppler ultrasound
Fetoplacental unit endocrinology dysfunction- related tests:
HCG
Alpha fetoprotein
Estriol
Inhibin A
Pregnancy associated plasma protein A
activinA
corticotrophin release hormone
Renal dysfunction related tests:
Serum uric acid
Microalbuminuria
Urinary calcium excretion
Urinary kallikrein
Microtransferrinuria
Endothelial and oxidant stress dysfunction related tests/ inflammatory markers:
Platelet count
Fibronectin
Platelet activation and endothelial cell adhesion molecules
Endothelin
Prostacyclins
Thromboxane
Homocysteine
Serum lipids
Insulin resistance
Antiphospholipid antibodies
Plasminogen activator inhibitor
Placental growth factor
Leptin
Total proteins
Antithrombin III
Haptoglobin
Atrial natriuretic peptide
Beta2 microglobulin
CRP
Genetic markers

1) Vascular Resistance Testing and Placental Perfusion

Most of these are cumbersome, time consuming, and overall inaccurate.

- **Provocative Pressor Tests:** Three tests have been extensively evaluated to assess the blood pressure rise in response to a stimulus. The roll-over test measures the hypertensive response in women at 28 to 32 weeks who are resting in the left lateral decubitus position and then roll over to the supine position. Increased blood pressure signifies a positive test. The isometric exercise test employs the same principle by squeezing a handball. The angiotensin II infusion testis performed by giving incrementally increasing doses intravenously, and the hypertensive response is quantified. In their updated metaanalysis, Conde-Agudelo and associates (2014) found sensitivities of all three tests to range from 55 to 70 percent, and specificities approximated 85 percent.
- **Uterine Artery Doppler Velocimetry:** Faulty trophoblastic invasion of the spiral arteries results in diminished placental perfusion and upstream increased uterine artery resistance. Increased uterine artery velocimetry determined by Doppler ultrasound in the first two trimesters should provide indirect evidence of this process and thus serve as a predictive test for preeclampsia (Gebb, 2009a, b;Groom, 2009). Increased flow resistance results in an abnormal waveform represented by an exaggerated diastolic notch. These have value for fetal-growth restriction but not preeclampsia (American College of Obstetricians and Gynecologists, 2013a). Several flow velocity waveforms, alone or in combination have been investigated for preeclampsia prediction. In some of these, predictive values for early-onset preeclampsia were promising (Herraiz, 2012).At this time, however, none is suitable for clinical use (Conde-Agudelo, 2014; Kleinrouweler, 2012; Myatt, 2012a).

- **Pulse Wave Analysis:** Like the uterine artery, finger arterial pulse "stiffness" is an indicator of cardiovascular risk. Investigators have preliminarily evaluated its usefulness in preeclampsia prediction (Vollebregt, 2009).

2)Fetal-Placental Unit Endocrine Function

Several serum analytes have been proposed to help predict preeclampsia. Many of these gained widespread use in the 1980s to identify fetal malformations and were also found to be associated with other pregnancy abnormalities such as neural-tube defects and aneuploidy. Although touted for hypertension prediction, in general, none of these tests has been shown to be clinically beneficial for that purpose.

3) Tests of Renal Function

- **Serum Uric Acid:** One of the earliest laboratory manifestations of preeclampsia is hyperuricemia (Powers, 2006). It likely results from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption and decreased secretion (Lindheimer, 2008a). It is used by some to define preeclampsia but Cnossen and coworkers (2006) reported that its sensitivity ranged from 0 to 55 percent, and specificity was77 to 95 percent.
- **Microalbuminuria.** As a predictive test for preeclampsia, microalbuminuria has sensitivities ranging from 7 to 90 percent and specificities between 29 and 97 percent (Conde-Agudelo,2014). Poon and colleagues (2008) likewise found unacceptable sensitivity and specificity for urine albumin:creatinine ratios.

4) Endothelial Dysfunction and Oxidant Stress

Endothelial activation and inflammation are major participants in the pathophysiology of the preeclampsia syndrome. As a result, compounds such as those listed in Table-3

are found in circulating blood of affected women, and some have been assessed for their predictive value.

- **Fibronectins:** These high-molecular-weight glycoproteins are released from endothelial cells and extracellular matrix following endothelial injury (Chavarria, 2002). More than 30 years ago, plasma concentrations were reported to be elevated in women with preeclampsia (Stubbs, 1984). Following their systematic review, however, Leeflang and associates (2007) concluded that neither cellular nor total fibronectin levels were clinically useful to predict preeclampsia.
- **Coagulation Activation:** Thrombocytopenia and platelet dysfunction are integral features of preeclampsia. Platelet activation causes increased destruction and decreased concentrations, and mean platelet volume rises because of platelet immaturity (Kenny, 2014). Although markers of coagulation activation are increased, the substantive overlap with levels in normotensive pregnant women stultifies their predictive value.
- **Oxidative Stress:** Increased levels of lipid peroxides coupled with decreased antioxidant activity have raised the possibility that markers of oxidative stress might predict preeclampsia. For example, malondialdehyde is a marker of lipid peroxidation. Other markers are various prooxidants or their potentiators. These include iron, transferrin, ferritin, blood lipids, including triglycerides, free fatty acids and lipoproteins and antioxidants such as ascorbic acid and vitamin E (Bainbridge,2005; Conde-Agudelo, 2014; Mackay, 2012; Powers, 2000).These have not been found to be predictive.

Hyperhomocysteinemia causes oxidative stress and endothelial cell dysfunction and is characteristic of preeclampsia. Although women with elevated serum homocysteine

levels at midpregnancy had a three to fourfold risk of preeclampsia, these tests have not been shown to be clinically useful predictors (D'Anna, 2004; Mignini, 2005; Zeeman, 2003).

5)Circulating Angiogenic Factors.

Host of recent studies throw light on the role of angiogenic proteins in the pathogenesis. There is an imbalance of pro and antiangiogenic factors. Two antiangiogenic factors implicated are soluble fms like tyrosine kinase1receptor/ sflt 1 and solubleendoglin /seng 1 whose levels are elevated in women with preeclampsia. Pro angiogenic proteins decreased in preeclampsia are vascular endothelial growth factor/vegf and placental growth factor/ plgf. Vegf- endothelial specific mitogen promotes angiogenesis mediated by 2 high affinity receptor tyrosine kinases vegfr-1 (flt 1) and vegfr- 2 (kinase insert domain region) selectively expressed on vascular endothelial cell surface. Vegfr 1 has 2 isoforms – a transmembranous isoform and a soluble isoform (svegfr 1 or sflt 1). Sflt 1 can antagonise biological activity of vegf and also of plgf. sflt 1 is elevated during clinical preeclampsia. This is associated with fall in free plgf and vegf.

Soluble endoglin (antiangiogenic) which is tgf b1 co-receptor impairs tgfb1 binding to cell surface receptors and decrease endothelial nitric oxide signalling. Recently seng is demonstrated in high concentration in sera of pregnant women, increased in preeclampsia. Urine screening with plgf assay followed by blood confirmation with sflt 1/plgf can be done. Recently isoforms of sflt 1-14 produced by the placenta is found.Vegf165b is a variant of vegf pre mRNA is upregulated in maternal circulation in normal pregnancy but this increase is delayed or diminished in women who develop preeclampsia. Sensitivities for all cases of preeclampsia ranged from 30 to 50

percent and specificity was about 90 percent. Their predictive accuracy was higher for early-onset preeclampsia. These preliminary results suggest a clinical role for preeclampsia prediction.

6) Cell-Free Fetal DNA

Cell-free fetal DNA can be detected in maternal plasma. It has been reported that fetal maternal cell trafficking is increased in pregnancies complicated by preeclampsia (Holzgreve, 1998). It is hypothesized that cell free DNA is released by accelerated apoptosis of cytotrophoblasts (DiFederico, 1999). From their review, Conde-Agudeloand associates (2014) concluded that cell-free fetal DNA quantification is not yet useful for prediction purposes.

7) Proteomic, Metabolomic, and TranscriptomicMarkers

Methods to study serum and urinary proteins and cellular metabolites have opened a new vista for preeclampsia prediction.

- **Placental protein 13/pp13**: It is the member of galectin family expressed predominantly by the placenta (syncytiotrophoblast) thought to be involved in implantation and maternal artery remodelling. Maternal serum 1st trimester pp 13 helps in predicting preeclampsia mainly the early onset preeclampsia. Various studies show that maternal serum pp 13 concentration are significantly reduced during the first trimester among women who subsequently develop preeclampsia – early onset.

ROLE OF DOPPLER ULTRASONOGRAPHY IN PREGNANCY INDUCED HYPERTENSION

The condition of pregnancy induced hypertension is often predictable with twin pregnancy, diabetes, in elderly women and certain autoimmune diseases and renal diseases like nephritic syndrome. In such conditions, vigilant obstetrician can always suspect and diagnose it early and treat accordingly. However, in some women this condition sets in a subtle way and gradually such women develop severe degree of preeclampsia leading to dreadful complications. Hence in routine antenatal care, if any predictive test can be applied as a screening test for all women, then this dreadful multisystemic condition can be treated in time[1].

Introduction to Doppler Ultrasonography

Doppler ultrasonography makes use of the concepts:

- Doppler Effect
- Doppler Shift

Doppler Effect: When a sound wave hits a moving object, the frequency of the reflected wave depends on the speed and direction of the moving object. When a source of a wave and the observer move closer the frequency of the reflected wave increases and when they move apart, the frequency decreases.

Doppler Shift: It is the difference in the frequency of the emitted and the reflected wave. It is also called frequency shift.

Doppler equation is given by and is shown in Figure 5.

$$fd = \frac{2(fo.cosA)V}{C}$$

fo: incident ultrasound beam frequency

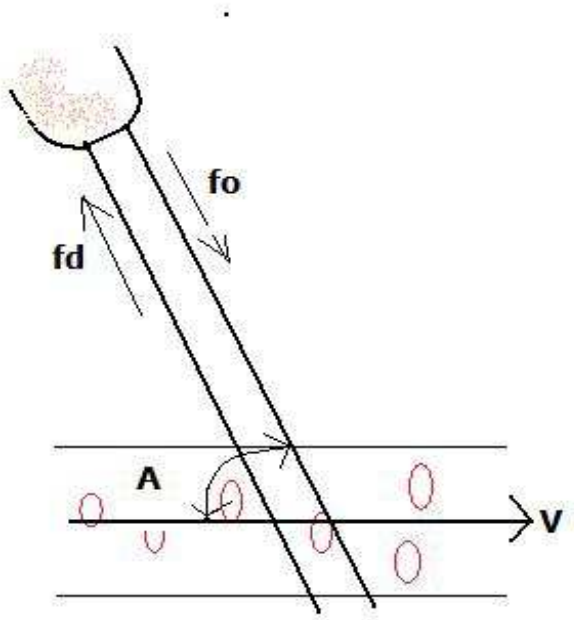
fd: frequency shift

A:angle between the incident ultrasound beam and axis of blood flow

C:speed of sound in medium

V:velocity of blood flow

FIGURE- 5[9].The Doppler shift and the derivation of equation.



The velocity of flow in a particular vascular bed is inversely proportional to the downstream impedance of flow.

The frequency shift depends on

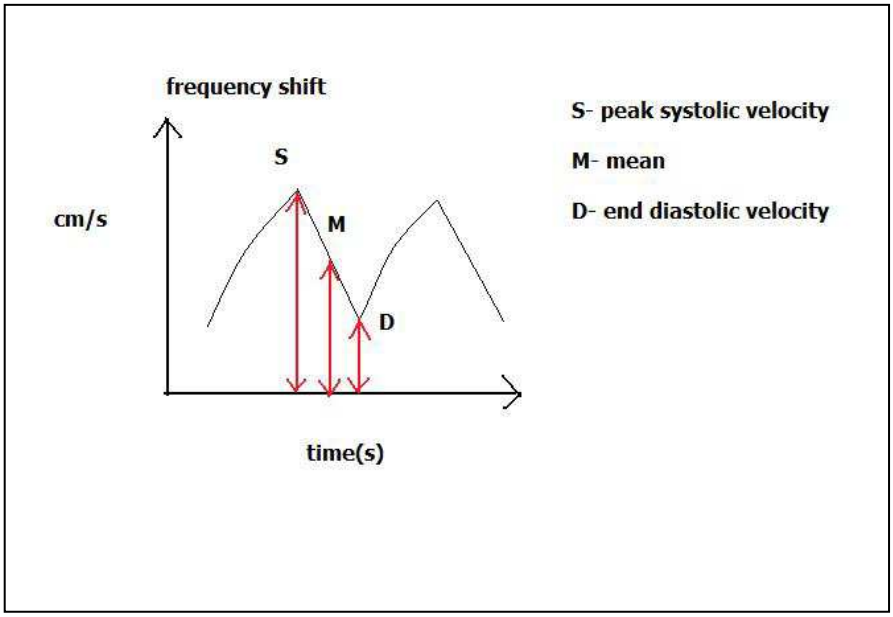
- The downstream impedance to flow and
- The cosine of angle the ultrasound beam makes with blood vessel. If $A=0^0$ $cosA=1$,the maximum velocity and if $A=90^0$, $cosA=0$,there is no Doppler shift as shown in figure-5.

Ideally one should measure velocity with as small an angle as possible. Usually 30-60^0 angle is used.

Doppler indices

Figure-6 shows the waveform obtained from the blood vessel and it has a first peak corresponding to systole(S) and a second peak corresponding to diastole(D). M is the mean of both the systolic and diastolic velocities.

FIGURE 6- .Doppler waveform.



The various Doppler indices used in clinical practice are

- Pulsatility index= peak systolic velocity – end diastolic velocity/mean velocity (S-D/M)

- Resistivity index= peak systolic velocity – end diastolic velocity/systolic velocity (S-D/S)
- Peak systolic velocity/ end diastolic velocity (S/D) ratio
- End diastolic velocity/ mean velocity (D/M) ratio

S/D ratio is simple and describes the rate at which flow velocities fall away during diastole. This closely corresponds to the peripheral resistance to blood flow. Increasing peripheral resistance causes an increase in pulsatility and PI. As peripheral resistance is increased, systolic peak decreases and thus decreased PI. When end diastolic frequencies disappear, D is 0 and S/D is infinity and RI is1.

Doppler modes

- **Continuous wave Doppler:** The transducer assembly contains two elements, one for continuous transmitting and other for receiving. Advantages are that it can be used for vascular diagnosis. E.g. Umbilical artery Doppler velocimetry, external fetal heart rate monitoring. It is inexpensive and has low acoustic energy output. Disadvantage is that it cannot discriminate between different locations from which the signal is originating.
- **Pulsed wave Doppler:** Here the same crystal functions both as transmitter and receiving transducer. The advantage is that it gives velocity information of specific target vessel and the disadvantage is that it fails if the operator is unable to identify the correct location and has sampling limitation and range velocity limitations. It is useful in uterine artery Doppler and assessing fetal circulation.
- **Colour flow Doppler:** It is an extension of pulsed Doppler where colour signal is assigned. It is conventional to use red to designate flow towards the probe and blue away from it. Advantage is that it can detect blood flow velocity in the same

plane and also direction and small blood vessels can be visualised. Disadvantage is that, there is absence of spectral display and absence of colour does not necessarily indicate absence of flow.

- **Power Doppler:** It is a recent development and quantifies and displays flow information as an amplitude of scatter of the ultrasound beam rather than as a frequency shift. The advantage is that the blood flow velocity is independent of the angle of insonation and helpful in high blood flow velocity assessment.

Other modes of Doppler are two dimensional Doppler and high definition Doppler.

Modes of Doppler ultrasound mapping

- Colour flow mapping: Map of vessels are obtained which is superimposed on the grey scale image
- Doppler spectrum: Graph showing flow characteristics as a waveform. These are then quantified as velocities, ratios and indices[9].

Uterine artery Doppler

Rationale for uteroplacental waveform analysis

Uteroplacental waveforms are acquired from the uterine artery by means of colour, pulsed Doppler ultrasound. As it was not always possible to determine whether these waveforms arose from the uterine artery or the arcuate artery by using pulsed wave Doppler alone, they are still commonly referred to as uteroplacental waveforms. With the use of color Doppler, the uterine artery can be reliably identified so that pulsed wave doppler information can be acquired. Failure or poor trophoblastic invasion is characteristic of pre-eclamptic and growth-restricted pregnancies. Assessment of

uterine artery blood flow is an established screening test for these pregnancy problems[7].

Finding the uterine artery waveform

Ideally, the equipment should be designed specifically for obstetric purposes as cardiovascular equipment has high power output levels. Ideally 4 MHz probe has to be selected and the vessel wall filter (also known as the thump filter) has to be set to 50 Hz, the frequency range to 4 kHz and the sweep speed to 5 m /s. It has to be ensured that the balance control is exactly at its midposition and that the gain control is set at about 50% of maximum.

Figure:7 Showing different probes and there specifications.

Use of color flow imaging to identify the bifurcation of the common iliac artery in longitudinal section.

The uterine artery originates from the internal iliac artery and meets the uterus just above the cervix. The main uterine artery branches into the arcuate arteries, which arch anteriorly and posteriorly and extend inward for about one third of the thickness

of the myometrium. They are tortuous and vary in thickness and in the area they supply. The arcuate artery network anastomoses near the midline. The radial arteries arise from this network, are directed towards the uterine cavity, and become spiral arteries when they enter the endometrium[5].

The probe is moved medially and angled slightly towards the symphysis pubis to reveal the uterine artery just medial to the bifurcation, as it ascends toward the uterus. It is conventional to place the uterine artery sample gate of the pulsed wave Doppler at the point of maximal colour brightness close to the bifurcation as shown in Figure 7. When the waveform is seen, the frequency range is altered on the equipment until the waveform fills about two-thirds of the height of the screen. The waveform itself will contain a range of frequencies, represented by a range of differing colours within it as shown in Figure 8. If the waveform obtained appears very bright, contains few colours and the background is noisy, then the Doppler gain is reduced until the optimal balance is obtained[7].

FIGURE-8. Localising uterine artery.

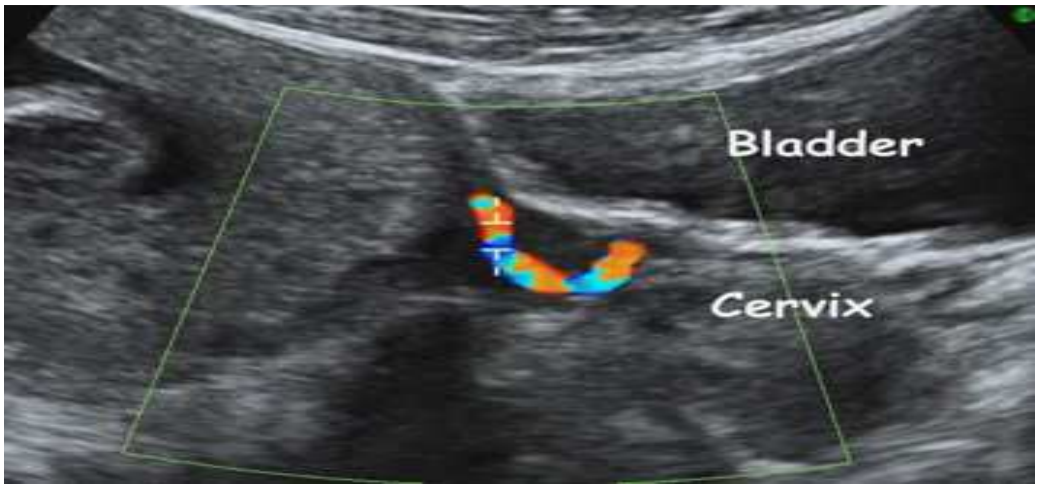
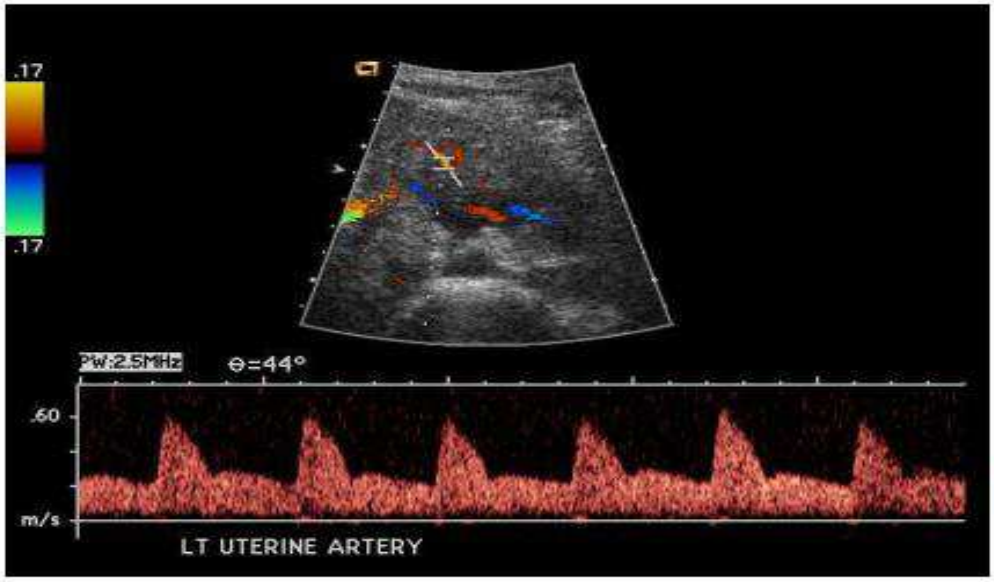


FIGURE:9- .Obtaining uterine artery waveform.(normal waveform)



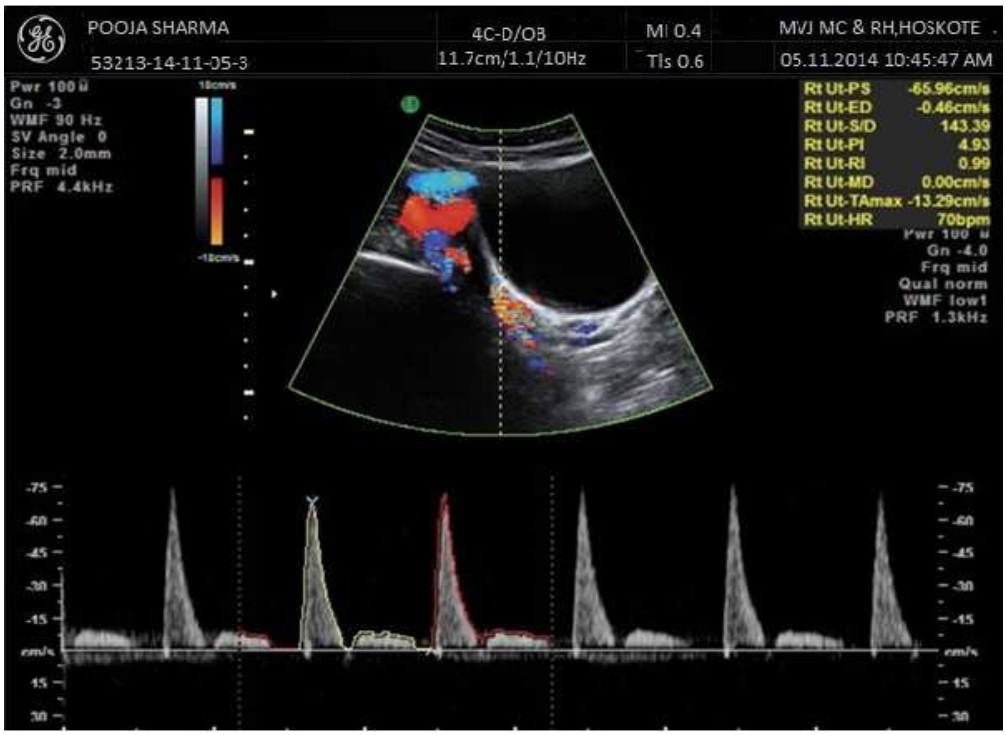


FIGURE: 10 Non pregnant uterine artery wave form

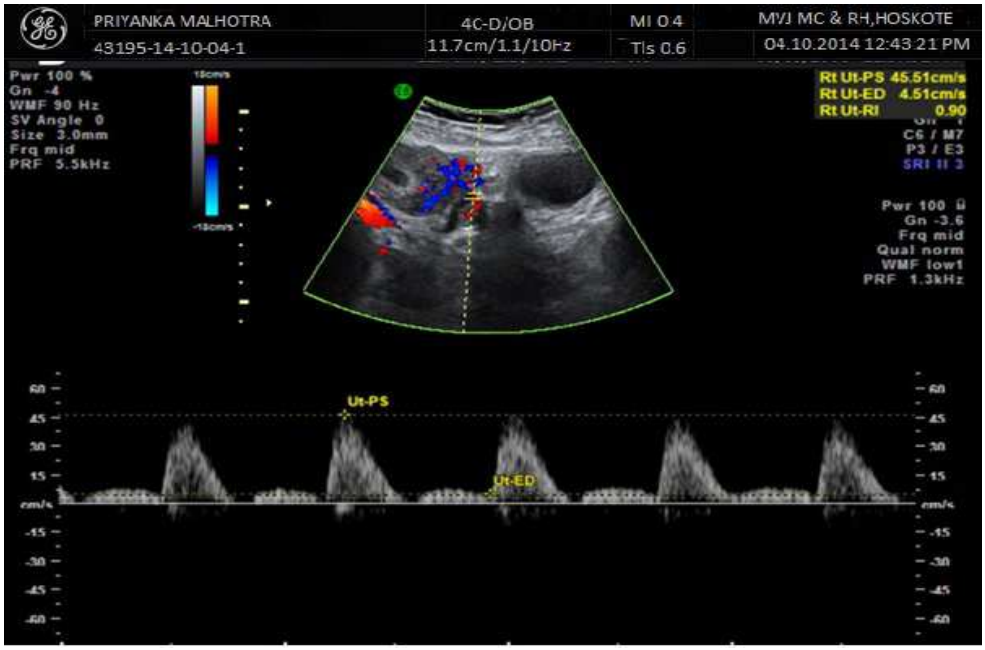


FIGURE: 11 First trimester uterine artery wave form.

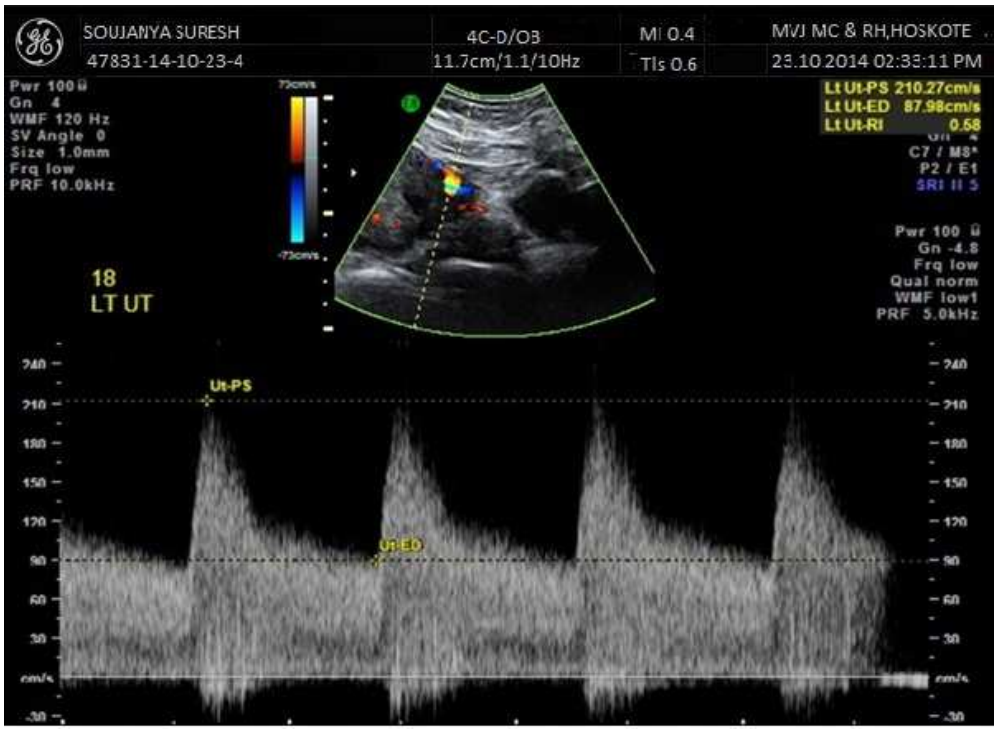


FIGURE: 12 Second trimester uterine artery wave form

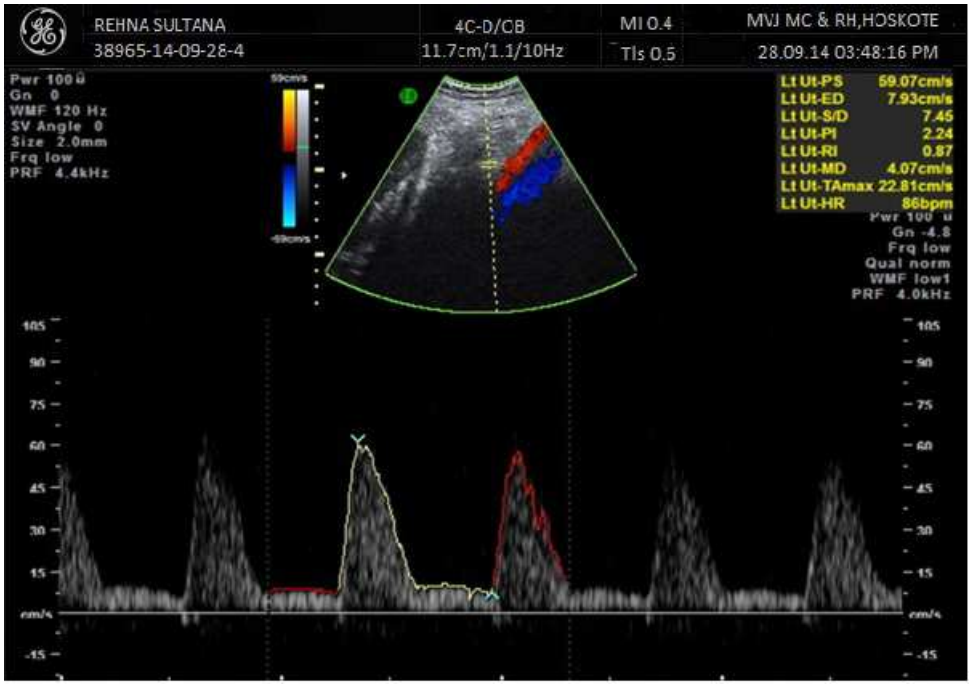


FIGURE: 13 Abnormal wave form with high RI

FIGURE: 14 Notching in second trimester.

Taking measurements

After obtaining an optimal waveform, the image has to be freezed when the automatic calculations are displayed. The three waveforms that the machine has chosen to ensure that they are free from substantial noise and that the machine has correctly chosen the maximum systolic point and the lowest frequency in end-diastole are examined. If the machine does not have a maximum frequency follower then the image is freezed and Doppler indices are measured manually. Various measurements of the uterine artery waveform can be calculated. The most commonly used is the resistance index (RI). The systolic/diastolic (S/D) ratio and pulsatility index (PI) can also be used as shown in figure 9 and 10.

FIGURE-15. Doppler indices commonly used.

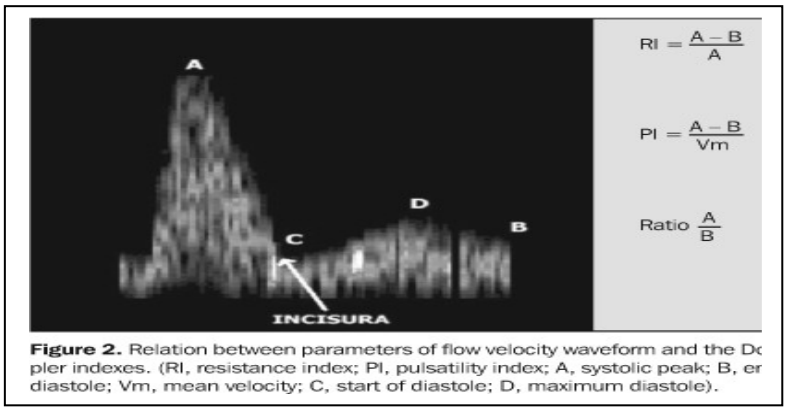
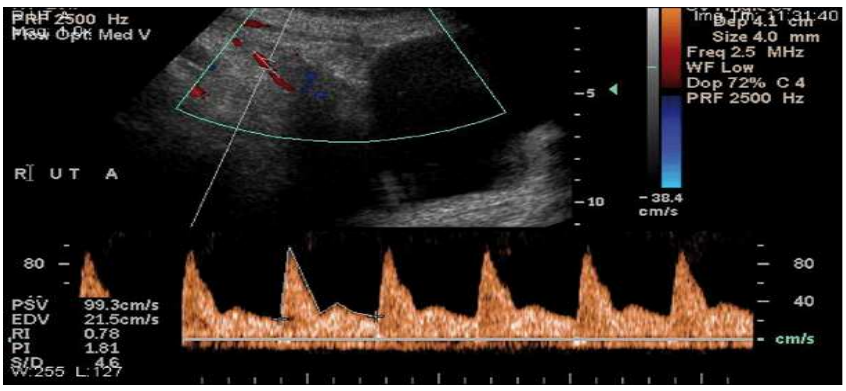


Figure 2. Relation between parameters of flow velocity waveform and the Do pler indexes. (RI, resistance index; PI, pulsatility index; A, systolic peak; B, er diastole; Vm, mean velocity; C, start of diastole; D, maximum diastole).

FIGURE- 16. Uterine artery Doppler study with reporting.(right side)



Reporting of uteroplacental waveforms

Loss of end-diastolic frequencies is extremely rare in the uteroplacental circulation so a simple index of impedance to flow, such as the RI or PI, is sufficient. A subjective assessment of the flow velocity waveform is also usually performed to note the presence or absence of notches. The waveforms from both sides of the uterus are recorded and reported as follows:

High resistance pattern:

- Persistent diastolic notch-bilateral notches.
- Persistent high impedance- RI>0.6 or more than 95th percentile for the gestational age or PI > 1.6 or more than 95th percentile for the gestational age.
- Significant difference between the flow of right and left uterine arteries.
- S/D > 2.6.

Impaired uterine artery Doppler is seen in

- Fetal growth restriction
- Preeclampsia
- Preterm delivery
- Non reassuring fetal status in labour.

Low resistance pattern: All other situations as shown in the Figure12 which is a normal Doppler waveform.

FIGURE 17 .Abnormal color Doppler waveform of the uterine artery at 24 weeks with the presence of a‘notch’ at the end of systole and reduced end-diastolic flow.

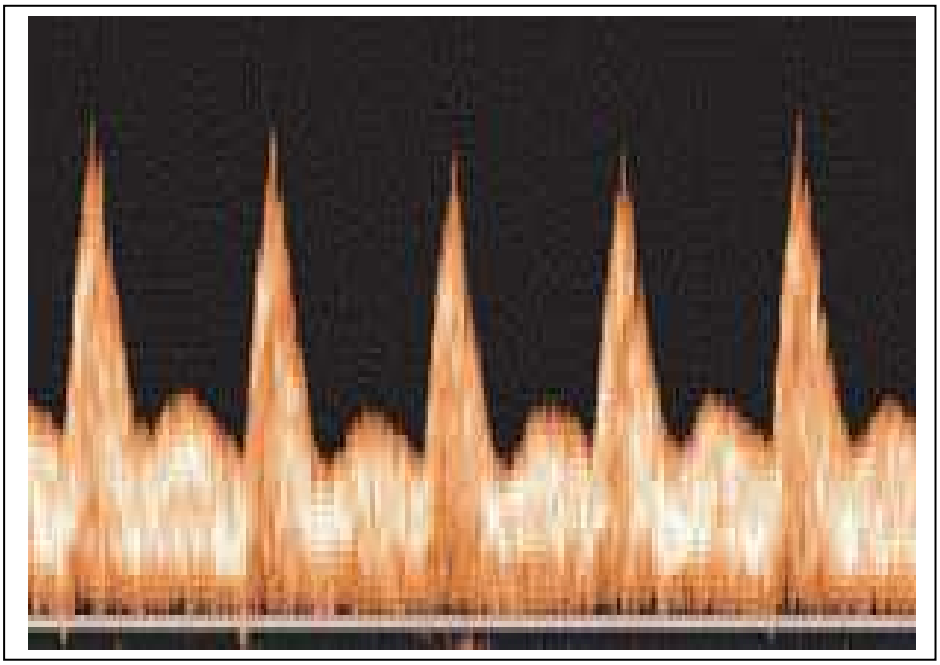
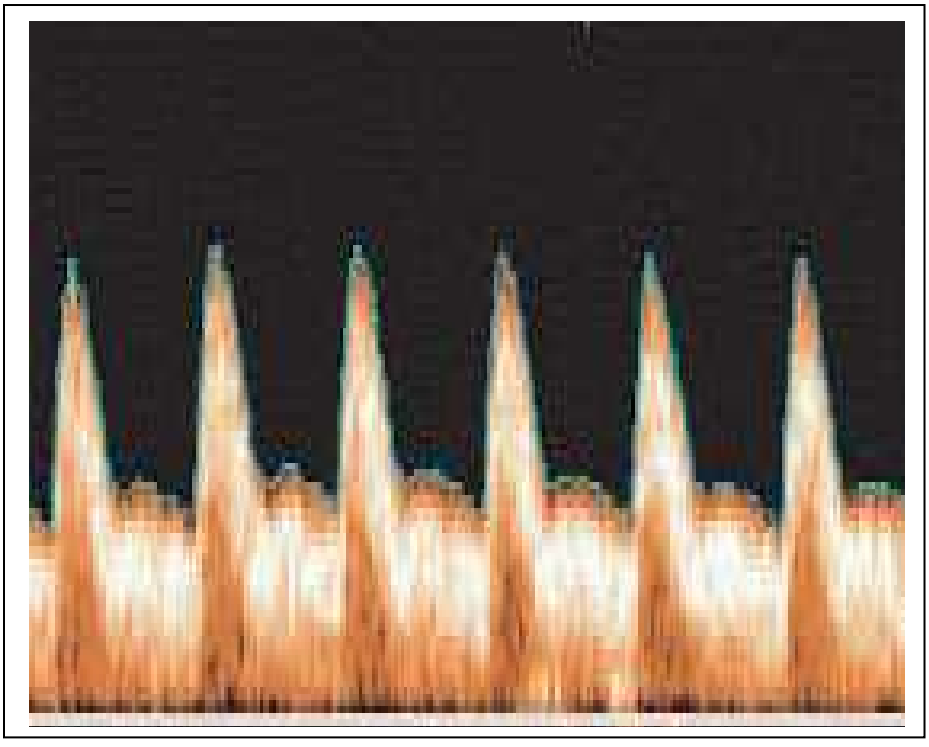


FIGURE18 -.Normal color Doppler waveform of the uterine artery at 24 weeks.



Problems

If the signal is not visualized the machine settings are checked and restarted. The vessel wall filter, frequency range, sweep speed and gain controls should be rechecked.

When there is difficulty in distinguishing waveforms from the Internal iliac artery from pathological Uteroplacental waveforms, pathologic uteroplacental waveforms are identified by a biphasic deceleration slope in systole, whereas those from the internal iliac artery have a smooth, steep slope.

FIRST TRIMESTERSCREENING

According to Pilalis*et al* (2007 : 532), 1st trimester abnormal uterine artery Doppler flow patterns are likely to identify the cases of pre-eclampsia associated with severe growth restriction and have a greater sensitivity in identifying early onset of severe disease. A 1st trimester uterine artery Doppler assessment is thus useful in identifying a subgroup of the population at n considerable risk for early, severe pre-eclampsia or growth restriction(Pilalis*etal*2007; 532)

In a study done by Pilalis *et al* the results suggest that uterine artery Doppler examinations are helpful in predicting pre-eclampsia from as early as the1sttrimester (Pilalis *et al.*, 2007 :139).

Melchiorre and co workers (2000 : 135) found that 1st trimester uterine artery Doppler indices and prevalence of bilateral notching in normal pregnancies were considerably different from those in women destined to develop preterm

pre-eclampsia but not term pre-eclampsia. The results of a study done by Melchiorre and coworkers (2009:528)indicated a significant relationship between 1st trimester uterine artery Doppler indices and the consequent development to small for gestational age fetuses.

SECOND TRIMESTERSCREENING

Second trimester uterine artery Doppler screening has proven to be a sensitive and accurate method for predicting preeclampsia and fetal growth restriction especially the severe forms and early onset of the disease(Pilalis2007:533)

Doppler screening in the second trimester is more sensitive than in the 1st trimester, in identifying the more severe and therefore clinically most relevant cases of pre-eclampsia and FGR.

IDEAL TIME FORSCREENING

Screening for pre-eclampsia by uterine artery Doppler assessments is possible from at least 11 weeks of gestation. Trophoblastic invasion is maximal in the 1sttrimesterand pre-eclampsia develops from a relative failure of this event, validates the evaluation of uterine artery Doppler assessment in the 1st trimester(Melchiorrie2008: 133), however screening too early leads to false positive rates and lower positive predictive values as what appears to be abnormal uterine artery Doppler waveforms in early second trimester may fully develop and normalize by late second trimester(Swanepoel2004 :6).

Screening in these second trimester leads to improvement in the false positive rates and positive predictive values(Swanepoel2004:6).

Cnossen and colleagues (2008: 703), echo Swanepoel's view that Doppler testing for both preeclampsia and FGR is less accurate in the 1st trimester than in

the 2nd trimester, while Papageorghiou (2008 : 308) argued that in the 1st trimester the sensitivity for predicting severe or early onset disease is much higher than is for mild or late onset disease. Melchiorrie (2005 : 134) is of the opinion that 1st andearlysecond trimester tests are only likely to be able to predict the development of preterm pre-eclampsia cases that have defective spiral artery changes.

Numerous studies found the potential advantage of earlier screening is that prophylactic intervention, such as maternal ingestion of low dose aspirin may be more effective in the prevention of the subsequent development of pre-eclampsia and FGR (Martin*etal.*,2001:586),

Aspirin therapy may be of specific benefit if started in the first trimester in women at high risk of developing the disease on the basis of history and abnormal first trimester uterine artery Doppler waveforms (Papageorghiou 2000 : 369). In a study by Yu and coworkers, (2003 :238) there is particular evidence that the administration of low dose aspirin to women with abnormal flow in theuterinearteriesatthisearlystagemayprovideeffectiveprophylaxisagainstpre-eclampsia.

A reason for a move towards first trimester screening is that prevention of pre-eclampsia by starting pharmacological intervention in the second trimester has by and large failed (Papageorghiou 2008 :369).

Screening of high-risk populations

Women at increased and/or high-risk for preeclampsia and intrauterine growth restriction are usually identified from the maternal history at pregnancy booking. The prevalence of complications in this group of pregnancies is much higher than in the

normal population. Uterine artery Doppler screening is a validated screening tool for this group.

Screening of low-risk pregnancies

Although several studies have used uterine artery Doppler as a screening tool for preeclampsia and fetal growth restriction in unselected populations, debate continues as to its value. Varying sensitivities are obtained depending on the type of Doppler used, the sampling site, the definition of abnormal uterine artery resistance, gestation of assessment and different end-points. Currently, the following statements are supported by at least one published study for two-stage (20- and 24-week) screening, using color pulsed wave doppler of the uterine arteries:

● The presence of a low resistance pattern is associated with a very low chance of pregnancy complications:

Less than 1% chance of developing proteinuric hypertension.

Less than 1% chance of a coexisting small for- gestational-age fetus.

● A high resistance pattern is associated with a higher rate of pregnancy complications:

70% chance of developing proteinuric hypertension

30% chance of a coexisting small-for-gestational- age fetus.[7]

Uterine artery Doppler studies in normal pregnancy

Schulman and colleagues determined that in the non pregnant state there is a rapid rise and fall in uterine artery flow velocity during systole and a notch in the descending waveform in early diastole. During pregnancy, they noted a significant increase in

uterine artery compliance between 8 and 16 weeks, which continued to a lesser extent until 26 weeks gestation. This physiological change in compliance resulted in the loss of the diastolic notch between 20 and 26 weeks gestation. This finding was corroborated by Jurkovic and Juaniaux who found similar changes in the resistance index(RI) and pulsatility index(PI) of the uterine artery Doppler signal. They determined that the RI decreased from 0.8 to 0.63 between 8 and 17 weeks, and that the PI decreased from 2.0 to 1.3 between 8 and 18 weeks gestation.[43]

Criteria for an abnormal test

The majority of research has centred on an elevation in the PI or the persistence of a uterine artery diastolic notch to detect the presence of increased uteroplacental vascular resistance.

A recent metaanalysis concluded that a PI with notching had the best predictive value for pregnancy outcomes (Cnossen's). It appears that as the impedance to flow increases in the placenta there is momentary closure of the uterine artery in the late systole or early diastole, or an increase in the downstream resistance as the relatively inflexible distal artery recoils from distension caused by the systolic pulse. This is manifested as an early diastolic notch in the Doppler waveform. Most studies use subjective criteria for the definition of a diastolic notch, but a drop of atleast 50 cm/s from the maximum diastolic velocity is a reasonable criteria after 20 weeks.[43]

There are no current standards for gestational age at testing or criteria for an abnormal uterine artery Doppler study. Once adequately trained in the technique, a reasonable approach would be to use an ultrasound machine with the capability to perform continuous wave and or pulsed wave Doppler studies of the uterine, arcuate and the subplacental arteries.

PI has been commonly reported but using levels above the 95th percentile or PI>1.6 appears to be appropriate. Recent reports show some utility in assessment of uterine artery flow in the first trimester. However the second trimester has yielded more consistent results. Performance at 18-20 weeks gestation is a reasonable approach. There is some evidence that repeating tests at 24- 26 weeks may add further benefits.[43]

STUDIES

Cnossen JS, Morris RK et al made a systematic review and bivariable meta-analysis in which they identified relevant studies through various databases of April 2006 and found that uterine artery Doppler ultrasonography provided a more accurate prediction when performed in the second trimester than in the first-trimester and an increased pulsatility index with notching was the best predictor of preeclampsia (positive likelihood ratio 21.0 among high-risk patients and 7.5 among low-risk patients). It was also the best predictor of overall (positive likelihood ratio 9.1) and severe (positive likelihood ratio 14.6) intrauterine growth restriction among low-risk patients.

Bhattacharyya Sanjoy Kumar, KunduSarmila and Kabiraj Sankar Prasad made a prospective study of 179 pregnant women of gestational age less than 16 weeks from August 1, 2007 to July 31, 2008 to predict the occurrence of preeclampsia using uterine artery Doppler velocimetry as a screening test at 24 to 26 weeks of gestation to note the abnormalities i.e., notching, resistivity index>0.6. They divided them into high and low risk group and followed up to look for the development of preeclampsia. It was found that sensitivity and specificity of abnormal uterine artery Doppler study for prediction of preeclampsia were 73.33 and 86.48% in high risk and 57.14 and

95.83% in low risk group. Relative risk with 95% confidence interval was 5.427(2.272-12.958) in high risk and 13.65(5.669-32.865) in low risk women and concluded that Doppler velocimetry of uterine artery at 24 weeks can be a reliable screening test for prediction of preeclampsia in both high risk and low risk women[19].

Steel SA, Pearce JM et al in January 2001 made a study on early Doppler ultrasound screening in prediction of hypertensive disorders of pregnancy in which they screened 1198 nulliparous women in early pregnancy by Doppler ultrasound waveforms (median 18 weeks). Among 1014 available for analysis, 118(12%) had persistently abnormal waveforms on repeat ultrasound scans at 24 weeks. Hypertension was significantly more frequent among those women than among women with normal Doppler waveforms [29/118 (25%) vs. 45/896 (5%)]. Hypertension in women with abnormal waveforms was more likely to be severe; 12 (10%) had proteinuria and 15 (13%) intrauterine growth retardation compared with 7 (0.8%) and 0, respectively, of those with normal waveforms. The sensitivity was high for hypertension associated with either proteinuria (63%) or intrauterine growth retardation (100%).

Caforio L, Testa AC et al studied uterine artery Doppler velocimetry performed at 18-20 and 22-24 weeks of gestation in predicting preeclampsia and adverse pregnancy outcome in high and low risk patients. 865 pregnant women were evaluated: 335 and 530 pregnant women represented the high and low-risk groups, respectively. At 18-20 weeks of gestation the sensitivity for the prediction of preeclampsia was 100 and 94% in low and high-risk groups, respectively. At 22-24 weeks of gestation the sensitivity for the prediction of preeclampsia was 100 and 97% in low and high-risk groups, respectively. They concluded that Doppler evaluation of the uterine artery at 18-20 and 22-24 weeks of gestation represents a useful predictive test in high-risk pregnancy and can also be used in prenatal surveillance of a low-risk population.

Schwarze A, Nelles I, et al in 2000 made a study to assess the role of uterine artery colour Doppler waveform analysis in the prediction of adverse pregnancy outcome such as preeclampsia, intrauterine growth retardation, placental abruption or a combination of outcome parameters. They found that in low risk pregnancies, the sensitivity of uterine artery notching for prediction of preeclampsia was 88 % and concluded that the predictive value of uterine artery Doppler for adverse pregnancy outcome in a low-risk population is of limited diagnostic value. Performing uterine artery Doppler studies at 23-26 weeks' gestation instead of 19-22 weeks' gestation increases the predictive value for adverse pregnancy outcomes.

Coleman et al made a study on mid trimester uterine artery Doppler screening as a predictor of adverse pregnancy outcome in high risk women. In their study, the sensitivity and specificity of RI>0.58 for preeclampsia was found to be 91 and 42 % respectively. Among women with RI ≥0.7, 58 % developed preeclampsia.

Ratanasiri T during 2004-2005 made a prospective study to assess the performance of diastolic notch of uterine arteries as a predictor for preeclampsia among 378 pregnant women between 18 to 22 weeks of gestation using Doppler studies. Diastolic notch was found in one or both uterine arteries in 51 subjects, yielding 78.6% sensitivity, 89.0% specificity, 21.6% positive predictive value, 99.1% negative predictive value, 88.6% accuracy, with likelihood ratio of positive and negative test result of 7.2 and 0.2 respectively in the prediction of preeclampsia. They concluded that although having high sensitivity and specificity, diastolic notch of uterine artery found in the second trimester provides too low predictive value to be used as a routine screening for preeclampsia.

Chien PF, Arnott N et al in 1999 made a quantitative systematic review of observational diagnostic studies using online searching of the medline database and found that in the low risk population a positive test result predicted preeclampsia with a pooled likelihood ratio of 6 x 4 (95% CI 5 x 7-7 x 1), while a negative test result had a pooled likelihood ratio of 0 x 7 (95% CI 0 x 6-0 x 8) and concluded that uterine artery Doppler flow velocity has limited diagnostic accuracy in predicting preeclampsia, intrauterine growth retardation and perinatal death.

ArisAntsaklis, George Daskalakis in 2010 in their study concluded that uterine artery Doppler screening meets all the requirements for a worthwhile screening program in prediction of preeclampsia. The sensitivity for predicting severe preeclampsia was between 80 and 90% for a false positive rate of 5 to 7% and that the detection rate could be better if they would have set a higher screen positive rate. Uterine artery screening at 20-24 weeks gestation was found to be superior to first trimester screening.

C K H Yu, O Khouri et al in 2008 made a multicentre prospective Doppler study of the uterine artery at 22-24 weeks of gestation in unselected women with singleton pregnancies and found that in 30,639 pregnancies, the median uterine artery pulsatality index was 1 and 95^{th} percentile was1.58. 614(2%) of cases developed preeclampsia and the mean uterine artery PI was above 95^{th} centile in 77.2% of women who developed preeclampsia requiring delivery before 34 weeks, in 35.9% of those delivering at 34-37 weeks and in 21.9% of those delivering after 37 weeks. The respective percentages were 82.3%, 46.9% and 28.8% for those with preeclampsia and small for gestational age infants and 43.8%, 21.2% and 8.4% for those with small for gestational age but without preeclampsia.

Progrojpaw D et al in 2008 screened 330 singleton high risk pregnancies with uterine artery Doppler between 20 and 24 weeks. Pulsatility index of > 1.58 or the presence of diastolic notch were defined abnormal and found that 27 (8.18%) women developed preeclampsia. 16 (4.84%) women has SGA babies. The sensitivity of PI > 1.58 and diastolic notch for preeclampsia, SGA were 59.25% and 56.25% respectively. The specificity of PI>1.58 and diastolic notch for these outcomes were 66.67% and 65.60% respectively and concluded that mid trimester uterine artery Doppler waveform analysis cannot be used as screening method in women at higher risk for the development of preeclampsia and SGA babies.

Onwudiwe N, Yu CK et al in 2008 studied 3529 singleton pregnancies at 22-24 weeks with combined screening with maternal demographic characteristics, uterine artery Doppler and mean arterial pressure. Multiple regression analysis was used to determine the significant predictors of pre-eclampsia, gestational hypertension and small for gestational age (SGA) among maternal characteristics, uterine artery pulsatility index and MAP. Among 3359 cases available, preeclampsia developed in 101 (3%) in which 23 (0.7%) delivered before 34 weeks and 78 (2.3%) after 34 weeks . 74 (2.2%) developed gestational hypertension, 366 (10.9%) delivered SGA new-borns with no hypersensitive disorders and 2806 (83.8%) were unaffected. Maternal characteristics, uterine artery-PI and MAP provided significant independent contribution for a false positive rate of 10%, the estimated detection rates of early and late preeclampsia were 100% and 56.4% respectively and concluded that the combination of test is an effective screening tool.

Asnafi N, Hajina K in 2011 studied 70 high risk pregnant women with Doppler ultrasonography between 18-24 weeks for evaluation of uterine artery notching and found that 27 women (39.20-%) had notching and birth weight range was

2,897.5±757.15 where as other 43 women with no notching had babies with birth weight 3,248.39±374.27. Preeclampsia, abruption and low birth weight babies were significantly higher in the group with notching but pre term delivery did not show any statistical difference between the two groups.

Elisa Llurba , Elena Casseras et al in 2008 made a prospective study in women with singleton pregnancies at 19-22 weeks. They studied mean pulsatility index (MPI) of both uterine arteries in 6586 women. Among 6035 women, preeclampsia developed in 75 (1.2%) and IUGR in 69 (1.1%) cases. Uterine artery mean PI was 0.99 and 90^{th} centile was 1.4. For 10% false positive rate, uterine Doppler mPI identified 70.60% of pregnancies that subsequently developed early onset preeclampsia and 73.3% of pregnancies that developed early onset IUGR and had a lower detection rate for late onset forms of the disease (23.5% for preeclampsia and 30% for IUGR)

MATERIALS AND METHODS

This was a prospective study involving 280 pregnant women. We excluded 30 cases because they had missing outcome data. In the remaining 250 pregnant women with gestational age 12 to 14 weeks and 20 to 26 weeks with correct LMP attending antenatal clinic at KGH Hospital, (tertiary health care centre) Triplicane & Institute of Obstetrics & Gynaecology, Egmore, Chennai, constituted the study population.

After taking the informed written consent from the pregnant women willing to participate in the study, a preliminary data was collected to include

Thorough history to know the patient demographics, gestational age and to know any high risk factors associated with the pregnancy.

BMI was calculated using the formula : weight (kg)/height (m^2).

Recording of blood pressure was done in sitting position after 10 minutes of rest the reading was repeated when above 140/90 mmHg after 4 hours.

Preeclampsia is defined as a blood pressure of at least 140/90 mmHg measured on two occasions each 4 hours apart, accompanied by proteinuria of atleast 300 mg per 24 hours, or at least 1+ on dipstick testing.

Severe preeclampsia is defined as having one or more of the following criteria:

- Blood pressure of at least 160/110 mm Hg measured on two occasions each 4 hours apart.
- Proteinuria of at least 5 g per 24 hr, or at least 3+ on dipstick testing, oliguria of less than 500ml per 24 hr.
- Cerebral or visual disturbances

- Epigastric or right upper quadrant pain
- Impaired liver function
- Thrombocytopenia
- Fetal growth restriction (defined as the condition in which the new-born has birth weight less than 10% for gestational age)

Proteinuria was diagnosed on 2 midstream urine samples collected at least 4 hours apart showing albumin "+"or more using dipstick. Urinary tract infection was excluded by routine urine analysis.

The protein portion of the dipstick reagent strip measures the protein based on the protein error of PH dye indicator, principle (method) using bromophenol blue. Development of colour range from yellow for negative through yellow green and green to green blue for a positive reaction[50,51].

Table -4.Showing sensitivity/ limit of detection of urinary protein.

Test result	Negative	Traces(+/-)	1+	2+	3+	4+
Protein(mg/dl)	0	10	30	100	300	1000

Routine haematological investigations were noted.

Clinical examination was done at each visit along with weight gain, blood pressure and protienuria.

Ultrasound scan was done at 12 to 14 weeks and 20 to 26 weeks.

Based on the following high risk factors, the women were categorized into two groups—high risk and low risk[19].

- H/o chronic hypertension
- Diabetes
- Renal disease
- Obesity (BMI >30);
- Age<20 or>35 years (in primigravida)
- Past bad obstetric history of—preeclampsia, intrauterine growth restriction, and intrauterine fetal demise.
- Family h/o preeclampsia or IUGR in mother or sister.

INCLUSION CRITERIA:

- All pregnancies with correct LMP
- Patients who gave informed written consent.

EXCLUSION CRITERIA:

- Patients who did not give consent
- Multiple pregnancy
- Anomalous foetus.

Sequential uterine artery Doppler recordings were taken at 12 to 14 weeks and 20 to 26 weeks of gestation. The woman was examined in a semi recumbent position after 10 minutes of bed rest under real time ultrasonography using volusionGEmachine with frequency of 2- 5 MHz.Transabdominally, the probe was placed longitudinally in the lower lateral quadrant of the abdomen, angled medially. Color flow mapping is useful to identify the uterine artery as it is seen crossing the external iliac artery. The

sample volume was placed 1 cm downstream from this crossover point. In a small proportion of cases if the uterine artery branches before the intersection of the external iliac artery, the sample volume should be placed on the artery just before the uterine artery bifurcation. The same process is repeated for the contralateral uterine artery. With advancing gestational age, the uterus usually undergoes dextrorotation. Thus, the left uterine artery does not run as lateral as does the right[21].

Impaired uterine artery flow was considered in the following.

- Persistent diastolic notch- unilateral or bilateral in the main uterine artery. An early diastolic notch is defined as a V shaped deflection towards the baseline in early diastole.
- Elevated mean PI > 1.6
- Both of the above.

All pregnant women under study were carefully followed up regularly and her blood pressure, weight gain, fundal height was measured and urinary protein analysis was done at each antenatal visit. The patient was followed up till delivery and the outcome was noted with respect to the gestational age at delivery, birth weight and the perinatal events.

The pulsatility index is defined as a measure of the variability of blood velocity in a vessel equal to the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle. Pulsatility index is an arterial blood-flow velocity waveform index designed to quantify the pulsatility or oscillations of the waveform.

PI is calculated with the aid of software installed on the ultrasound machine using the following formula:

Pulsatility index = (Vmax-Vmin)/Vmaxmean.

Where Vmax is the peak systolic velocity, Vmin is the minimum forward diastolic velocity in unidirectional flow, or the maximum negative velocity in diastolic flow reversal, and Vmax mean is the maximum velocity averaged over (at least) one cardiac cycle.

Table 5: Showing pulsatility index by Gomez et.al

Gestational age	1st trimester(Pl)	2nd trimester(Pl)	3rd trimester(Pl)
5th centile	1.1	0.7	0.6
50th centile	1.7	1.0	0.8
95th centile	2.7	1.5	1.2

The above table shows the Pl values for the 5th, 50th and 95th centiles for the different gestational ages. Ideally as gestation increases the pulsatility index should decrease.

FIGURE: 19 Showing pulsatility index at different gestational age

METHODS FOR STATISTICAL ANALYSIS

Demographic data of the included women is presented as descriptive statistics using range, mean and standard deviation for metric data and range, median and interquartile range for discrete data.

Data were analysed using SPSS version 20 for windows. Frequency distribution of category variables were computed and Chis square test for proportions were used to analyse PI values and notching positivity with clinical preeclampsia or no preeclampsia& IUGR. Sensitivity, specificity, positive predictive value, negative predictive values were determined for both PI and notching in 1^{st} and second trimesters. Notching and preeclamsia was also correlated with IUGR.

FIGURE: 20 :ULTRASOUND MACHINE GE VOLUSION 730 USED IN THIS STUDY

FIGURE: 21 –Different probes.

OBSERVATIONS AND RESULTS

In this prospective study a total of 280 pregnant women were recruited, however 30 participants had to be excluded from the final analysis due to the following reasons:

1) Did not return for follow up scans

2) Pregnancy outcomes were not available.

Records of 250 participants were available for the final analysis due small sample size did not allow for regression models could not be used and instead cross tabulations were employed. Out of these 250 women 55 women belong to high risk group and rest of 195 women belong to low risk group according to the risk factors already mentioned.55(22.5%) and 195(78%) were in high risk and low risk groups respectively.

BASELINE OBSTETRIC ANDDEMOGRAPHIC CHARACTERISTICS

Table: 6- Baseline obstetric and demographic data

DATA	N = 250	MEAN	± STANDARD DEVIATION
Age range(years) 18-29 30-34 35-39 40+	170 (68%) 24 (20%) 14 (12%) 1 (1%)	27.0	± 5.42
Parity 1st pregnancy 2nd pregnancy 3rd pregnancy 4th pregnancy	87 (35%) 65(26%) 52 (21%) 45(18%)	NIA	N/A

As shown in table 6, it can be seen that majority of participants, 170 (68%)were in the age group 18 - 29, while 24 (20%) were between 30 and 34 years of age, and 14 (12%) were older than 35 years of age, with the mean age being 27.0 (±SD 5.42).

Parity : 87 (35%) patients it was their first pregnancy while

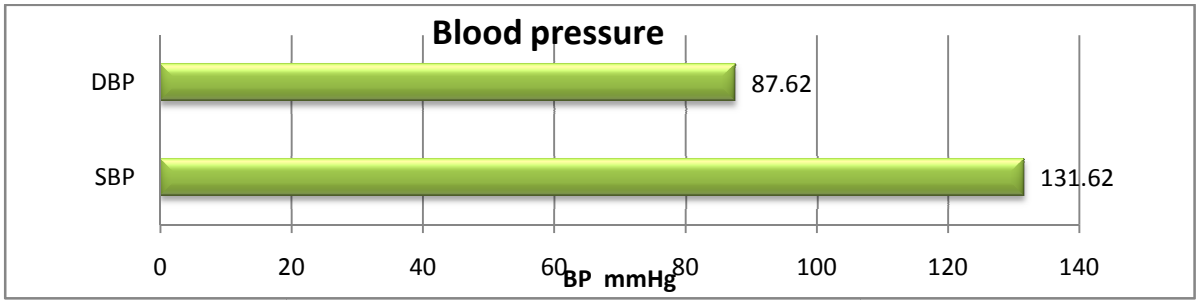
65(26%) were gravida 2,52 (21%) gravida 3 and 45(18%) gravida 4.

BLOOD PRESSURE

The systolic blood pressure (mean±SD) was 131.62±12.74

The diastolic blood pressure (mean±SD) was 87.62±10.67.

The mean systolic and diastolic blood pressure of the population is represented in the graph .



GRAPH- 1. Mean systolic and diastolic blood pressure.

HIGH RISK FACTORS

Various high risk factors and the associated risk of preeclampsia was studied like age, maternal history of chronic hypertension, diabetes, renal disease, past bad obstetric history and family history was taken into account as these factors have been seen to be associated with the higher incidence of preeclampsia and is shown in Table 8

TABLE-7.Distribution of various risk factors in the high risk group and the association between various risk factors and development of preeclampsia

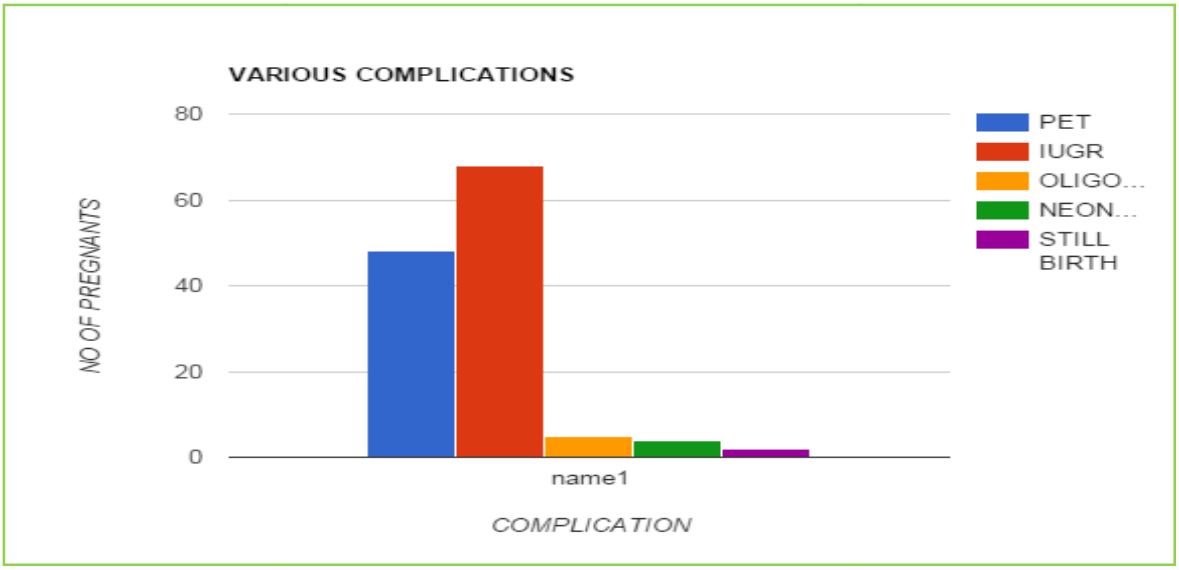
Risk factors	No. of women (55)	Preeclampsia
Age <20	13	3(19%)
Age>35	6	2(36%)
h/o chronic hypertension	7	5(60%)
h/o diabetes	2	0
h/o chronic renal disease	-	-
Past h/o preeclampsia, IUGR, IUFD	27	10(38%)

COMPLICATIONS

The women in study group developed various complications associated with the decreased uteroplacental blood flow, the most important being preeclampsia. 48(19.2%).The incidence of IUGR were 68(27%).The rate of still birth and early neonatal death were 2(0.8%),4(1.6%) in respectively which was statistically not significant as there were other causative factors like birth asphyxia, congenital anomalies contributing significantly for the perinatal mortality in the low risk group. The incidence of oligohydramnios was 5(2%) of women developing oligohydramnios as shown in Table 9 and Graph 6.

TABLE – 8 Various complications in the study group

Complications in the study group	
Preeclampsia	48(19%)
IUGR	68(27%)
Still birth	2(0.8%)
Early neonatal death	4(1.6%)
Oligohydramnios	5(2%)



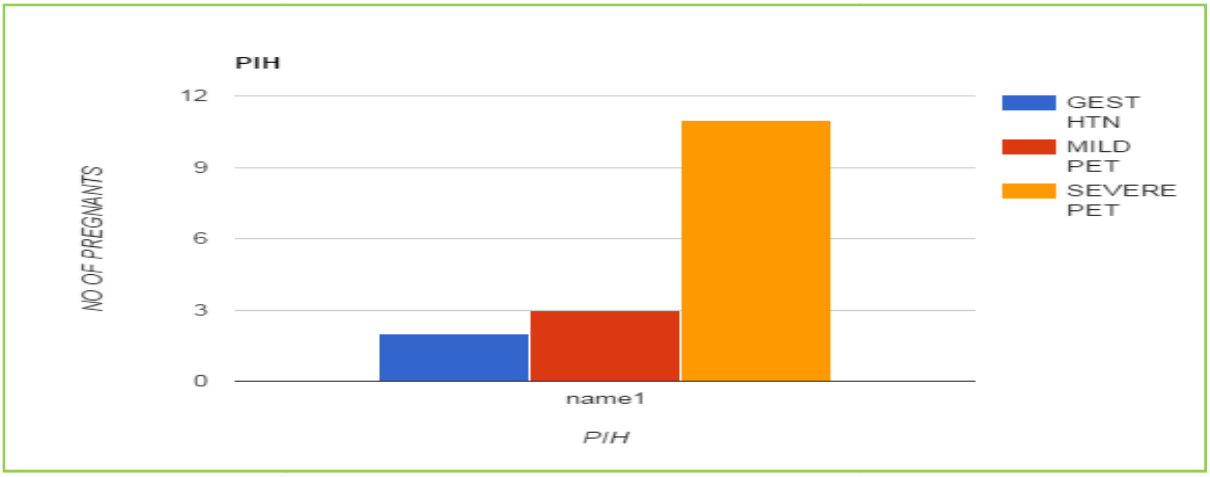
Graph 2: Various complications in the study group.

PREGNANCY INDUCED HYPERTENSION.

Among the 55 high risk patients, 16 developed pregnancy induced hypertension. Gestational hypertension was seen in 2(2%) and mild, severe preeclampsia was seen in 3(15%),12(75%).

TABLE 9. Severity of pregnancy induced hypertension

Complication	**HR PIH**
Gestational hypertension	2(12%)
Mild preeclampsia	3(18%)
Severe preeclampsia	11(75%)



Graph 3-.showing types of pregnancy induced hypertension

PREDICTIVE VALUE OF UTERINE ARTERY DOPPLER FOR PREECLAMPSIA

UTERINE ARTERY DOPPLER SCREENING

Uterine artery Doppler screening was performed in the 1nd and 2nd trimester of pregnancy for each patient to assess its sensitivity in predicting PET &IUGR

Table 10: UTERINE ARTERY DOPPLER PULSATILITY INDICES (CURRENT STUDY)

DEPENDANT VARIABLE	NUMBER	RANGE	±STD DEVIATION
Uterine artery PI 1st trimester 2nd trimester	250	(0.6-2.9)	±0.47
	250	(0.5-2.3)	±0.33

The above table demonstrates the mean pulsatility index (Pl) for each trimester.

Table 11 UTERINE ARTERY DOPPLER SPECTRAL WAVEFORM ANALYSIS

DEPENDANT VARIABLE	NUMBER
Notching (1st trimester)	N=250
Yes	70(28%)
No	180 (72%)
Notching (2nd trimester)	N=250
Yes	48 (23%)
No	202 (76%)

Participants with notching decreased from 70 in the 1st trimester to 48 in the 2nd trimester. The majority of participants (72%-in the 1st 1rimester), (76%-in the 2nd trimester) had a uterine artery spectral waveform which displayed no notching, in keeping with normal trophoblast invasion of the maternal spiral arteries.

PREGNANCY OUTCOME:

32 pregnant women delivered before 37 week of gestation and rest of 198 pregnant women delivered between 37 to 42 weeks of gestation.

TABLE 12: PREGNANCY OUTCOMES

OUTCOME	N =250
Gestational age at delivery	
<37 weeks	32(14%)
37 - 42 weeks	198(80%)
>42 weeks	0
Birth weight	
<2500g	68(27%)
>2500g	182 (72%)
Developed PET	48 (19.2%)
Intrauterine fetal death	2(0.8%)

Babies weighing less than 2500 g at term were considered small for gestational age, whereas fetal growth restriction (FGR) implies that a fetus has not achieved its optimal growth potential.

PI FIRST TRIMESTER

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NEGATIVE	164	65.6	65.6	65.6
	PI POSITIVE	86	34.4	34.4	100.0
	Total	250	100.0	100.0	

Interpretation: 86 women out of 250 women shows pulsatility index above cutoff value in first trimester and 164 women had PI within normal range.

NOTCHING FIRST TRIMESTER

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NEGATIVE	180	72.0	72.0	72.0
	POSITIVE	70	28.0	28.0	100.0
	Total	250	100.0	100.0	

Interpretation: 70 women out of 250 women shows diastolic notching in first trimester and 180 women had no diastolic notching.

PI SECOND TRIMESTER

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	PI NEGATIVE	174	69.6	69.6	69.6
	PI POSITIVE	76	30.4	30.4	100.0
	Total	250	100.0	100.0	

Interpretation: 76 women out of 250 women shows pulsatility index above cutoff value in second trimester and 174 women had PI within normal range.

NOTCHING SECOND TRIMESTER

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NEGATIVE	192	76.8	76.8	76.8
	POSITIVE	58	23.2	23.2	100.0
	Total	250	100.0	100.0	

Interpretation: 58 women out of 250 women shows diastolic notching in second trimester and 192 women had no diastolic notching.

PREECLAMPSIA

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO PREECLAMPSIA	202	80.8	80.8	80.8
	PREECLAMPSIA	48	19.2	19.2	100.0
	Total	250	100.0	100.0	

Interpretation: 48 women out of 250 women had developed preeclampsia and 202 women had no evidence of preeclampsia.

IUGR

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO IUGR	182	72.8	72.8	72.8
	IUGR POSITIVE	68	27.2	27.2	100.0
	Total	250	100.0	100.0	

Interpretation: 68 fetus had developed IUGR out of 250 birth remaining 182 foetus had no evidence of IUGR.

Association between Notching in 1st trimester and preeclampsia

40% of patients who had notching in 1st trimester had significantly higher preeclampsia while 88.9% of them who did not have notching had no preeclampsia ($\chi 2=27.1$, $p<0.001$)

Association between Notching in1st trimester and preeclampsia Cross tabulation

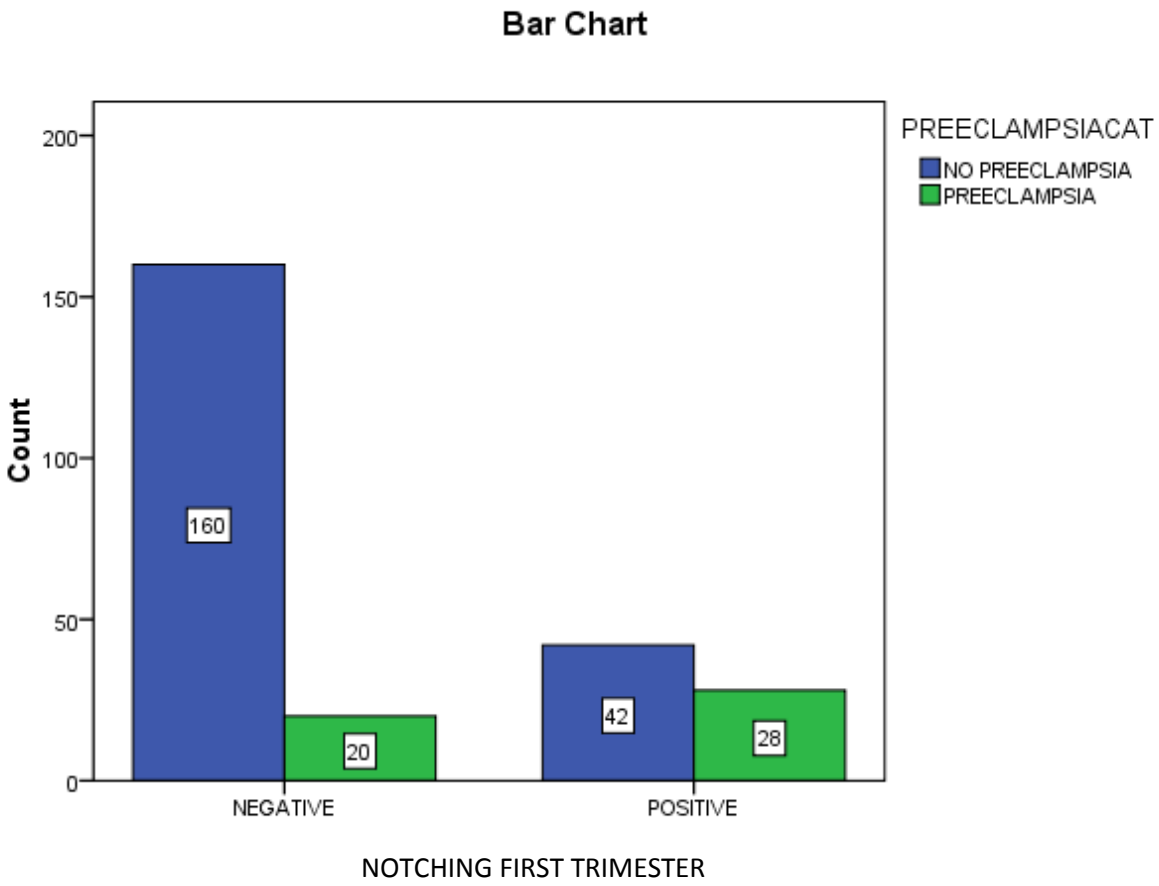
			PREECLAMPSIA CAT		Total
			NO PREECLAMPSIA	PREECLAMPSIA	
NOTCAT1	NEGATIVE	Count	160	20	180
		Expected Count	145.4	34.6	180.0
		% within NOTCAT1	88.9%	11.1%	100.0%
		% within PREECLAMPSIACAT	79.2%	41.7%	72.0%
		% of Total	64.0%	8.0%	72.0%
	POSITIVE	Count	42	28	70
		Expected Count	56.6	13.4	70.0
		% within NOTCAT1	60.0%	40.0%	100.0%
		% within PREECLAMPSIACAT	20.8%	58.3%	28.0%
		% of Total	16.8%	11.2%	28.0%
Total		Count	202	48	250
		Expected Count	202.0	48.0	250.0
		% within NOTCAT1	80.8%	19.2%	100.0%
		% within PREECLAMPSIACAT	100.0%	100.0%	100.0%
		% of Total	80.8%	19.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	27.113[a]	1	.000		
Continuity Correction[b]	25.283	1	.000		
Likelihood Ratio	24.754	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	27.005	1	.000		
N of Valid Cases	250				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 13.44.

b. Computed only for a 2x2 table



Sensitivity of notching was only 58% (95% CI between 43% and 72%) while specificity was 79% (95% CI between 72% and 84%.The positive predictive value was 40% and negative predictive value was 88%.

	Condition		
	Absent	**Present**	**Totals**
Test Positive	42	28	70
Test Negative	160	20	180
Totals	202	48	250

	Estimated Value	95% Confidence Interval	
		Lower Limit	Upper Limit
Prevalence	0.192	0.146204	0.247495
Sensitivity	0.583333	0.432754	0.720676
Specificity	0.792079	0.728257	0.844524
For any particular test result, the probability that it will be:			
Positive	0.28	0.226144	0.340752
Negative	0.72	0.659248	0.773856
For any particular positive test result, the probability that it is:			
True Positive	0.4	0.286898	0.524136
False Positive	0.6	0.475864	0.713102
For any particular negative test result, the probability that it is:			
True Negative	0.888889	0.831419	0.929149
False Negative	0.111111	0.070851	0.168581
likelihood Ratios: [C] = conventional [W] = weighted by prevalence			
Positive [C]	2.805556	1.957342	4.021342
Negative [C]	0.526042	0.375443	0.737049
Positive [W]	0.666667	0.472231	0.941159
Negative [W]	0.125	0.082579	0.189212

Association between Notching 2nd trimester and pre-eclampsia

Notching was positive in 65.5% of patients with preeclampsia and negative in 94.8% of patients without preeclampsia ($\chi 2=104.4$, $p<0.001$)

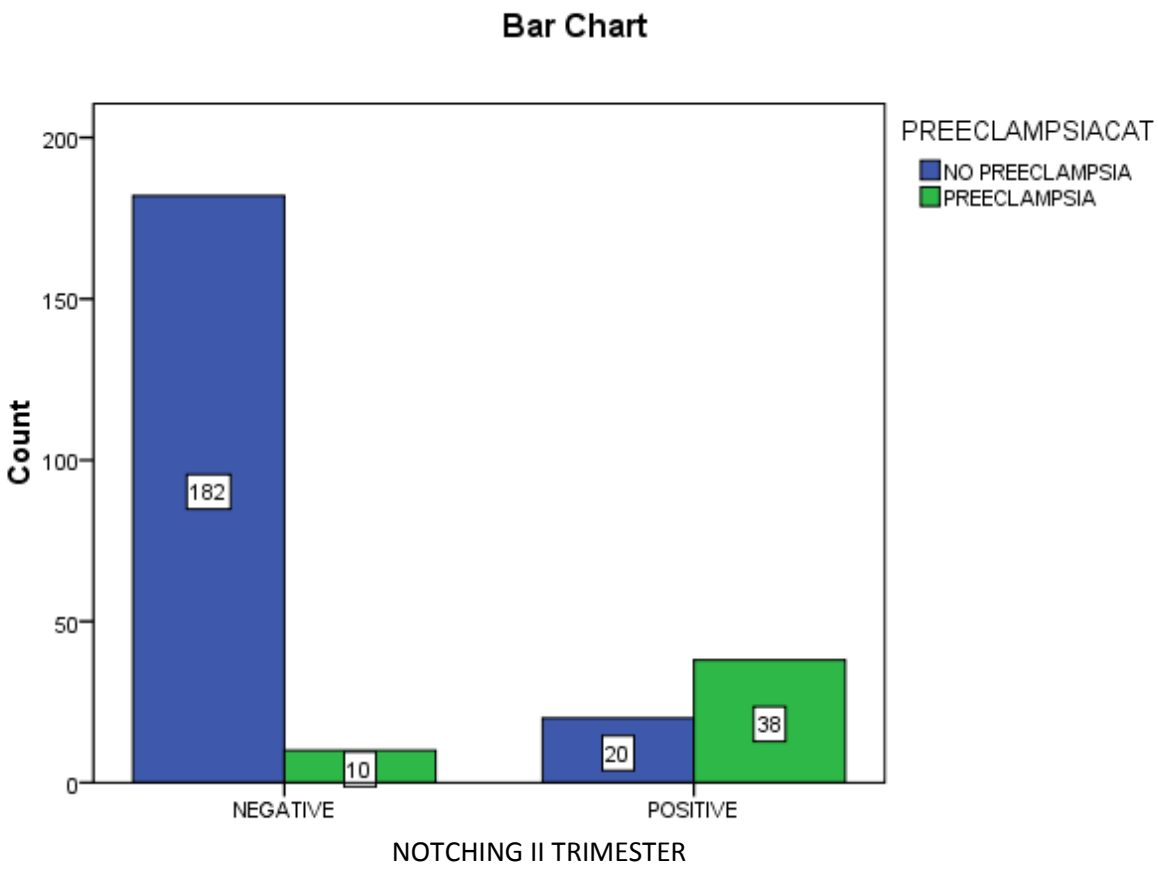
NOTCHING 2ND TRIMESTER VS PREECLAMPSIA Cross tabulation					
			PREECLAMPSIACAT		Total
			NO PREECLAMPSIA	PREECLAMPSIA	
NOTCAT2	NEGATIVE	Count	182	10	192
		Expected Count	155.1	36.9	192.0
		% within NOTCAT2	94.8%	5.2%	100.0%
		% within PREECLAMPSIACAT	90.1%	20.8%	76.8%
		% of Total	72.8%	4.0%	76.8%
	POSITIVE	Count	20	38	58
		Expected Count	46.9	11.1	58.0
		% within NOTCAT2	34.5%	65.5%	100.0%
		% within PREECLAMPSIACAT	9.9%	79.2%	23.2%
		% of Total	8.0%	15.2%	23.2%
Total		Count	202	48	250
		Expected Count	202.0	48.0	250.0
		% within NOTCAT2	80.8%	19.2%	100.0%
		% within PREECLAMPSIACAT	100.0%	100.0%	100.0%
		% of Total	80.8%	19.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	104.433[a]	1	.000		
Continuity Correction[b]	100.582	1	.000		
Likelihood Ratio	91.261	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	104.016	1	.000		
N of Valid Cases	250				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 11.14.

b. Computed only for a 2x2 table



Sensitivity of notching in 2nd trimester was 79% (95% CI between 64% and 89%) while specificity was 90% (95% CI between8 4% and 93%). The positive predictive value was 65% and negative predictive value 94%.

	Condition		
	Absent	Present	Totals
Test Positive	20	38	58
Test Negative	182	10	192
Totals	202	48	250

	Estimated Value	95% Confidence Interval	
		Lower Limit	Upper Limit
Prevalence	0.192	0.146204	0.247495
Sensitivity	0.791667	0.645963	0.890442
Specificity	0.90099	0.849161	0.936976
For any particular test result, the probability that it will be:			
Positive	0.232	0.182155	0.290263
Negative	0.768	0.709737	0.817845
For any particular positive test result, the probability that it is:			
True Positive	0.655172	0.517957	0.771798
False Positive	0.344828	0.228202	0.482043
For any particular negative test result, the probability that it is:			
True Negative	0.947917	0.903557	0.973316
False Negative	0.052083	0.026684	0.096443
likelihood Ratios: [C] = conventional [W] = weighted by prevalence			
Positive [C]	7.995833	5.146593	12.42246
Negative [C]	0.231227	0.133069	0.401791
Positive [W]	1.9	1.272497	2.836943
Negative [W]	0.054945	0.030034	0.100518

Association between PI first trimester and preeclampsia

PI was above cutoff in 23.3% of patients with preeclampsia and below cutoff in 82.9% of patients without preeclampsia though not significant ($\chi 2=1.39$, $p=0.24$)

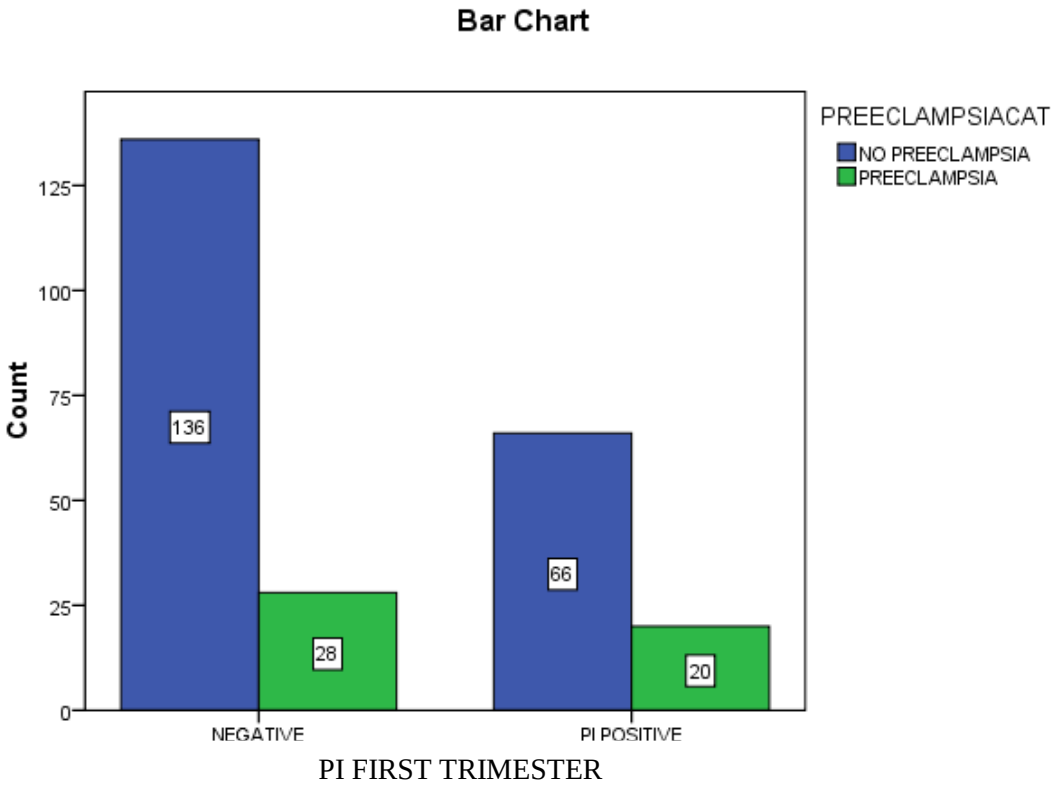
PI 1ST TRIMESTER VS PREECLAMPSIA Cross tabulation					
			PREECLAMPSIA CAT		Total
			NO PREECLAMPSIA	PREECLAMPSIA	
PICAT1	NEGATIVE	Count	136	28	164
		Expected Count	132.5	31.5	164.0
		% within PICAT1	82.9%	17.1%	100.0%
		% within PREECLAMPSIACAT	67.3%	58.3%	65.6%
		% of Total	54.4%	11.2%	65.6%
	PI POSITIVE	Count	66	20	86
		Expected Count	69.5	16.5	86.0
		% within PICAT1	76.7%	23.3%	100.0%
		% within PREECLAMPSIACAT	32.7%	41.7%	34.4%
		% of Total	26.4%	8.0%	34.4%
Total		Count	202	48	250
		Expected Count	202.0	48.0	250.0
		% within PICAT1	80.8%	19.2%	100.0%
		% within PREECLAMPSIACAT	100.0%	100.0%	100.0%
		% of Total	80.8%	19.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.390[a]	1	.238		
Continuity Correction[b]	1.020	1	.312		
Likelihood Ratio	1.360	1	.243		
Fisher's Exact Test				.242	.156
Linear-by-Linear Association	1.385	1	.239		
N of Valid Cases	250				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 16.51.

b. Computed only for a 2x2 table



Sensitivity of PI in1st trimester was 41% (95% CI between 27% and 56%) while specificity was 67% (95% CI between 60% and 73%). The positive predictive value was 65% and negative predictive value 94%.

	Condition		
	Absent	**Present**	**Total**
Test Positive	66	20	86
Test Negative	136	28	164
Totals	202	48	250

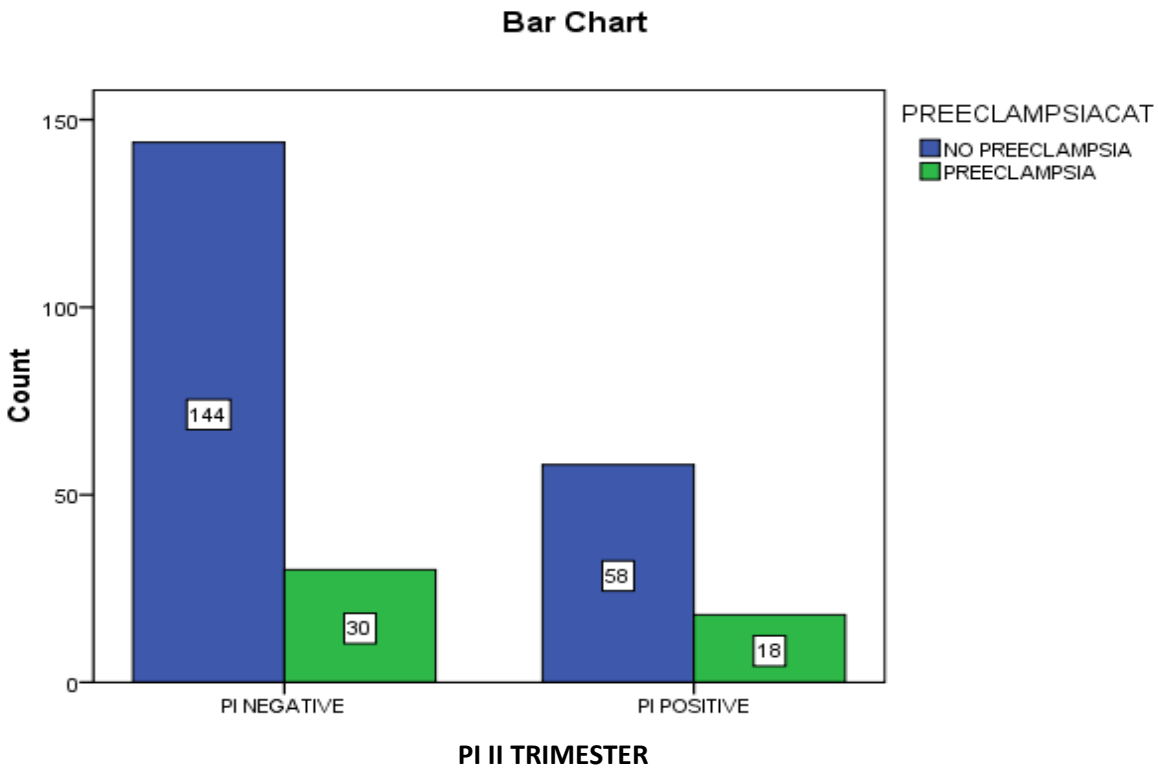
	Estimated Value	**95% Confidence Interval**	
		Lower Limit	**Upper Limit**
Prevalence	0.192	0.146204	0.247495
Sensitivity	0.416667	0.279324	0.567246
Specificity	0.673267	0.603329	0.736493
For any particular test result, the probability that it will be:			
Positive	0.344	0.285985	0.406895
Negative	0.656	0.593105	0.714015
For any particular positive test result, the probability that it is:			
True Positive	0.232558	0.151059	0.338373
False Positive	0.767442	0.661627	0.848941
For any particular negative test result, the probability that it is:			
True Negative	0.829268	0.760944	0.881739
False Negative	0.170732	0.118261	0.239056
likelihood Ratios: [C] = conventional [W] = weighted by prevalence			
Positive [C]	1.275253	0.864385	1.881418
Negative [C]	0.866422	0.678967	1.10563
Positive [W]	0.30303	0.202889	0.452599
Negative [W]	0.205882	0.146576	0.289185

Association between PI 2nd trimester and preeclampsia

PI was above cutoff in 23.7% of patients with preeclampsia and below cutoff in 82.8% of patients without preeclampsia though not significant ($\chi 2=1.41$, p=0.23)

Association between PI 2nd trimester and preeclampsia Crosstabulation					
			PREECLAMPSIA CAT		**Total**
			NO PREECLAMPSIA	**PREECLAMPSIA**	
PICAT2	PI NEGATIVE	Count	144	30	174
		Expected Count	140.6	33.4	174.0
		% within PICAT2	82.8%	17.2%	100.0%
		% within PREECLAMPSIACAT	71.3%	62.5%	69.6%
		% of Total	57.6%	12.0%	69.6%
	PI POSITIVE	Count	58	18	76
		Expected Count	61.4	14.6	76.0
		% within PICAT2	76.3%	23.7%	100.0%
		% within PREECLAMPSIACAT	28.7%	37.5%	30.4%
		% of Total	23.2%	7.2%	30.4%
Total		Count	202	48	250
		Expected Count	202.0	48.0	250.0
		% within PICAT2	80.8%	19.2%	100.0%
		% within PREECLAMPSIACAT	100.0%	100.0%	100.0%
		% of Total	80.8%	19.2%	100.0%

Chi-Square Tests					
	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	1.415[a]	1	.234		
Continuity Correction[b]	1.031	1	.310		
Likelihood Ratio	1.375	1	.241		
Fisher's Exact Test				.295	.155
Linear-by-Linear Association	1.410	1	.235		
N of Valid Cases	250				
a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 14.59.					
b. Computed only for a 2x2 table					



Interpretation: Using Pearson Chi-square test it is found that PI is significantly associated with Pre-eclampsia.

Sensitivity of PI in 2nd trimester was 37% (95% CI between 24% and 52%) while specificity was 71% (95% CI between 64% and 77%). The positive predictive value was 23% and negative predictive value 83%.

	Condition		
	Absent	**Present**	**Total**
Test Positive	58	18	76
Test Negative	144	30	174
Totals	202	48	250

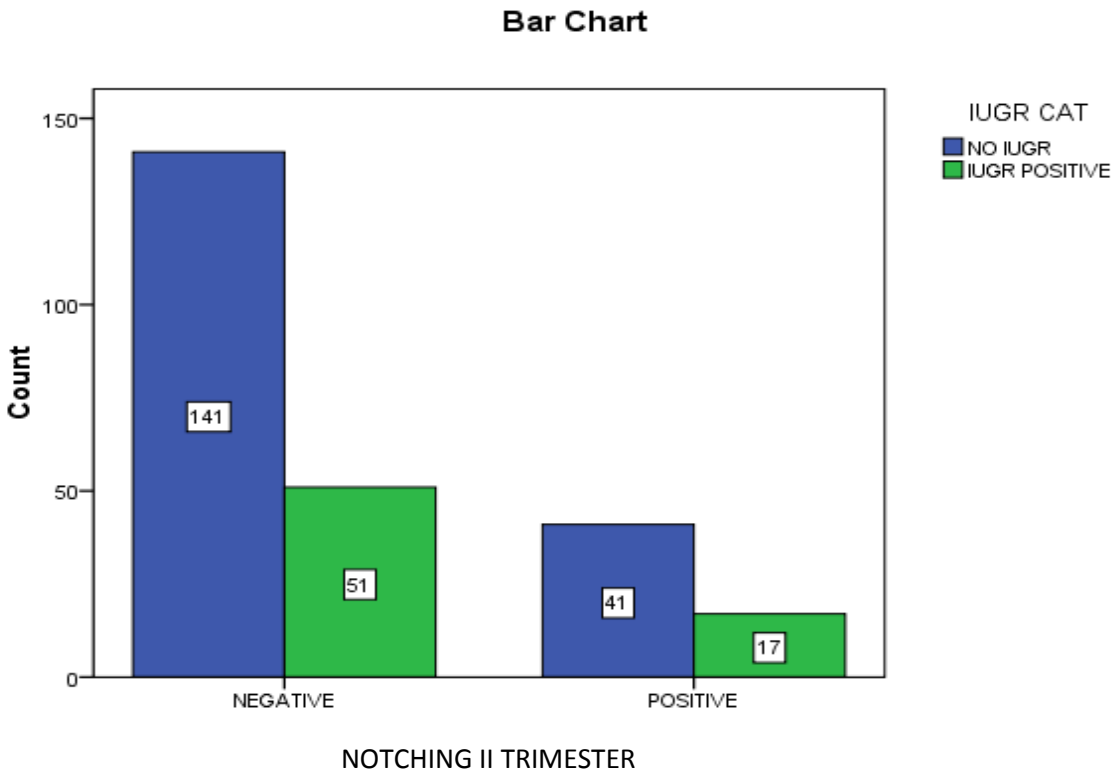
	Estimated Value	**95% Confidence Interval**	
		Lower Limit	**Upper Limit**
Prevalence	0.192	0.146204	0.247495
Sensitivity	0.375	0.243214	0.526663
Specificity	0.712871	0.644382	0.773103
For any particular test result, the probability that it will be:			
Positive	0.304	0.248437	0.365702
Negative	0.696	0.634298	0.751563
For any particular positive test result, the probability that it is:			
True Positive	0.236842	0.149988	0.350704
False Positive	0.763158	0.649296	0.850012
For any particular negative test result, the probability that it is:			
True Negative	0.827586	0.76138	0.878929
False Negative	0.172414	0.121071	0.23862
likelihood Ratios: [C] = conventional [W] = weighted by prevalence			
Positive [C]	1.306034	0.853873	1.997635
Negative [C]	0.876736	0.701463	1.095805
Positive [W]	0.310345	0.20339	0.473542
Negative [W]	0.208333	0.150094	0.289171

Association between Notching and IUGR

70.7% who had notching had no IUGR and 26.6% without notching had IUGR ($\chi 2=0.17$, p=0.68)

Association between Notching and IUGR Crosstabulation					
			IUGR CAT		
			NO IUGR	**IUGR POSITIVE**	**Total**
NOTCAT2	NEGATIVE	Count	141	51	192
		Expected Count	139.8	52.2	192.0
		% within NOTCAT2	73.4%	26.6%	100.0%
		% within IUGR CAT	77.5%	75.0%	76.8%
		% of Total	56.4%	20.4%	76.8%
	POSITIVE	Count	41	17	58
		Expected Count	42.2	15.8	58.0
		% within NOTCAT2	70.7%	29.3%	100.0%
		% within IUGR CAT	22.5%	25.0%	23.2%
		% of Total	16.4%	6.8%	23.2%
Total		Count	182	68	250
		Expected Count	182.0	68.0	250.0
		% within NOTCAT2	72.8%	27.2%	100.0%
		% within IUGR CAT	100.0%	100.0%	100.0%
		% of Total	72.8%	27.2%	100.0%

Chi-Square Tests					
	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	.170[a]	1	.680		
Continuity Correction[b]	.059	1	.807		
Likelihood Ratio	.168	1	.682		
Fisher's Exact Test				.737	.399
Linear-by-Linear Association	.169	1	.681		
N of Valid Cases	250				
a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 15.78.					
b. Computed only for a 2x2 table					



The sensitivity of notching with IUGR was poor at 25% and specificity was 77%)

	Condition		
	Absent	**Present**	**Total**
Test Positive	41	17	58
Test Negative	141	51	192
Totals	182	68	250

	Estimated Value	**95% Confidence Interval**	
		Lower Limit	**Upper Limit**
Prevalence	0.272	0.218755	0.332393
Sensitivity	0.25	0.156329	0.372248
Specificity	0.774725	0.705774	0.831813
For any particular test result, the probability that it will be:			
Positive	0.232	0.182155	0.290263
Negative	0.768	0.709737	0.817845
For any particular positive test result, the probability that it is:			
True Positive	0.293103	0.18463	0.429102
False Positive	0.706897	0.570898	0.81537
For any particular negative test result, the probability that it is:			
True Negative	0.734375	0.665009	0.794168
False Negative	0.265625	0.205832	0.334991
likelihood Ratios: [C] = conventional [W] = weighted by prevalence			
Positive [C]	1.109756	0.678509	1.815096
Negative [C]	0.968085	0.841313	1.11396
Positive [W]	0.414634	0.269006	0.639099
Negative [W]	0.361702	0.284843	0.4593

Diastolic notch is not significantly associated with IUGR.

Association between PI in first trimester and IUGR

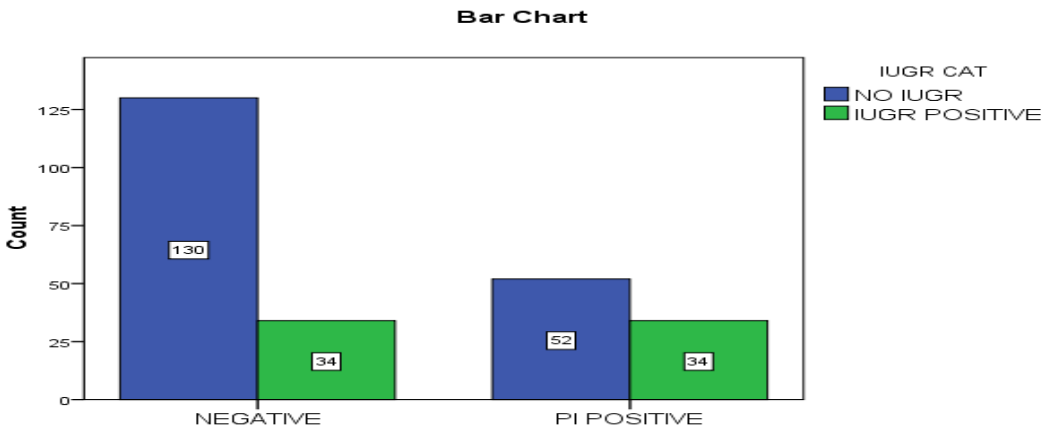
PI FRIST TRIMESTER VS IUGR Crosstabulation					
			IUGR CAT		
			NO IUGR	IUGR POSITIVE	Total
PICAT1	NEGATIVE	Count	130	34	164
		Expected Count	119.4	44.6	164.0
		% within PICAT1	79.3%	20.7%	100.0%
		% within IUGR CAT	71.4%	50.0%	65.6%
		% of Total	52.0%	13.6%	65.6%
	PI POSITIVE	Count	52	34	86
		Expected Count	62.6	23.4	86.0
		% within PICAT1	60.5%	39.5%	100.0%
		% within IUGR CAT	28.6%	50.0%	34.4%
		% of Total	20.8%	13.6%	34.4%
Total		Count	182	68	250
		Expected Count	182.0	68.0	250.0
		% within PICAT1	72.8%	27.2%	100.0%
		% within IUGR CAT	100.0%	100.0%	100.0%
		% of Total	72.8%	27.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	10.073[a]	1	.002		
Continuity Correction[b]	9.146	1	.002		
Likelihood Ratio	9.788	1	.002		
Fisher's Exact Test				.003	.001
Linear-by-Linear Association	10.033	1	.002		
N of Valid Cases	250				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 23.39.

b. Computed only for a 2x2 table



PI FIRST TRIMESTER

	Condition		Total
	Absent	**Present**	
Test Positive	52	34	86
Test Negative	130	34	164
Totals	182	68	250

	Estimated Value	95% Confidence Interval	
		Lower Limit	**Upper Limit**
Prevalence	0.272	0.218755	0.332393
Sensitivity	0.5	0.377433	0.622567
Specificity	0.714286	0.641884	0.777463
For any particular test result, the probability that it will be:			
Positive	0.344	0.285985	0.406895
Negative	0.656	0.593105	0.714015
For any particular positive test result, the probability that it is:			
True Positive	0.395349	0.293312	0.506827
False Positive	0.604651	0.493173	0.706688
For any particular negative test result, the probability that it is:			
True Negative	0.792683	0.720991	0.850331
False Negative	0.207317	0.149669	0.279009
likelihood Ratios: [C] = conventional [W] = weighted by prevalence			
Positive [C]	1.75	1.257433	2.435517
Negative [C]	0.7	0.549546	0.891645
Positive [W]	0.653846	0.478467	0.893509
Negative [W]	0.261538	0.19329	0.353885

Association between PI in second trimester and IUGR

Association between PI in second trimester and IUGR Crosstabulation

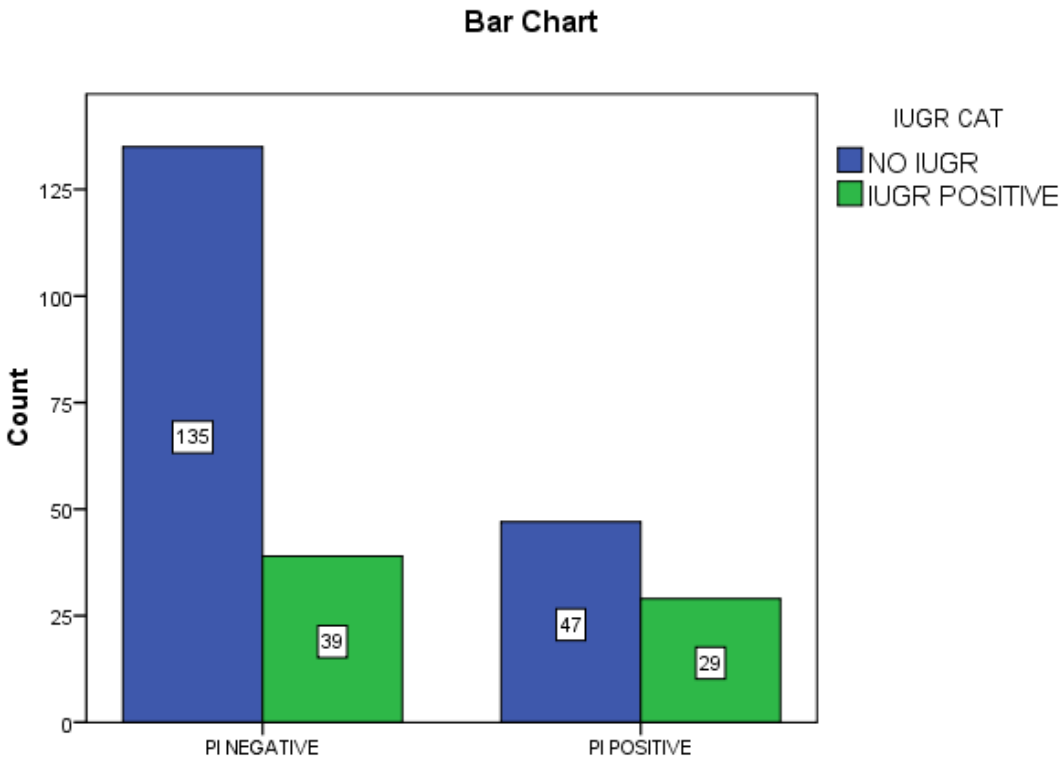
			IUGR CAT		
			NO IUGR	IUGR POSITIVE	Total
PICAT2	PI NEGATIVE	Count	135	39	174
		Expected Count	126.7	47.3	174.0
		% within PICAT2	77.6%	22.4%	100.0%
		% within IUGR CAT	74.2%	57.4%	69.6%
		% of Total	54.0%	15.6%	69.6%
	PI POSITIVE	Count	47	29	76
		Expected Count	55.3	20.7	76.0
		% within PICAT2	61.8%	38.2%	100.0%
		% within IUGR CAT	25.8%	42.6%	30.4%
		% of Total	18.8%	11.6%	30.4%
Total		Count	182	68	250
		Expected Count	182.0	68.0	250.0
		% within PICAT2	72.8%	27.2%	100.0%
		% within IUGR CAT	100.0%	100.0%	100.0%
		% of Total	72.8%	27.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.622[a]	1	.010		
Continuity Correction[b]	5.850	1	.016		
Likelihood Ratio	6.395	1	.011		
Fisher's Exact Test				.013	.009
Linear-by-Linear Association	6.595	1	.010		
N of Valid Cases	250				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 20.67.

b. Computed only for a 2x2 table



PI II TRIMESTER

	Condition		
	Absent	**Present**	**Total**
Test Positive	47	29	76
Test Negative	135	39	174
Totals	182	68	250

	Estimated Value	95% Confidence Interval	
		Lower Limit	Upper Limit
Prevalence	0.272	0.218755	0.332393
Sensitivity	0.426471	0.309264	0.552019
Specificity	0.741758	0.670736	0.80236
For any particular test result, the probability that it will be:			
Positive	0.304	0.248437	0.365702
Negative	0.696	0.634298	0.751563
For any particular positive test result, the probability that it is:			
True Positive	0.381579	0.274653	0.500569
False Positive	0.618421	0.499431	0.725347
For any particular negative test result, the probability that it is:			
True Negative	0.775862	0.705244	0.834018
False Negative	0.224138	0.165982	0.294756
likelihood Ratios: [C] = conventional [W] = weighted by prevalence			
Positive [C]	1.651439	1.141172	2.389869
Negative [C]	0.773203	0.627558	0.952648
Positive [W]	0.617021	0.4408	0.863691
Negative [W]	0.288889	0.218403	0.382122

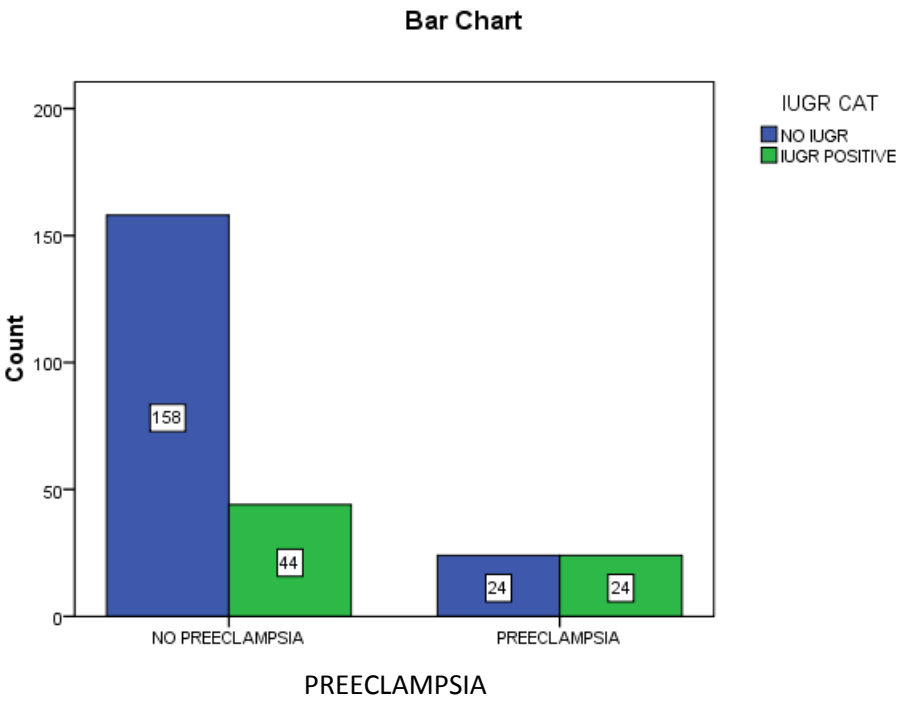
Severe IUGR is best predicted in second trimester by increased pulsatility index (positive likelihood ratio1.65, negative likelihood ratio 0.77(CI 0.62-0.95).

Association between Preeclampsia and IUGR

50% of patients with preeclampsia had IUGR while 21.8% of patients without preeclampsia had IUGR ($\chi 2=15.6$, $P<0.001$)

ASSOCIATION BETWEEN PREECLAMPSIA AND IUGR CROSS TABULATION					
			IUGR		Total
			NO IUGR	IUGR POSITIVE	
PREECLAMPSIA	NO PREECLAMPSIA	Count	158	44	202
		Expected Count	147.1	54.9	202.0
		% within PREECLAMPSIACAT	78.2%	21.8%	100.0%
		% within IUGR CAT	86.8%	64.7%	80.8%
		% of Total	63.2%	17.6%	80.8%
	PREECLAMPSIA	Count	24	24	48
		Expected Count	34.9	13.1	48.0
		% within PREECLAMPSIACAT	50.0%	50.0%	100.0%
		% within IUGR CAT	13.2%	35.3%	19.2%
		% of Total	9.6%	9.6%	19.2%
Total		Count	182	68	250
		Expected Count	182.0	68.0	250.0
		% within PREECLAMPSIACAT	72.8%	27.2%	100.0%
		% within IUGR CAT	100.0%	100.0%	100.0%
		% of Total	72.8%	27.2%	100.0%

Chi-Square Tests					
	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	15.595[a]	1	.000		
Continuity Correction[b]	14.203	1	.000		
Likelihood Ratio	14.325	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	15.533	1	.000		
N of Valid Cases	250				
a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 13.06.					
b. Computed only for a 2x2 table					



Interpretation: Using Pearson Chi-square test it is found that Preeclampsia is significantly associated with IUGR at 0.001 level of significance.

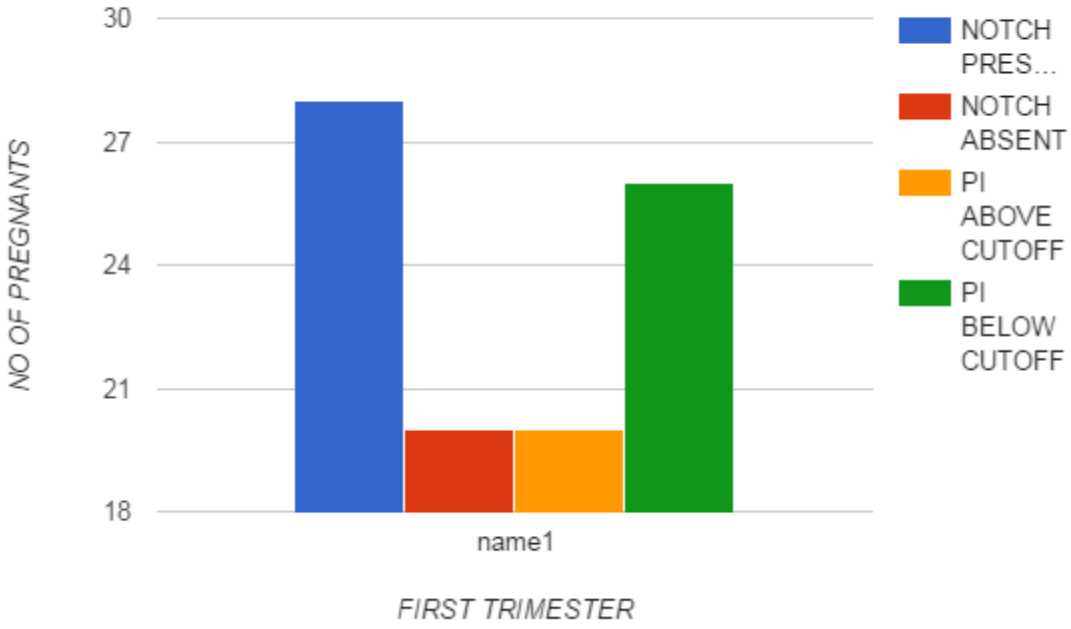
Using pulsatility index >1.6 and diastolic notch as the abnormal Doppler study the predictive value of the test was calculated.

In the first trimester screening 70(28%) patients had diastolic notching on Doppler study of which 28 patients developed preeclampsia &remaining 42 patients even though had notching had no preeclampsia. In 180 patients without diastolic notching on Doppler, 20 developed preeclampsia. In 86 patients who had PI>2.3, 20 patients developed preeclampsia and 66 patients had no preeclampsia even though PI was above 50^{th} centile level. The sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratios for the abnormal test using uterine artery notching and PI>2.3 were 58%, 79%,40%, 88%,4.02 and 0.73 respectively and 41%,67%, 65%,94%,1.8 and 1.1 respectively.

In the second trimester screening 58(23%) patients had diastolic notching on Doppler study of which 38 patients developed preeclampsia remaining 20 patients even though had notching had no preeclampsia . In 192 patients without diastolic notching on Doppler, 10 developed preeclampsia. In 76 patients who had PI>1.6 , 18 patients developed preeclampsia and 58 patients had no preeclampsia even though PI was above cut off level. The sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratios for the abnormal test using uterine artery notching and PI>1.6 were 79%, 90%,65%, 94%,12.4 and 0.4 respectively and 37%,71%, 23%,83%,0.8 and 0.2 respectively.

The relative risk of development of preeclampsia with abnormal uterine artery Doppler in the HR and LR group were 3.482 and 3.158 respectively with the p value of <0.0001 which is statistically significant

Proportion of patients developing preeclampsia with normal and abnormal uterine artery Doppler in first trimester.



Proportion of patients developing preeclampsia with normal and abnormal uterine arterydoppler in second trimester.

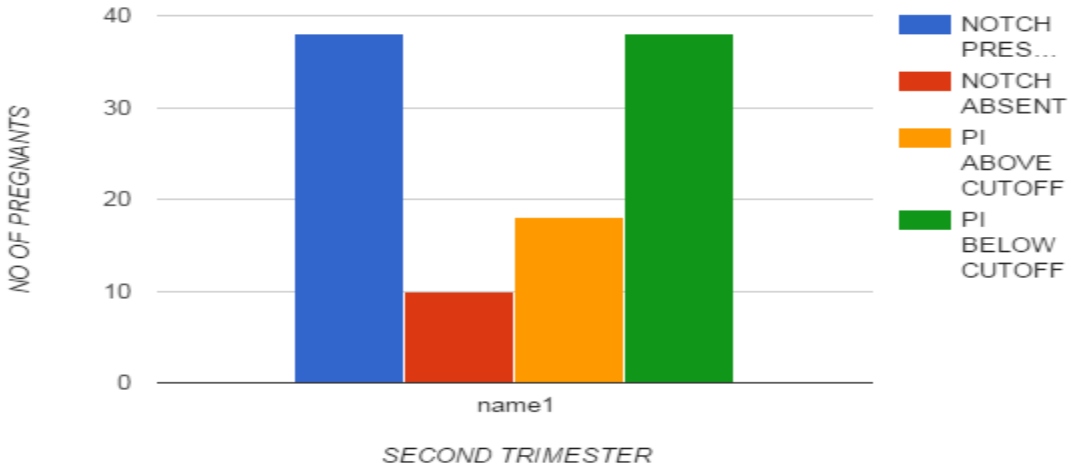


TABLE-13.Relative risk of developing preeclampsia in abnormal uterine artery Doppler velocimetry using PI.

		P value	Level of significance
High risk	5.094 95%CI 2.423-16.15	<0.0001	Significant
Low risk	7.071 95% CI4.268-15.41	<0.0001	Significant

BIRTH WEIGHT

The mean ±SD of birth weight in high and low risk group was 2.522±0.655 kg and 2.730±0.467 kg with the t value of 2.2856 and p value of 0.0234 which was statistically significant as given in Table 18 and in Graph 14.

TABLE- 14. Mean birth weight in HR and LR group.

	HR	LR	T value	P value	Statistical significance
Birth weight (kg)	2.522±0.655	2.730±0.467	2.2856	0.0234	Significant

DISCUSSION

The findings of this study will be summarized in this chapter so that conclusions can be drawn on the sensitivity of uterine artery Doppler screening in predicting preeclampsia and fetal growth restriction.

Pre-eclampsia is the most common pregnancy complication associated with serious maternal-fetal morbidity and mortality. At present the only effective treatment is delivery of the placenta. Uterine artery Doppler waveforms can identify women with obstetric complications related to abnormal placentation, since Doppler ultrasonography is a useful method to assess the velocity of uterine artery blood flow. An abnormal velocity waveform is characterised by a high resistance to flow and or an early diastolic notch. Early screening for pre-eclampsia by uterine artery Doppler has been suggested based on the concept that the pathogenic mechanisms of pre-eclampsia may be modified if prophylactic therapies are initiated early in pregnancy (Herraiz 2009 : 1123).

Abnormal uterine artery Doppler waveforms are also able to identify foetuses at high risk of preterm delivery and low birth weight (Ghidini2008 : 259). Pregnancies complicated by FGR warrant close surveillance for maternal and fetal complications and interventions in anticipation of a preterm delivery due to an apparent high risk for the development of pre-eclampsia (Mitani*et al.,* 2009 : 886). It is hypothesised that the ability to predict those women at risk for pre-eclampsia early in pregnancy might decrease maternal and fetal morbidity through closer surveillance programmes.

The purpose of this study was to assess the sensitivity of uterine artery Doppler screening in predicting pre-eclampsia and FGR before the onset of the disease. The Results of this study could be used to evaluate whether it is worthwhile implementing a routine screening program for pre-eclampsia.

In this prospective study First and second-trimester Doppler screening was carried out in 280 consecutive singleton pregnancies at 12-14 and 20-26 weeks of gestation We excluded 30 cases because they had missing outcome data. In the remaining 250 pregnant women there were 48 (19.2%) pregnant who developed pre-eclampsia, including 11 (23%) in which delivery was before 34 weeks (early preeclampsia) and 37 (76%) with delivery at 34 weeks or later (late pre-eclampsia), 6(2.3%) who developed gestational hypertension, 68(27%) who delivered IUGR. This was slightly higher than the various other studies which showed a higher incidence of IUGR associated with abnormal Doppler values and also significantly higher in the high risk group. In the study by Bhattacharya et al, incidence of IUGR was 36.54%. In various other studies the incidence of preeclampsia was ranging from 8.18% to39.2%.The tests used to predict preeclampsia include clinical history, examination findings, laboratory and hemodynamic tests. In general, tests in early pregnancy for predicting later development of preeclampsia have better specificity than sensitivity as alpha fetoprotein, fibronectin and uterine artery Doppler (bilateral notching) all have specificities above 90%.Only uterine artery Doppler pulsatility index and combinations of indices have a sensitivity of over 60%.In other such similar studies, various demographic factors were studied and the predictive value of the uterine artery Doppler was also studied.

MATERNAL AGE

Preeclampsia is more common in extremes of age group. Pregnant women below 20 years and above 35 years are at an increased risk, and in the latter group preeclampsia superimposed on chronic hypertension is seen. In our study majority (89%) of the patients who developed PET were between the ages of 18 and 34 years, 3(19%) patients were <20 years & 2 (36%) patients was >35years out of the 48 pregnant who developed pre-eclampsia Data suggests that the risk of pre-eclampsia increases by 30% for every additional year over the age of 34. In our study age, therefore, did not play a role as a risk factor for PET

PARITY

Pre-eclampsia is twice as common in primi gravid women as compared to women for whom it is their second or more pregnancy . Women with pre-eclampsia are therefore twice as likely to be nulliparous as women without preeclampsia. In DuGkitts study (2005:2) nulliparity almost triples the risk for developing pre-eclampsia. In our study, 12 (25%) patients out of the 48 who developed pre-eclampsia were primigravida, thus indicating that gravidity was not a strong predisposing factor for the disease.

BLOOD PRESSURE

The mean systolic blood pressure in the in the third trimester of pregnancy was 131.62±12.74 mmHg. The diastolic blood pressure (mean±SD) was 87.62±10.67 mmHg. The raised blood pressure in preeclampsia is due to release of placental anti angiogenic factors and other factors which causes maternal endothelial cell activation/ endothelial dysfunction.

BIRTH WEIGHT

The mean ±standard deviation of birth weight was 2.522±0.655kg. In the study by Bhattacharya et al,mean birth weight was 2.25±0.58kg. Many studies show a lower birth weight in high risk patients with abnormal uterine artery Doppler studies[26, 36]. In our study since more number of high risk patients had abnormal uterine artery Doppler and subsequently intrauterine growth restriction, the birth weight had a statistically significant p value.

UTERINE ARTERY DOPPLER WAVEFORM ANALYSIS

Uterine artery Doppler waveforms were performed to assess uteroplacental circulation in the first and second trimester in all participants. A series of screening studies involving assessment of impedance to flow in the uterine arteries, have examined the potential value of doppler assessment in identifying pregnancies at risk of complications due to impaired placentation.

Increased impedance to flow in the uterine arteries in pregnancies attending routine antenatal care identifies about 50% of those patients that subsequently develop preeclampsia and it identifies about 30% of those patients that subsequently develop FGR. Shear and colleagues (2005: 1119) reported a relationship between pre-eclampsia and FGR. Their study showed critical maternal complications more frequently in pre-eclamptic patients with associated FGR.

The current study assessed the sensitivity of Pl and diastole notching as a diagnostic tool to predict pre-eclampsia and IUGR. 33 out of the 48 patients who developed pre-eclampsia had abnormal Doppler waveforms which were evident from as early as the first trimester. The study therefore demonstrated that an abnormal uterine artery waveform with early diastolic notching could predict 58% of cases that developed PET from as early as the 1st trimester. What is however significant is that uterine artery waveform, analysis was able to predict PET in the most severe cases in patients who presented with early manifestations of the disease and had the worst pregnancy outcomes.

Pl VALUES

A study done by Melchiorre (2008: 135) reported that uterine artery Doppler indices were significantly higher in women who developed preterm pre-eclampsia.

In the current study Pl values up to the 95^{th1} centile of the Pl chart was considered as normal. The following table was populated with data obtained from a study done by Gomez and co workers(2000 :130).

TABLE 15 UTERINE ARTERY DOPPLER INDICES

Gomez *et al*	**1st trimester (Pl)**	**2"n trimester (Pl)**
5^{th} centile	1.1	0.7
50^{th} centile	1.7	1.0
95^{th} centile	2.7	1.5

These values represent the 50^{th}centile for each of the trimesters of pregnancy at 12 weeks and 22 weeks of gestation and are also used as cut off values by the Fetal Medicine Unit at Chris Hani Baragwanath Hospital in ,Johannesburg (Nicolaou, 2011).

Table 16.UTERINE ARTERY DOPPLER INDICES (50thcentile-current study)

Current study	1st trimester (Pl)	2ndtrimester (Pl)
50thcentile	1.3	0.9

Comparing the mean values in our study to the mean values in the study done by Gomez and colleagues, a difference in the mean (50thcentile) in the 1st trimester is noted. The 2nd trimester mean values in this study were similar to the values obtained by Gomez *et al.* In both studies it can be seen that the mean Pl values decreased as gestation increased as is to be expected in a normal pregnancy.

In our study the 1st trimester Pl values in patients who developed pre-eclampsia was not a strong predictor of PET. None of the values recorded were above the 95th centile when compared to the values by Gomez and co-workers. However, in clinical practice a 1st trimester Pl value of >1.5 is deemed as elevated and warrants monitoring (Nicolaou, 2011: Personal communication). In the group that developed PET, 1st trimester Pl values ranged between 0.9 and 1.75 respectively. It is thus evident that only in selected cases an increased resistance to flow was recorded in the 1st trimester.

In the 2nd trimester most of PET cases hada Pl value above the 50th centile signifying that Pl performed better as a predictor of PET in the 2nd trimester.

Comparing the mean Pl values in the patients who developed pre-eclampsia to the mean Pl values developed by Gomez *et al.*, only 6out of 20 cases were recorded values were on the 50thcentile in the 1st trimester, while 12 out of 18 2nd trimester values were above the 50thcentile. Doppler Pl values obtained in this study were above

the 50th centile. a few patients had increased Pl values of who most were marginally elevated.

Predictive value of uterine artery Doppler

In our study when the predictive value of PI in1st trimester was evaluated, the sensitivity and specificity were 41% and 67% respectively in the 1st trimester which was similar to the studies by Coleman et al and Caforio et al. The positive and negative predictive value was similar to the study by Cnossens et al, the positive and negative likelihood ratios were similar to other studies by Chien et al and our study had negative likelihood ratio of 1.2 and positive likelihood ratio of 0.8, P-0.24. Our study also gives the higher sensitivity and specificity compared to other studies

TABLE- 17. Various studies showing predictive value of the uterine artery Doppler using PI in 1st trimester.

	Type of study	Sample size	Sensitivity%	Specificity	Ppv	Npv	Plr	Nlr
Present study	Prospective	250	41	67	65	94	1.2	0.8
Cnossen et al	Prospective	4966	25	95	-	-	5.4	0.78

It was found that mean PI in the first trimester had reduced statistical significance in detecting preeclampsia .This is consistent with the findings of another study by martin et al and holis, who have shown an unchanged PI throughout the 11-14 weeks interval, but gomez et al demonstrated a lower impedance in the uterine artery of normal outcome pregnancy than in complicated cases suggesting lack of a normal uteroplacental circulation at this early stage of pregnancy may predict the later development of some pregnancy complications. The existing data suggest that increased impedance to flow in the uterine arteries identify about 25% of those who subsequently develop preeclampsia.

In 2nd trimester, the sensitivity and specificity for the uterine artery pulsatility index were 37% and 71% using PI>1.6 as the abnormal Doppler study criteria which was similar to the studies by Cnossens et al. In other studies by Papageorghiouet al and Ratanasiri et al, the sensitivity and specificity was higher compared to the present study. The present study has the positive and negative predictive value similar to studies by Bhattacharya et al and Ratanasiri et al. The positive and negative likelihood ratio of the present study were 1.99 and 1.09 which was similar to the study by Cnossens et al, Jimmy Espinoza et al and Chien et al, but Ratanasiri et al showed a higher positive likelihood ratio implicating better predictive value of the test as shown in Table.

TABLE-18.Various studies showing predictive value of the uterine artery Doppler using PI in 2nd trimester.

	Type of study	**Sample size**	**Sensitivity**	**Specificity**	**Ppv**	**Npv**	**Plr**	**Nlr**
Prajapati et al	Prospective	200	30.30	94.01	50	87.22	5.06 (2.29, 11.18)	0.74 (0.59, 0.93)
Jimmy Espinoza et al	Prospective	4190	33.3	90.5	11	97.5	3.49	0.74
Pongrojpaw et al	Prospective	330	59.25	65.60	-	-	-	-
Cnossen JS et al	Systematic review	351	19	99	-	-	21	0.82
Present study	Prospective	250	37	71	23	83	1.99	1.0

The predictive value of the uterine artery was more when pulsatility index was used with a higher sensitivity, specificity, predictive value, higher positive likelihood ratio and lower negative likelihood ratio. Also, the relative risk was higher when pulsatility index was used. Various studies have proved a higher predictive value of uterine artery Doppler study for preeclampsia and other adverse pregnancy outcomes when pulsatility index is used as seen in the present study also.

Swanepoel (2004:6) suggested that the presence of notch is a significantly better predictor of poor pregnancy outcome than the pulsatility index; however, in other studies the presence of notching in the 2nd trimester in a low risk population has been associated with a high probability for developing FGR and preeclampsia. In high-risk pregnancies the risk increases up to 60% (Hernandez-Andrade *et al.,* 2002: 441). It has been established that uterine artery notching that persist after 26 weeks of gestation be considered a risk factor for poor pregnancy outcomes (Andrarle*et al.,* 2002 : 440). An early diastolic was found to persist in 25-40% of cases after 26 weeks gestation (Swanepoel: 2004:6)

In our study the presence of notching in the second trimester was the best predictor for the development of pre-eclampsia.

Uterine artery Doppler analysis in the high risk population has shown potential for predicting adverse pregnancy outcomes (Harrington *et al.,* 2004: 50).

The results of our study confirm the work done by Pilalis (2007 : 533) and Harrington (2004:54) who both found that second trimester uterine artery Doppler screening has proven to be a sensitive and accurate tool for predicting pre-eclampsia and fetal growth restriction in high risk populations.

In 1st trimester, the sensitivity and specificity for the uterine artery diastolic notch were 58 and 79% as the abnormal Doppler study criteria which was lower to the studies by Cnossens et al. The positive and negative likelihood ratio of the present study were 2.8 and 0.5 which was higher to the study by Cnossens et al, Jimmy Espinoza et al and Albaiges G et al.

In 2nd trimester, the sensitivity and specificity for the uterine artery diastolic notch were 79 and 90% as the abnormal Doppler study criteria which was similar to the studies by Cnossens et al. The positive and negative likelihood ratio of the present study were 4 and 1.09 which was also similar to the study by Cnossens et al, Jimmy Espinoza et al and Chien et al.

We found that 151 trimester notching persisted into the 2nd trimester in (23)43% patients who developed pre-eclampsia. The presence of notching, even with a normal Pl index, places the patient at a higher risk for adverse fetal outcomes.

The findings of our study thus concur with the findings by Mcleod (2009:728) who states that the presence of an early diastolic notch is associated with adverse pregnancy outcomes. Our study also supports the findings of Kurdi (1998:344) who found that women with notching represent a group with an increased risk of developing complications, in particular those that require early delivery.

PREGNANCY OUTCOMES IN THE STUDY POPULATION

In the current study 80% of the population delivered at term, and 72% of the population delivered babies weighing more than 2500g. 19%patients developed pre-eclampsia, and 2 patient who developed pre-eclampsia had an IUFD at twenty eight weeks gestation.

CROSS TABULATIONS IN LOW BIRTHWEIGHT BABIES

Cross tabulations were done on low birth weight babies using notching in the first &second trimesters as predictors for FGR. Notching in the second trimester was once again the best predictor. Mothers with notching in the second trimester are six(6) times more likely to deliver a low birth weight baby than mothers with no notching in the second trimester.

Intrauterine growth restriction in low-risk patients was best predicted in the second trimester by an increased pulsatility index with notching (positive likelihood ratio 1.6, 95% CI –1.1 -2.3; negative likelihood ratio 0.77, 95% CI 0.62–0.95).

ASSOCIATION BETWEEN PREECLAMPSIA AND IUGR

It has been proved beyond doubt, in the previous studies and in the present study that preeclampsia is significantly associated with IUGR. The sensitivity in the present study of finding IUGR in patients with preeclampsia was 50% and specificity was 21%. This proves that both these entities preeclampsia and IUGR, stems from a common pathophysiology which has been known to be early defective placentation.

SUMMARY

Preeclampsia is a pregnancy specific disorder of unknown aetiology accounting for 14% of maternal deaths worldwide. Incidence of this disorder is around 8-10%. Uterine artery Doppler screening meets all the requirements of a worthwhile screening program in prediction of preeclampsia. Uterine artery screening at 22 to 24 weeks gestation is superior to first trimester screening in prediction of preeclampsia and other adverse pregnancy outcomes. Despite these impressive results, few hospitals have established uterine artery screening programs in the second trimester as there is no effective preventive therapy when treatment is commenced after 24 weeks and also patients may develop adverse pregnancy outcome before 24 weeks gestation.

A study was conducted in our hospital to know the predictive value of uterine artery Doppler to 14 weeks and 24 to 26 weeks gestation using diastolic notching and pulsatility index as the abnormal test results in both the high risk and low risk groups.

The results showed that abnormal uterine artery Doppler had a good predictive value in predicting women who developed preeclampsia, more so in the high risk group and that pulsatility index is a better Doppler index in the prediction of preeclampsia. This was in accordance to various other studies.

Doppler ultrasound is anon-invasive and reliable method for prediction of preeclampsia and adverse pregnancy outcome, but currently there are no effective interventions to prevent adverse outcomes based on an abnormal result. Studies are needed to find out such an intervention. Until such time, routine uterine artery Doppler screening of women is not required. Only screening in high risk women will suffice as to be more cautious during the pregnancy.

CONCLUSION

Preeclampsia accounts for 10% of perinatal mortality and 14% of maternal mortality and morbidity. Early recognition of women of preeclampsia will help in identifying high risk women who may benefit from early prophylaxis &enhanced surveillance.

Abnormal uterine artery Doppler studies in the first and second trimester have been associated with subsequent adverse pregnancy outcomes including preeclampsia, fetal growth restriction, and perinatal mortality.

Mid trimester uterine artery Doppler velocimetry can be used as a reliable screening test for prediction of preeclampsia especially in the high risk group and it helps to reduce maternal and fetal complications by elective delivery.

Increased pulsatility index with notching in second trimester predicted overall preeclampsia in high risk and low risk patients, increased pulsatility index or bilateral notching predicted severe preeclampsia. However the prediction is of not much use as there are no effective pharmacological treatment in preventing preeclampsia and other complications. As this is a small study, the usefulness of the uterine artery Doppler study has to be evaluated using a large cohort.

Pre-eclampsia is significantly associated with IUGR in the low risk population.

The mean PI cut-off which can differentiate patients who develop pre-eclampsia and IUGR was >1.6 in second trimester.

BIBLIOGRAPHY

1. Cunningham,Leveno, Bloom Hauth, Rouse,Spong .Williams Obstetrics,McGraw Hill 2009, 23rd edition, Chapter 34, Pregnancy Hypertension. Page 706-707.
2. N. Onwudiwe, C. K. H. Yu, et al. Prediction of preeclampsia by a combination of Maternal history, Uterine artery Doppler and Mean arterial pressure. Ultrasound ObstetGynecol2008; 32: 877–883.
3. WHO, 2004. Betesda, MD. Global burden of disease for the year 2001 by World Bank region, for use in disease control priorities in developing countries, National Institutes of Health: WHO. Make every mother and child count. World Health Report, 2005, Geneva: World Health Organisation, 2005. 2ndEdition.
4. Roberts, J. M. (1998).Pregnancy related Hypertension in Maternal Fetal Medicine, (Creasy, R.K and Resnik., eds.), page 883-872.4th Edition.W .B. Saunders, Philadelphia.
5. John C Hobbins. Obstetric Ultrasound artistry in practice.Chapter 15, Preeclampsia, Page 128.Blackwell Publishing.
6. Schwarze A, Nelles I et al. Doppler ultrasound of the uterine artery in the prediction of severe complications during low risk pregnancies. British Journal of Obstetrics and Gynecology,2000 February; 107(2):196-208. PMID: 15185101.
7. Edited by Trish Chudleigh, BaskyThilaganathan. Obstetric ultrasound-How, Why and When. 3rd edition .Chapter 16, Evaluating the pregnancy using Doppler, page 225-226. Churchill Livingstone.
8. James M Roberts, Judith L Balk, Lisa M Bodnar et al .Nutrient involvement in Preeclampsia, Journal of Nutrition. 2003; 133:1684-1692.
9. Peter W. Callen, Ultrasonography in Obstetrics and Gynaecology, 5th edition,The role of Doppler ultrasound in obstetrics. Page 794-807.Elsevier Saunders publication.
10. Editor DevMaulik, Doppler ultrasound in Obstetrics and Gynecology. DevMaulik,chapter 1,Dopplersonography : A brief history,page 1-6.
11. Edwin R Guzman,EftichiaKontopoulos, IvicaZalud, chapter 16, Dopplervelocimetry of the uteroplacentalcirculation,page 227.Springer publication.
12. D. C. Dutta, Text book of obstetrics, Hypertensive disorders in pregnancy. New central book agency 2004,6th edition, page 222.
13. Geoffrey Chamberlain, Philip J Steer, 2001, Turnbull's obstetrics, 3rd edition, Churchill Livngstone.

14. ACOG committee on obstetric practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. No. 33, january 2002. American college of obstetricians and gynecologists.Obstet gynecol. 2002; 99:159-67.
15. Report of the National high blood pressure education program working group on high blood pressure in pregnancy. American journal ofobstet gynecol. 2000; 183:s1-22.
16. Solmon C G, Seely E W. Preeclampsia, Searching for the cause. N Engl j med 2004; 350:641-2
17. Karumanchi S A, Maynard S E, Stillman I E, et al. Preeclampsia: a renal perspective. Kidney Int 2005;67:2107.
18. Friedman SA, Schiff E, Emeis JJ, et al. Biochemical corroboration of endothelial involvement in severe preeclampsia. Am J Obstet Gynecol. Jan 1995; 172(1):202-3.
19. Edited by Alexander Heazell et al. Chapter 4, screening for hypertensive disorders of pregnancy, page no 45.Cambridge.
20. Bhattacharyya SanjoyKumar ,KunduSarmila , KabirajSankar Prasad. Prediction of preeclampsia by midtrimester uterine artery Dopplervelocimetry in high-risk and low-risk women. The journal of obstetrics and gynecology of india, (may–june 2012) 62(3):297–300.
21. James Steer et al , High risk pregnancy – Management options, 4th edition, page 611, elseviersaunders publication.
22. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound obstetgynecol 2013;41:233-239.
23. Thangaratinam S et al, Prediction and Primary prevention of Preeclampsia. Best practice and research clinical Obstetrics and Gynaecology, Volume 25, Issue 4, August 2011, page 419-433.
24. ArisAntsaklis, George Daskalakis, Uterine artery Doppler in the prediction of preeclampsia and adverse pregnancy outcome, Donald school Journal of ultrasound in Obstetrics and Gynecology, april-june 2010;4(2):117-122.
25. Steel S A et al, Early Doppler ultrasound screening in prediction of hypertensive disorders of pregnancy, The Lancet, Volume 357, issue 9249, pages 53-56, 6 January 2001. Pmid 1972486.
26. Ratanasiri T, Prediction of preeclampsia in a low risk population using diastolic notch of uterine arteries, Arch Gynecol Obstet.2005 jan;271(1):46-52.epub 2004 jun8.pmid:21218589.
27. Asnafi N et al, Mid trimester uterine artery Doppler ultrasound as a predictor of adverse obstetric outcome in high risk pregnancy.Taiwan J Obstet Gynecol. 2011 March;50(1):29-32. doi: 10.1016/j.tjog.2009.08.002. PMID:21482371.

28. Pongrojpaw D et al, Second trimester uterine artery Doppler screening in prediction of adverse pregnancy outcome in high risk women.J Med Assoc Thai. 2010 Dec;93Suppl 7:S127-30.PMID:21294407.
29. Onwudiwe N, Yu CK et al, Prediction of preeclampsia by a combination of maternal history, uterine artery doppler and mean arterial pressure.Ultrasound Obstet Gynecol. 2008 Dec;32(7):877-83. doi: 10.1002/uog.6124.PMID:18991324.
30. Elisa Llurba, Elena Carreras et al. Maternal history and uterine artery Doppler in the assessment of risk for development of early and late onset preeclampsia and intrauterine growth restriction.ObstetGynecol Int. 2009;2009:275613. doi: 10.1155/2009/275613. E pub 2009 May 27.PMID:19936122
31. Sibai B, Dekker G, Kupferminc M. Preeclampsia. Lancet2005; 365:785-99.
32. Montan S, Sjoberg NO, Svenningsen N. Hypertension in pregnancy- Fetal and infant outcome: a cohort study. Clinexphypertens- part B hypertens pregnancy 1987;6:337-48.
33. Khan K S, Wojdyla D et al. WHO analysis of causes of maternal death: a systematic review. Lancet2006; 367:1066-74.
34. Rich Edwards JW, ColditzG A, et al. Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann inter med 1999;130:278-84.
35. Caforio L, Testa AC et al. Predictive value of uterine artery velocimetry at midgestation in low and high risk populations: a new prospective.FetalDiagnTher. 1999 Jul-Aug;14(4):201-5. PMID10420041.
36. C K H Yu, O Khouri et al. Prediction of preeclampsia by uterine artery doppler imaging: relationship to gestational age at delivery and small for gestational age. Ultrasound obstetgynecol 2008; 31:310-313.
37. Barker DJ. The developmental origins of chronic adult disease.Actapaediatrsuppl 2004;93:26-33
38. Jeltsje S Cnossen, Rachel K Morris et al. Use of uterine artery doppler ultrasonography to predict preeclampsia and intrauterine growth restriction: a systematic review and bivariablemeta analysis.CMAJ.2008 March 11:178(6):701-711.
39. Patrick F W Chien, Neil Arnott, et al. How useful is uterine artery Doppler flow velocimetry in the prediction of preeclampsia, intrauterine growth retardation and perinatal death? An overview.BJOG 2000,107(2),pp.196-208
40. Bower S, Bewley S, Campbell S. Improved prediction of preeclampsia by two stage screening of uterine arteries using the early diastolic notch and colourDoppler imaging. ObstetGynecol 1993;82:596-602.

41. Coleman Mag, Mc Cowan Lme, North Ra. Mid trimester uterine artery Doppler screening as a predictor of adverse pregnancy outcome in high risk women. Ultrasound Obstet Gynecol. 2000;15:7–12. Doi: 10.1046/j.1469-0705.2000.00014.x. PMID:10776006
42. Harrington K. et al. The use of uterine artery Doppler in pregnancy induced hypertensive disorders. Switzerland: Obstetrics and Gynaecology, MD Kaunus University; 1997. P. 16–8.
43. Jimmy Espinoza,Juan Pedro Kusanovic et al.Should bilateral uterine artery notching be used in the risk assessment for preeclampsia, small-for-gestational-age, and gestational hypertension?,J Ultrasound Med 2010; 29:1103–1115
44. Anthony C Sciscione, Edward J Hayes. Uterine artery Doppler flow studies in Obstetric practice. American journal of Obstetrics and Gynaecology, August 2009. Page 121-126.
45. Saloni R. Prajapati, NanditaMaitra. Prediction of preeclampsia by a combination of Maternal history, Uterine Artery Doppler and Mean Arterial Pressure(A Prospective Study of 200 Cases).J ObstetGynaecol India. 2013 March; 63(1): 32–36. PMCID: PMC3650143
46. Marina Noris et al.Mechanisms of Disease:Preeclampsia. Nature Clinical Practice Nephrology(2005)1, 98-114.
47. Elaine Bell, A bad Combination, Nature Reviews Immunology 4, 927(December 2004).
48. Stephen Lee. The role of ultrasound in the diagnosis and management of the growth restricted fetus. Australasian Journal of Ultrasound in Medicine. August 2010; 13(3):31-36
49. Fabricio da Silva Costa et al. Which is the best period to perform Uterine artery Doppler in the prediction of pregnancy complications?.RadiologiaBrasilika,Volume 39, no. 2 Sao Parlo March/April 2006.
50. MarckPietryga et al. Abnormal uterine Doppler is related to vasculopathy in pregestational Diabetes Mellitus, Vascular Medicine, Circulation.2005:112:2496-2500.
51. Free AH, Free HM. Urinanalysis, Critical Discipline of Clinical Sciences.CRC Crit. Rev. Clin.Lab.Sci: 1972:3(4):481-531.
52. Henry, J B et al.Clinical Diagnosis and management by Laboratory Methods, 18th ed.Philadelphia: Saunders:1991: page 396-397,415.

PROFORMA

I. Particulars of the patient:

1. Name
2. Age
3. Occupation
4. Address
5. Phone number

II. History:

1. Duration of amenorrhea
2. Any history of high risk factors:

a. Age <20 years
b. Age> 35 years
c. H/o diabetes
d. H/o chronic hypertension
e. H/o chronic renal disease
f. Past bad obstetric history of preeclampsia, iugr and iufd
g. Family history of preeclampsia/ iugr

III. Obstetric history: married life, consanguinity, obstetric index, history of present pregnancy

IV. Menstrual history: previous cycles, regularity, last menstrual period (LMP), estimated date of delivery(EDD) and period of gestation.

V. Investigations

- Haemoglobin
- Urine albumin
- Urine routine
- Ultrasonography at 16 to 18 weeks:

  Single/multiple:

  Gestational age:

  EDD according to scan:

  Any fetal anomalies:

VI. Category of the patient: high risk / low risk

VII. Uterine artery doppler ultrasonography at 12 to 14 weks and at 24 to 26 weeks:

- Diastolic notch: present/ absent unilateral/ bilateral
- Pulsatality index: right left

NORMAL/ ABNORMAL

VIII. Follow up chart:

Date	Gestational age	Any complaints	BP	Urinary protien	USG findings

IX. Outcome:

- Mode of delivery: vaginal/caesarean/instrumental
- Gestational age at delivery: preterm/term/postterm
- Any comlications: abruption/imminent symptoms/eclampsia/IUGR/still birth
- Perinatal outcome: birth weight/NICU admission

INFORMATION SHEET

- We are conducting a study on "First Trimester and Midtrimester Uterine Artery Doppler Sonography in Predicting Preeclampsia and IUGR" your participation in the study is very valuable to us.

- The purpose of this study is to find out whether First Trimester and Midtrimester Uterine Artery Doppler Sonography changes is significant in predicting preeclampsia and IUGR in pregnant women.

- We will do Uterine Artery Doppler Sonography in pregnant women between 12-14 weeks and 20-26 weeks.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

தகவல் தாள்

- கர்ப்பிணிப் பெண்களின் 12-14 வாரங்கள் மற்றும் 20-26 வாரங்கள் கருப்பை தமனி டாப்ளரை நாம் ஆய்வு செய்து வருகிறோம். ஆய்வில் உங்கள் பங்களிப்பு எங்களுக்கு மிகவும் மதிப்புமிக்கதாகும்.

- இந்த ஆய்வின் நோக்கம், கர்ப்பிணி பெண்களுக்கு கர்ப்ப காலத்தில் கருப்பை தமனி டாப்ளர் மாற்றத்தை குறிப்பான்களாக முன்சூல் வலிப்பு மற்றும் குழந்தையின் வளர்ச்சி குன்றை அறிய பயன்படுத்தலாமா என்பதை கண்டுபிடிக்கவே.

- நாங்கள் கர்ப்பிணிப் பெண்களின் கருப்பை தமனி டாப்ளரை மதிப்பீடு செய்வோம்.

- ஆய்வில் நோயாளிகளின் தனியுரிமை ஆய்வு முழுவதும் பராமரிக்கப்படும். ஆராய்ச்சியின் விளைவாக எந்தவொரு வெளியீடும் ஏற்பட்டால், தனிப்பட்ட நபரின் அடையாளம் வெளியிடப்படாது.

- இந்த ஆய்வில் பங்கு பெறுவது தனிநபரின் விருப்பமாக உள்ளது. இந்த ஆய்வில் பங்கேற்க வேண்டுமா அல்லது எப்போது வேண்டுமானாலும் விலகலாமா என்பதைத் தீர்மானிக்க நீங்கள் சுதந்திரமாக இருக்கின்றீர்கள்.

- ஆய்வின் முடிவுகளின் முடிவில் அல்லது சிறப்புப் பரீட்சையின் பெறுபேறுகள் உங்களை ஆய்வுக்கு உட்படுத்தியிருக்கலாம் அல்லது ஆய்வு அல்லது சிகிச்சையில் உதவுவதற்கு ஏதேனும் அசாதாரணமானவை எனக் கண்டறிந்து இருக்கலாம்.

புலன்விசாரணியின் கையொப்பம் பங்கேற்பாளரின் கையொப்பம்

INFORMED CONSENT FORM

Title: "First Trimester and Midtrimester Uterine Artery Doppler Sonography in Predicting Preeclampsia and IUGR"

Name of the investigator: Dr. PRIEYA DHARSHINI.J

Name of the participant:

Name of the institution: Govt. Kasturba Gandhi Hospital & Institute of obstetrics and gynaecology, MMC, Chennai.

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and exercising my power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.

2. I have read the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained my rights and responsibilities by the invigilator,

5. I have informed the investigator of all the treatments I am taking or have taken in the past months/years including any native treatments

6. I have been advised about the risks associated with my participation in the study

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8. I have not participated in any research study within the past.

9.I am aware of the fact that I can opt out of the study at any time without having to give any reason. This will not affect my future treatment in the hospital.

10. I am also aware that the investigators may terminate my participation in this study at any time, for any reason, without my consent.

11. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regularity authorities, Govt. agency and IEC if required.

12. I understand that my identity will be kept confidential if my data are publicly presented.

13. I have had my questions answered to my satisfaction.

14. I consent voluntarily to participate in the research/study

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

FOR ADULT PARTICIPANTS

1. Name and signature /thumb impression of the participant(or legal representative if participant incompetent)
   Name_____ Signature_____ Date_____

2. Name and signature of impartial witness(required for illiterate patients)
   Name_____ Signature _____Date_____

3. Name and signature of the investigator or his representative obtaining consent
   Name_____ Signature_____ Date_____

தகவல் தொடர்பு படிவம்

தலைப்பு: முதல் மூன்று மாதம் மற்றும் இரண்டாம் மூன்று மாத கருப்பை தமனி டாப்ளர் மாற்றத்தை குறிப்பான்களாகக் கொண்டு முன்சூல் வலிப்பு மற்றும் குழந்தையின் வளர்ச்சி குன்றை அறிதல்.

புலன்விசாரணியின் பெயர்: டாக்டர். ஜெ. பிரியதர்ஷினி

பங்கேற்பாளரின் பெயர்:

நிறுவனத்தின் பெயர்: மகப்பேறியல் மற்றும் பெண்ணோயியல் நிறுவனம், எம்.எம்.சி, சென்னை.

நான் _____ இந்த படிவத்தில் தகவலைப் படித்திருக்கிறேன் (அல்லது அது எனக்குப் படிக்கப் பட்டுள்ளது). நான் எந்த கேள்விகளையும் கேட்க தயங்கவில்லை, அவை அனைத்திற்கும் பதில் கிடைத்தது. நான் 18 வயதிற்கு மேல் இருக்கிறேன், தேர்வு செய்ய என் ஆற்றலைப் பயன்படுத்துகிறேன், இந்த ஆய்வில் பங்கேற்பாளராக சேர்க்கப்பட என் அனுமதியினை அளிக்கிறேன்.

1. இந்த ஒப்புதல் படிவத்தையும் எனக்கு வழங்கப்பட்ட தகவலையும் நான் வாசித்து புரிந்து கொண்டேன்.

2. ஒப்புதல் ஆவணத்தை நான் படித்திருக்கிறேன்.

3. ஆய்வின் தன்மை பற்றி நான் விளக்கப்பட்டுள்ளேன்.

4. எனது உரிமைகள் மற்றும் பொறுப்புகள் பற்றி நான் விளக்கப்பட்டுள்ளேன்.

5. கடந்த சில மாதங்களில் நான் எடுக்கும் அனைத்து சிகிச்சைகளுக்கும் புலன்விசாரணை அறிவித்திருக்கிறேன்

6. ஆய்வில் என் பங்களிப்புடன் தொடர்புடைய அபாயங்கள் பற்றி நான் அறிவுறுத்தப்பட்டிருக்கிறேன்

7. நான் புலனாய்வாளருடன் ஒத்துழைக்க ஒத்துக்கொள்கிறேன் மற்றும் நான் அசாதாரண அறிகுறிகளை அனுபவித்தால் உடனடியாக அவரை / அவளுக்கு தெரிவிப்பேன்.

8. கடந்த காலத்திற்குள் நான் எந்த ஆராய்ச்சியிலும் பங்கேற்கவில்லை.

9. எந்த நேரத்திலும் எந்தவொரு காரணத்திற்காகவும் நான் இந்த ஆய்வில் இருந்து விலகிக் கொள்ள முடியும் என்பதை நான் அறிந்திருக்கிறேன். இது என் எதிர்கால சிகிச்சையை மருத்துவமனையில் பாதிக்காது என்பதையும் அறிந்திருக்கிறேன்.

10. எந்தவொரு காரணத்திற்காகவும், என் அனுமதியின்றி ஆய்வாளர் என் பங்கேற்பை நீக்க முடியும் என்பதை அறிந்திருக்கிறேன்.

11. இந்த ஆய்வில் பங்கேற்பாளர்களான, ஆய்வாளர்கள் அரசு நிறுவனம் மற்றும் IEC ஆகியவற்றிற்கு தேவைப்பட்டால், என்னிடமிருந்து பெறப்பட்ட தகவலை வெளியிட புலனாய்வுக்கு அனுமதி அளித்தேன்.

12. எனது தரவு பகிரங்கமாக வழங்கப்பட்டால், எனது அடையாளத்தை ரகசியமாக வைத்திருப்பதை நான் புரிந்துகொள்கிறேன்.

13. என் திருப்திக்கு என் கேள்விகளுக்கு பதில் அளிக்கப்பட்டது.

14. ஆராய்ச்சி / ஆய்வுகளில் பங்கேற்க நான் தன்னார்வத்துடன் ஒப்புக்கொள்கிறேன்

இந்த ஆய்வின் போது எனக்கு ஏதாவது கேள்விகள் இருந்தால், நான் புலனாய்வாளரை தொடர்பு கொள்ள வேண்டும் என்று எனக்கு தெரியும். இந்த ஒப்புதலுக்கான படிவத்தை கையொப்பமிடுவதன் மூலம், இந்த ஆவணத்தில் கொடுக்கப்பட்ட தகவல்கள் தெளிவாக எனக்கு விளக்கப்பட்டு எனக்கு புரிந்துவிட்டது என்பதை நான் சான்றளிக்கிறேன். இந்த ஒப்புதல் ஆவணத்தின் நகலை எனக்கு வழங்கப்படும்.

பழங்குடி வகுப்பாளர்களுக்கு

பங்கேற்பாளரின் பெயர் மற்றும் கையொப்பம் / கட்டைவிரல் உணர்வை (அல்லது பங்கேற்பாளர் தகுதியற்றவர் எனில் சட்ட பிரதிநிதி)

பெயர்_____ கையொப்பம் _____ தேதி _____

பாரபட்சமற்ற சாட்சியின் பெயர் மற்றும் கையொப்பம் (படிப்பறிவற்ற நோயாளிகளுக்கு தேவை)

பெயர்_____ கையொப்பம் _____DATE_____

புலன்விசாரணை அல்லது அவரது பிரதிநிதி அனுமதிப்பத்திரத்தின் பெயர் மற்றும் கையொப்பம்

பெயர்_____ கையொப்பம் _____ தேதி _____

KEY TO MASTER CHART

GA- gestational age at delivery(weeks)
Sbp- systolic blood pressure
Dbp- diastolic blood pressure
C-caesarean delivery
N- normal delivery
In-instrumental delivery
Sp- severe preeclampsia
Mp- mild preeclampsia
Gh- gestational hypertension
Ie- imminent eclampsia
Ape- antepartum eclampsia
Iugr-intrauterine growth restriction
Abr- abruption
Oligo-oligohydramnios
L-live birth
D- still birth
BW-birth weight in gms
n- no NICU admission
y- NICU admission

SN- serial no.
BMI- body mass index kg/m^2
Gra- gravidity
m- multigravida
p- primigravida
H-high risk
L- low risk
UAD- uterine artery Doppler
DN+/- : diastolic notching
Rt- right side
Lt – left side
Pi- pulsatality index
N- normal