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

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ABSTRACT

BACKGROUND: Pre-eclampsia is the most common pregnancy complication associated with serious maternal-foetal 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, 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

- **AIMS AND OBJECTIVES**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.

METHODOLOGYThis 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 weekswith correct LMP attending antenatal Hospital constituted the study population

RESULTSIn thisprospective study First and second-trimester Doppler screening was carried out in 280 consecutive singleton pregnancies at 12-14 and 22-26 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.

CONCLUSION

Preeclampsia accounts for 10% of perinatal mortality and 14% of maternal mortality and morbidity.

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 foetal 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.   .

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

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).

The trophoblast normally invades the decidual portion of the spiral arteries beginning by the 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 preeclampsia, 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].

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.

Incidence

Hypertensive disorders complicate 5 - 10 percent of all pregnancies.

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
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

Microangiopathic Hemolysis—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

MATERNAL COMPLICATIONS

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

NEONATALCOMPLICATIONS

Fetalcomplications of preeclampsia include:
- ● Preterm delivery (15-67%)
- ● FGR (10-25%)
- ● Hypoxia-neurologic injury (<1%)
- ● Perinatal death (1-2%)

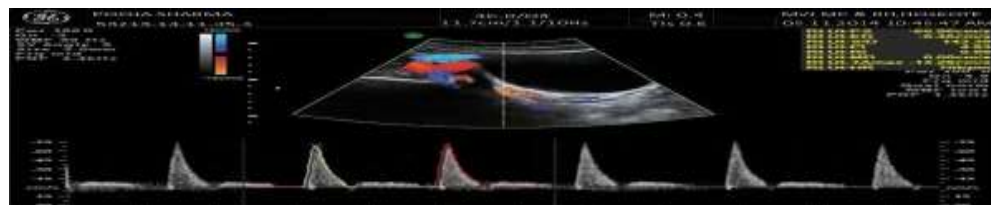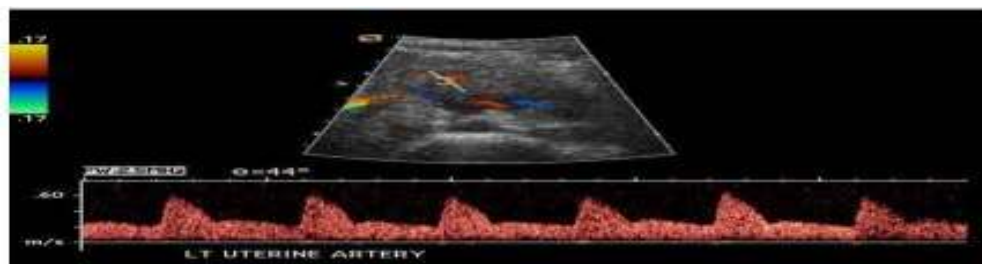FIGURE:9- **.**Obtaining uterine artery waveform.(normal waveform)

FIGURE: 10 Non pregnant uterine artery wave form

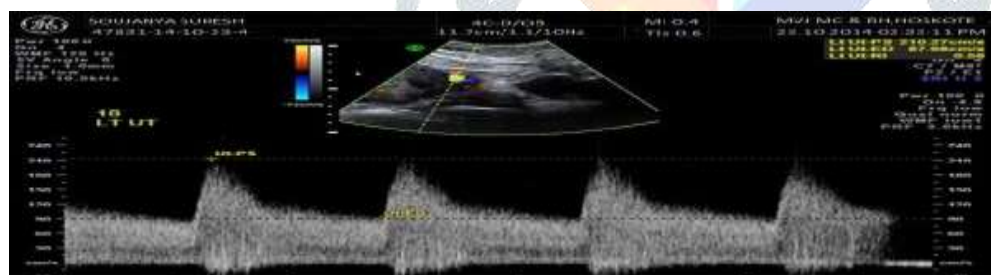

FIGURE: 11 First trimester uterine artery wave form.

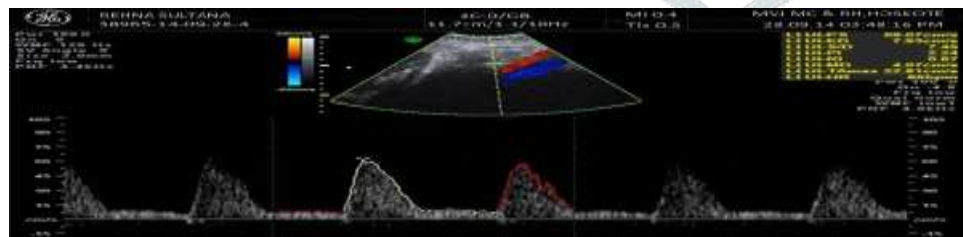FIGURE: 12 Second trimester uterine artery wave form

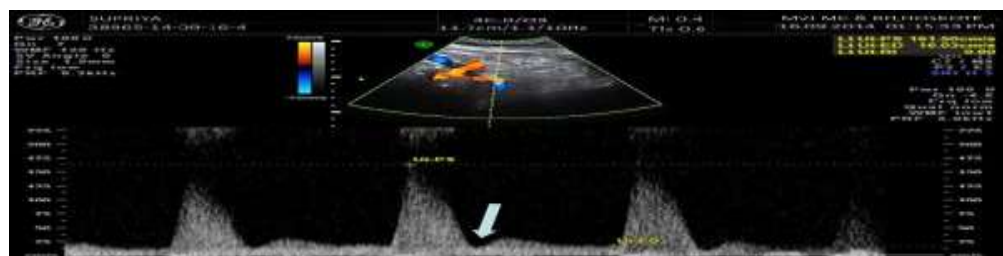FIGURE: 13 Abnormal wave form with high RI

FIGURE: 14 Notchingin second trimester.

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.

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.
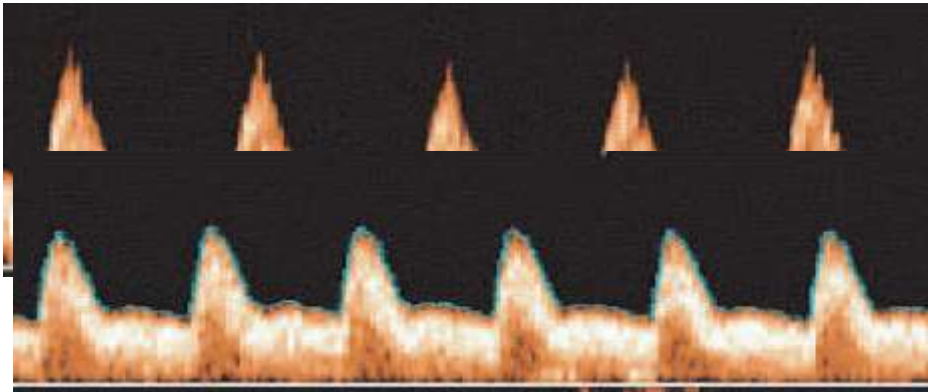

FIGURE18 -.Normal color Doppler waveform of the uterine artery at 24 weeks.

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 Hospital

 BMI was calculated using the formula:weight (kg)/height (m^2). & Recording of blood pressure was done

Preeclampsia is defined as a blood pressure of at least 140/90 mmHg measured on two occasions each 4 hours apart, accompanied by protienuria 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
- ● 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)

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 foetal 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.

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.

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 ,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.

HIGH RISK FACTOR

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(48)
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%)
Family h/o preeclampsia, IUGR	4	1(25%)

COMPLICATIONS

TABLE - 8Various 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%)
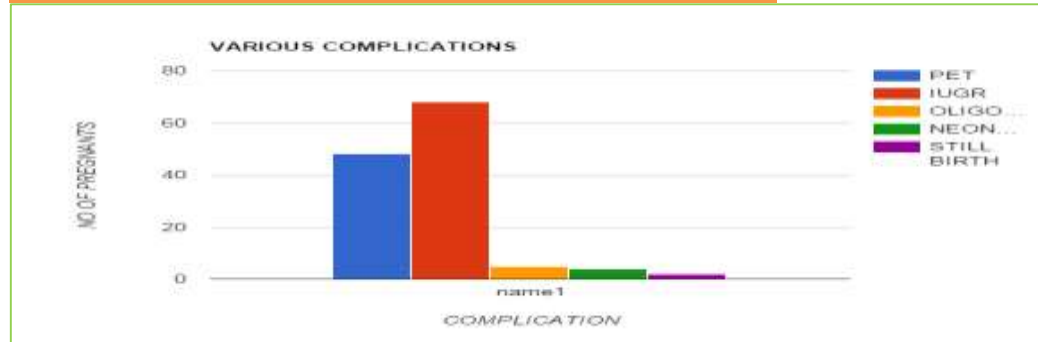
Graph 2: Various complications in the study group.

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
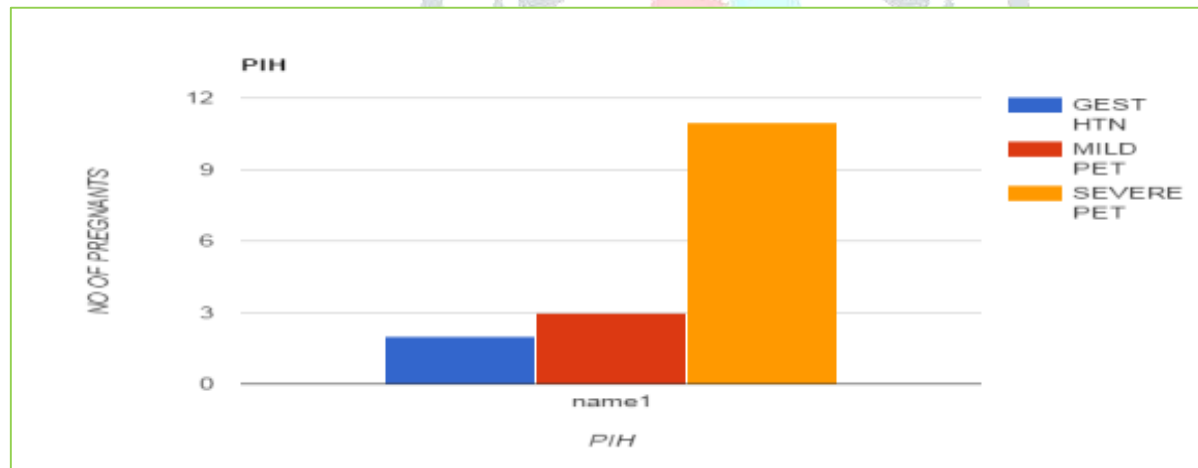
Graph 3-.showing types of pregnancy induced hypertension

PREGNANCY OUTCOME:

32 pregnant womens delivered before 37 week of gestation and rest of 198 pregnant womens 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 foetal death	2(0.8%)

Babies weighing less than 2500 g at term were considered small for gestational age, whereas foetal 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 foetus had developed IUGR out of 250 birth remaining 182 foetus had no evidence of IUGR.
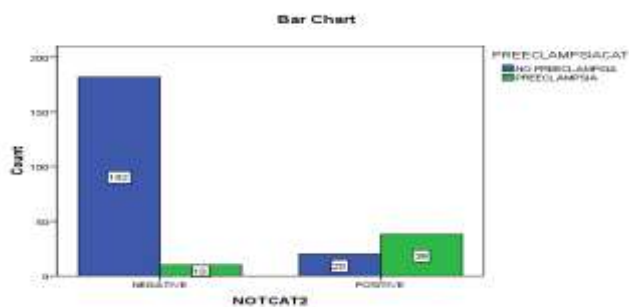
Association between Notching in1ˢᵗ trimester and preeclampsia

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

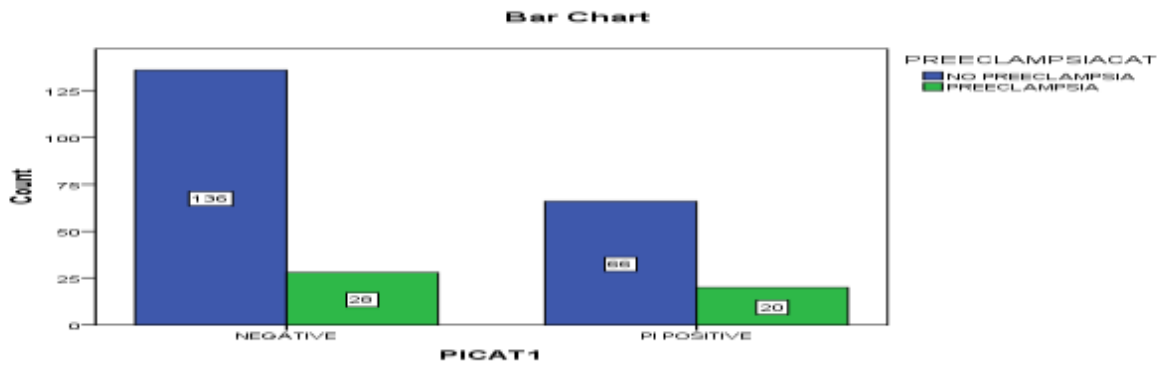**Association between Notching 2ⁿᵈ trimester and preeclampsia**

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

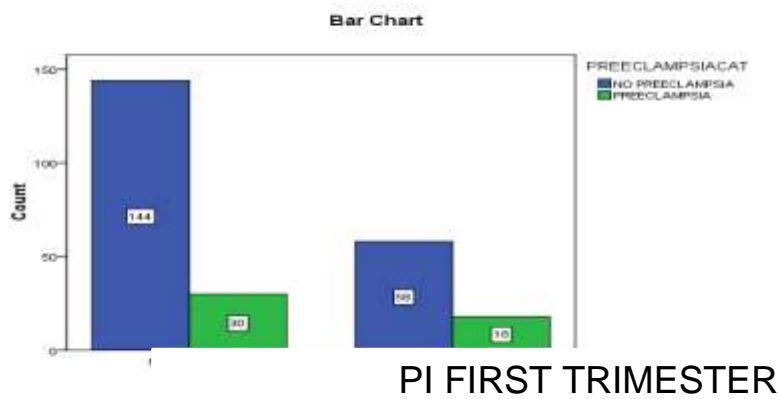**Association between PI first trimester and preeclampsia**

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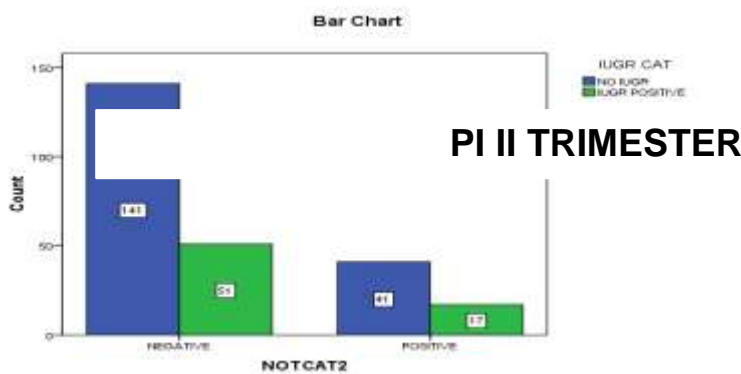
NOTCHING FIRST TRIMESTER

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 ($\chi2=1.41$, p=0.23)

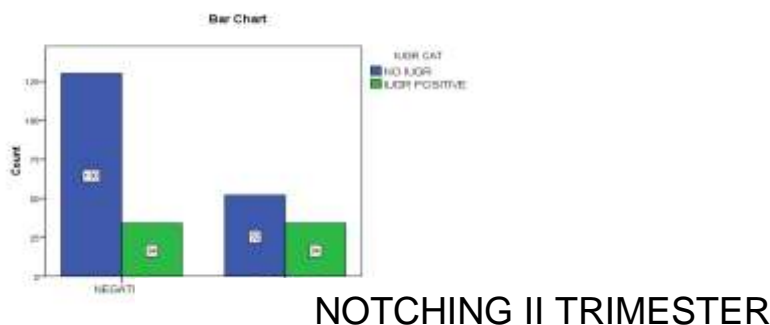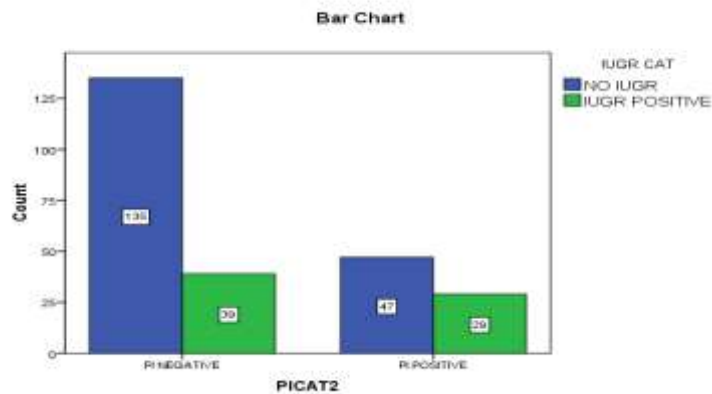PI FIRST TRIMESTER

Association between Notching and IUGR

70.7% who had notching had no IUGR and 26.6% without notching had IUGR ($\chi2=0.17$, p=0.68)

PI II TRIMESTER

## Association between PI in first trimester and IUGR

NOTCHING II TRIMESTER

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 ($\chi2$=15.6, P<0.001)
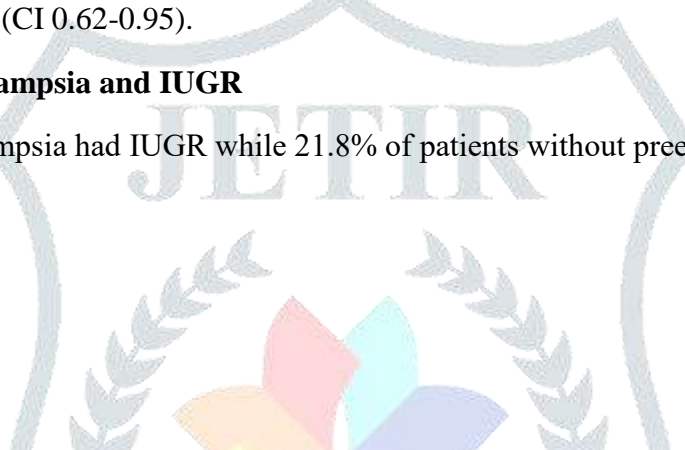
PI II TRIMESTER
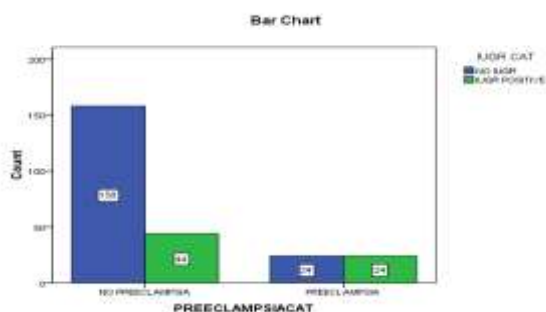
Using pulsatility index >1.6 and diastolic notch as the abnormal Doppler study the predictive value of the test was calculated.

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 50th 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 respectivelyand 41%,67%, 65% 94% 1.8 and 1.1 respectively

PREECLAMPSIA

In the s[ ] 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 cutoff 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.
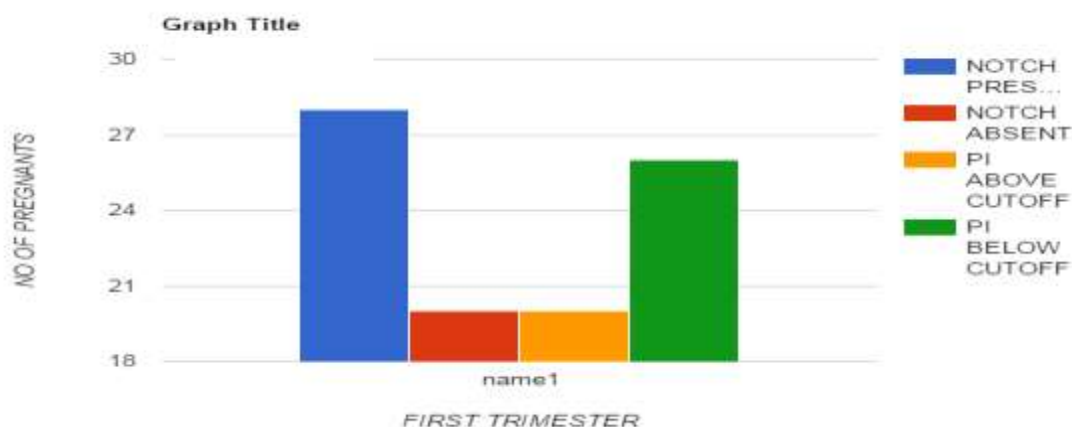
Proportion of patients developing preeclampsia with normal and abnormal uterine artery doppler in second trimester.
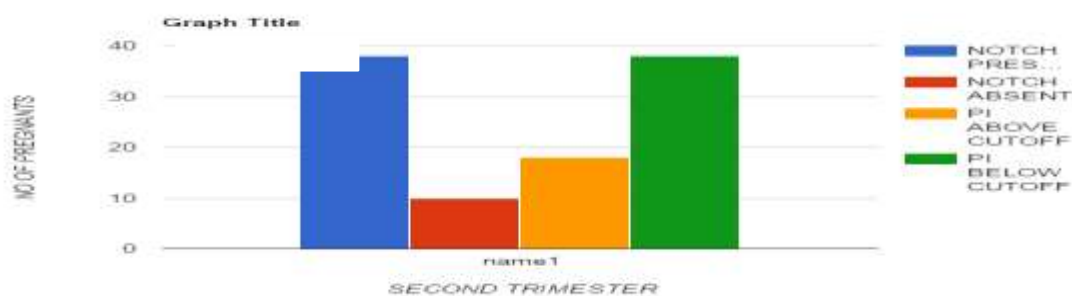
DISCUSSION

.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.

In this prospective study First and second-trimester Doppler screening was carried out in 280 consecutive singleton pregnancies at 12-14 and 22-26 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%..

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.

Pl VALUES

TABLE 15UTERINE ARTERY DOPPLER INDICES

Gomez *et al*	1st trimester (Pl)	2"n trimester (Pl)
5th centile	1.1	0.7
5ot[11] centile	1.7	1.0
95th centile	2.7	1.5

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.

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

In the 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.

TABLE-18.Various studies showing predictive value of the uterine artery Doppler using PIin 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
Pongro Paw 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.

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).

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, foetal 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 foetal complications by elective delivery.

Increased pulsatility index with notching in the 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 treatments 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.

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 outcomes 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 with various other studies.

Doppler ultrasound is a non-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.

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