



# **Uterine Artery Doppler Screening in 2<sup>nd</sup> Trimester of Pregnancy for Prediction of Pre-eclampsia and Fetal Growth Restriction**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. Author NAM designed the study, wrote the protocol, performed the analyses and revised the manuscript, Author TIC co-ordination of the research activity and manuscript preparation. Author TRC prepared the first draft of the manuscript and managed the literature searches. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** Pre-eclampsia is a pregnancy specific disorder characterized by hypertension and proteinuria after 20 weeks of gestation. Uterine artery Doppler velocimetry analysis has been extensively studied in the second trimester of pregnancy as a predictive investigation for the future development of pre-eclampsia and Fetal Growth Restriction.

**Aims:** To predict the probability of developing pre-eclampsia of pregnant women and Fetal Growth Restriction in relation with normal and abnormal Doppler velocimetry of uterine artery at 2nd trimester of pregnancy.

**Methods:** A total of 97 pregnant women of 2nd trimester of pregnancy were included in this study.

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After taking informed written consent of the participants, all they underwent uterine artery Doppler velocimetry at 22<sup>nd</sup> and 24<sup>th</sup> week of pregnancy. They again examined clinically during delivery at different gestational age. Pre-eclampsia (PE) was diagnosed on the basis of measurement of blood pressure as well as urine routine and microscopic examination. Fetal Growth Restriction (FGR) was determined by measuring birth weight and gestational age at the time of delivery. Development of PE and FGR was observed in relation to severity of Uterine Artery Doppler Velocimetry findings. A pre-structured data collection sheet was used as a research tool for data collection. Statistical analyses of the results were obtained by using windows-based computer software devised with Statistical Packages for Social Sciences (SPSS-23).

**Results:** More than half (52.6%) of the subjects belonged to age 21-25 years and 52(53.6%) subjects were nulliparous. More than half (56.7%) of the subjects came from low income group family. Pre-eclampsia developed 11(11.3%) of the patients, 15(15.5%) had FGR and 12(12.4%) had notching in 2<sup>nd</sup> UADV at 24<sup>th</sup> week. Presence of Pre-diastolic notch in 2<sup>nd</sup> UADV study at 24<sup>th</sup> week to predict pre-eclampsia has sensitivity 72.7%, specificity 95.4%, accuracy 92.8% and positive predictive values 66.7% and negative predictive value 96.5%. Presence of Pre-diastolic notch in 2<sup>nd</sup> UADV study at 24<sup>th</sup> week to predict FGR has sensitivity 20.0%, specificity 89.0%, accuracy 78.4% and positive predictive values 25.0% and negative predictive value 85.9%. The mean age was 28.69±7.81 years who had per-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week and 24.13±6.11 years who had normal UADV and the p value is 0.022 which is significant. The mean para was 1.29±0.33 who had per-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week and 1.77±0.29 who had normal UADV together with remarkable p value which is 0.001. The mean BMI was 23.59±1.09 Kg/m<sup>2</sup> who had per-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week and 21.57±0.47 Kg/m<sup>2</sup> who had normal UADV with notable p value 0.001 in this study.

**Conclusion:** Uterine artery Doppler velocimetry in early pregnancy can be a good investigating tool for prediction of subsequent development of pre-eclampsia and Fetal Growth Restriction.

*Keywords: Pre-eclampsia; uterine artery doppler velocimetry; pregnancy; second trimester.*

## 1. INTRODUCTION

Pregnancy induced hypertension (PIH) is a hypertensive disorder in pregnancy that occurs after 20 weeks of pregnancy in the absence of other causes of elevated blood pressure (BP) ( $\geq 140/90$  mm of Hg measured 2 times with at least of 6 h interval) in previously normotensive woman. When PIH is associated with multi-organ failure with significant proteinuria (protein in urine  $\geq 0.3$  g/in 24 h) it is termed as pre-eclampsia. When pre-eclampsia is associated with grand mal seizures and/or coma, it is defined as eclampsia [1]. Pre-eclampsia and eclampsia are nothing but the grave consequences of pregnancy induced hypertension.

Pre-eclampsia is a major cause of morbidity and mortality for the woman and her child. Globally, each year more than four million women develop pre-eclampsia and approximately 100,000 women will have eclamptic convulsion with over 90% occurring in developing countries [2]. It results in 12% of maternal deaths globally, up to 40% of maternal death in some countries and is responsible for occurrence of up to 13% of still births and 20% of early neonatal deaths [3]. Approximately 10-15% of maternal deaths in

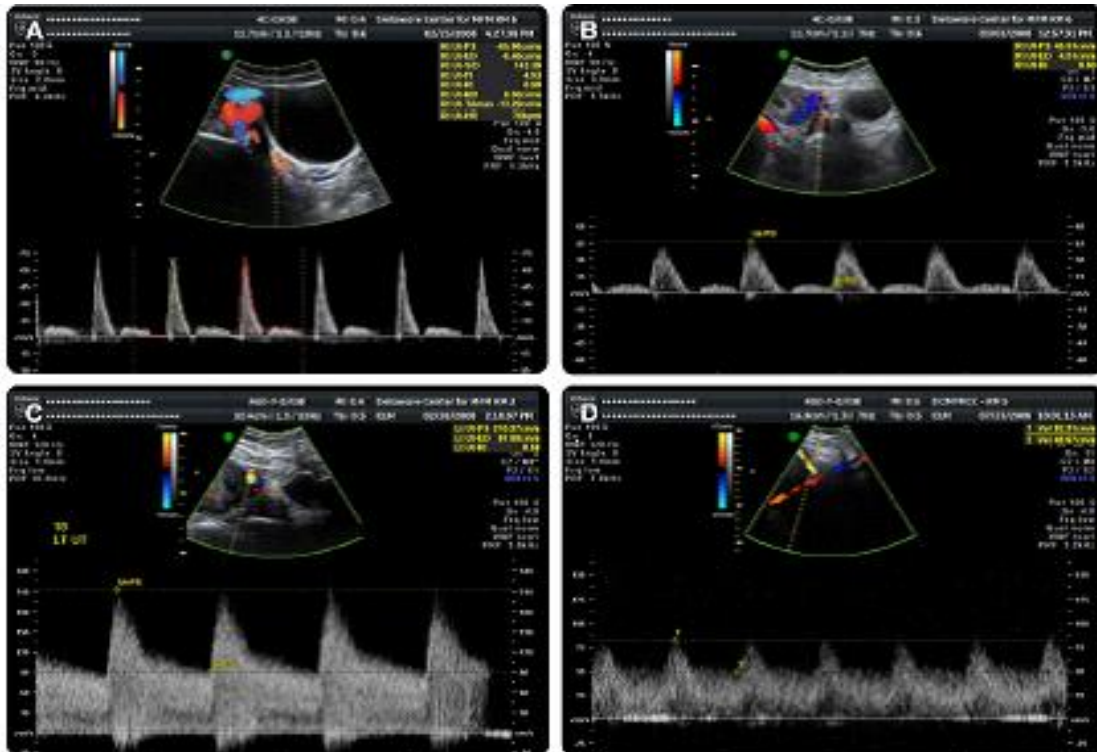
developing countries are associated with pre-eclampsia leading to eclampsia [4]. There is no concrete data found on incidence of pre-eclampsia in our country, but calculated from the US Census Bureau, International Data Base, 2004, the extrapolated annual incidence of pre-eclampsia in Bangladesh is 76,032 [5]. Our neighboring country, India has the incidence of pre-eclampsia, as recorded from hospital statistics, varying widely from 5 to 15% [6]. Bangladesh, the most densely populated country in South East Asia has high maternal mortality as well as fetal mortality rate. According to WHO severe pre-eclampsia accounts for 16.1% of maternal deaths in developed countries over the past 2 decades [7].

Pre-eclampsia is a multiorgan disease process of unknown etiology characterized by the development of hypertension and proteinuria after 20 weeks of gestation. Delivery is the only cure for pre-eclampsia. Decisions regarding the timing and mode of delivery are based on a combination of maternal and fetal factors. Eclampsia is the occurrence of convulsions in association with the signs and symptoms of pre-eclampsia. It is traditionally considered a more severe form of pre-eclampsia and complicates

nearly one in 2000 pregnancies [8]. Severe pre-eclampsia can be defined as the development of hypertension characterized by systolic blood pressure exceeding 160mm Hg and/or diastolic blood pressure exceeding 110mmHg. It can be accompanied by symptoms or signs of imminent eclampsia, pulmonary edema, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome [9]. Fetal complications include placental abruption, intrauterine growth restriction, premature delivery, and intrauterine fetal death. The incidence of stillbirths and neonatal deaths in mothers who suffered severe pre-eclampsia was 22.2/1000 and 34.1/1000, respectively, in the UK with a higher incidence in developing countries [10]. The impact of the disease is felt more severely in developing countries where, unlike other more prevalent causes of maternal mortality (such as hemorrhage and sepsis), medical interventions may be ineffective due to late presentation of cases. The problem is confounded by the continued mystery of the etiology and the unpredictable nature of the disease. Pre-eclampsia is leading reason of maternal ICU admissions, and responsible for 15–20% of maternal deaths worldwide [11]. In India the

incidence of pre-eclampsia is 7.6% during pregnancy of which 3.3% is severe pre-eclampsia [12]. Severe pre-eclampsia is associated with progressive deterioration of maternal and fetal conditions, and the only known definitive treatment is delivery. However, delivery at a gestational age remote from term (early preterm delivery) is associated with increased risk for adverse neonatal outcome.

Early risk estimation would allow more individualized prenatal care by reduction of routine visits for the majority of women classified as being at low risk for pregnancy complications. At the same time surveillance in specialist clinics would be more readily available for women at high risk; for example women with a history of previous pre-eclampsia. Furthermore, low-dose acetylsalicylic acid treatment could be initiated early in pregnancy and potentially half the risk for subsequent development of pre-eclampsia [13]. Uterine Artery Doppler Velocimetry(UADV) reflects the utero-placental blood flow and seems to be a good, non-invasive prognostic tool in the prediction of adverse pregnancy outcomes, especially pre-eclampsia and FGR.



**Fig. 1. Uterine artery Doppler ultrasound in the nonpregnant and pregnant patient**  
 A. Nonpregnant patient. B. First trimester. C. Second trimester. D. Third trimester



**Fig. 2. Uterine artery notching**

In normal pregnancy, placental trophoblast cells invade the inner third of the myometrium and migrate the entire length of the maternal spiral arteries. Remodeling of these high resistance arteries results in a low resistance and high flow state in the intervillous space, which optimizes delivery of oxygen and nutrients to the fetus. This change in resistance is reflected in uterine artery Doppler studies by a high diastolic velocity with continuous flow during diastole. In women who develop pre-eclampsia there is failure of trophoblast invasion of the uterine vasculature with the result that the spiral arteries retain the muscle elastic coating and impedance to blood flow persists [14]. A similar mechanism of failed trophoblast invasion and high resistance has been described in women who subsequently deliver infants with growth restriction [15]. Theoretically, a pathological increase in placental vascular resistance should be detectable by abnormal Doppler flow studies of the maternal uterine vessels, and this could offer the potential to detect women at risk for diseases like pre-eclampsia and Fetal Growth Restriction.

In non-pregnant state and in 1<sup>st</sup> trimester of pregnancy Doppler velocimetry of uterine artery usually have an early diagnostic notch (Fig. 1). After 20<sup>th</sup> weeks of gestation velocimetry of

diastolic notching starts to decrease gradually. At the end of 24<sup>th</sup> week the notch completely disappears in normal cases (Fig. 1). If it persists after 24 weeks it can be a good predictor of development of future complication of current pregnancy (Fig. 2).

## 2. MATERIALS AND METHODS

### 2.1 Literature Search

The presence of a diastolic notch was a better predictor of pre-eclampsia than an elevated RI. In an evaluation of women at increased risk for pre-eclampsia or fetal growth restriction, [16]. The presence of a diastolic notch carried a 57% positive predictive value for subsequent severe complications and 93% predictive value for any complication [16]. Although this combination had the strongest positive predictive value, the sensitivity remained low for any complications (21%) and for severe complications (27%). PI has been less commonly reported, but using levels above the 95 percentile or a 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 the tests at 24-26 weeks may add further benefit [17].

## 2.2 Sequential Screening

### 2.2.1 Screening in low risk populations

Abnormal uterine artery Doppler studies in both the first and second trimesters have been shown to be associated with subsequent perinatal complications. For women with abnormal testing in the first trimester, the likelihood ratio (LR) for the development of pre-eclampsia is approximately 5, while those with normal Doppler flow studies have an LR of 0.5 [18]. Similarly, an abnormal test carries an LR of 2 for fetal growth restriction, with an LR of 0.9 after a normal test result [18]. Though this relationship persists with testing in the second trimester, the sensitivity may be lower [18]. However, Antsaklis et al (2000) found the sensitivity and specificity of screening for pre-eclampsia to be 81% and 87% at 20 weeks, and 76% and 95% at 24 weeks' gestation [19].

The largest systematic review judging the utility of uterine artery Doppler assessment was published by Chien and colleagues [20]. Strict criteria regarding diagnostic interventions and outcome measures were used for inclusion. Twenty-eight studies met their criteria, encompassing a total of 12,994 patients. Analysis of studies involving low risk populations revealed that an abnormal velocity waveform with or without a diastolic notch carried an LR of 6.4 for subsequent development of pre-eclampsia (95% confidence interval [CI], 5.7-7.1, and a negative result carried an LR of 0.7 (95% CI, 0.6-0.8). Women with a positive test had an LR of 3.6 (95% CI, 3.2-4.0) for the development of fetal growth restriction and a negative result carried a 0.8 LR (95% CI, 0.8-0.9). Results for the prediction of perinatal death were less robust with an LR of 1.8 (95% CI, 1.2-2.9) for a positive test result, and 0.9 (95% CI, 0.8-1.1) for a negative result. A recent meta-analysis found a positive LR for pre-eclampsia of 7.5 (95% CI, 5.4-10.2) and a negative LR of 0.59 (95% CI, 0.47-0.71), and for severe pre-eclampsia a positive LR of 15.6 (95% CI, 13.3- 17.3) and a negative LR of 0.4 (95% CI, 0.2-0.6). Furthermore, in women with abnormal uterine artery Doppler studies a positive LR of 9.1 (95% CI, 5.0-16.7) and a negative LR of 0.89 (95% CI, 0.85- 0.93) were found for the occurrence of growth restriction [20].

### 2.2.2 Screening in high risk populations

Restriction of screening to populations at increased risk for adverse outcomes can improve the predictive value of the test. Based on this principle it is plausible that uterine artery Doppler studies could prove more useful when performed on at-risk women. The meta analysis by Chien et al included 12 studies of high risk patients which met stringent inclusion criteria [20]. The LR for pre-eclampsia after an abnormal test was 2.8 (95% CI, 2.3-3.4), resulting in an increase in the pretest probability from 9.8-23%. Similar results were obtained for the prediction of fetal growth restriction, with an LR of 2.7 (95% CI, 2.1-3.4), with the probability increasing from 17.8-36.7% with a positive test. The LR of perinatal death after an abnormal test was 4.0 (95% CI, 2.4-6.6), increasing the pretest probability from 8.9-27.8%. A recent meta-analysis on uterine artery Doppler and adverse pregnancy outcomes in high risk gravidas included 83 studies with approximately 18,000 women, and found that the presence of notching had a positive LR of 20.2 (95% CI, 7.5-29.5) and a negative LR of 0.17 (95% CI, 0.03-0.56) for pre-eclampsia. In the same analysis, women with an RI <0.58 had a positive LR of 10.9 (95% CI, 10.4-11.4) and negative LR of 0.20 (95% CI, 10.4-11.4) for growth restriction.

Though an effective intervention to avoid complications has not been identified for high risk women with an abnormal uterine artery Doppler study, it is plausible that testing could be used to select those who are at lower risk based on a reassuring test. The patient with a negative study could then undergo fewer evaluations during the pregnancy, with a reduction in health care costs and time lost. Axt-Flidner et al (2005) considered this possibility in a prospective study of at risk singleton pregnancies (history of essential hypertension or pre-eclampsia, prior infant with fetal growth restriction or intrauterine death, or prior placental abruption) [21]. Bilateral uterine artery notching was associated with a positive predictive value of 33% (RR, 12.7) for a composite morbidity defined as the occurrence of pre-eclampsia or fetal growth restriction requiring delivery before 34 weeks, or fetal demise or placental abruption at any gestational age. Alternatively, the negative predictive value was also high at 93-97%. The highest negative predictive value (97%) was seen for women with both a normal RI and the lack of bilateral uterine artery notching. The authors concluded that high-risk women who had normal uterine artery Doppler studies at 19-26 weeks' gestation could

be considered to be a low risk group suitable to less intensive antenatal care. Subsequent studies have also found high negative predictive values among high-risk populations. Harrington et al found reassuring testing to carry a negative predictive value of 99.2% for pre-eclampsia, 95.9% for SGA, 100% for abruption, and 97.7% for stillbirth and/or neonatal death [22]. Similarly, Frusca et al found superimposed pre-eclampsia to develop in 12% of women with abnormal flow studies and in none of those with reassuring studies among 78 gravidas with chronic hypertension. The rate of fetal growth restriction was also low among women with reassuring Doppler studies (2% vs 52%) [23].

### 2.3 Design of the Study

This prospective observational study was carried out among pregnant mothers of 2<sup>nd</sup> trimester of pregnancy on January 2017 to December 2017 in the department of Obstetrics and Gynaecology, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh.

### 2.4 Estimation of Sample Size

$$n = \left[ \frac{Z_{\alpha} \sqrt{2P(1-2P)} + Z_{\beta} \sqrt{p_1(1-p_1) + p_2(1-p_2)}}{p_1 - p_2} \right]^2$$

Where

$Z_{\alpha}$ , = Standard normal deviation. Usually assumed at 1.96 which corresponds to 95% confidence limit

$Z_{\beta}$ , = 1.28 at 90% power (when  $\beta=0.1$ )

P is the average of  $(p_1+p_2)/2$ ,

$p_1$  = 0.04 (15/379) [24]

$p_2$  = 16.1% [7]

$$n = \left[ \frac{Z_{\alpha} \sqrt{2 \times 0.1 \times (1 - 2 \times 0.1)} + Z_{\beta} \sqrt{0.04(1 - 0.04) + 0.16(1 - 0.16)}}{0.04 - 0.161} \right]^2$$

$n=124.49$

Therefore the estimated sample size was 125.

### 2.5 Sampling Methods

Purposive sampling is the method of choice to select the sample from the pregnant mothers at 22<sup>nd</sup> and 24<sup>th</sup> weeks of gestation attending Department of Obstetrics & Gynecology in Dhaka Medical College Hospital for ante natal checkup.

## 2.6 Selection Criteria

### 2.6.1 Inclusion criteria

This study encompassed pregnant women at 2<sup>nd</sup> trimester.

### 2.6.2 Exclusion criteria

The women with multiple gestations as they have higher incidence of placental insufficiencies, who had major structural malformation of fetus as they have possibilities of termination of pregnancy and data collection would thus be incomplete, with hypertensive disorders who were already on medication will not provide a true reflection on result, with previous collagen vascular disease, previous PE, renal disease as they are belongs to high risk group were excluded in this study.

### 2.7 Prime Variables

The participants were examined for various variables including (a) independent variables (findings of uterine artery velocimetry at 2<sup>nd</sup> trimester of pregnancy), (b) dependent variables (mode of delivery, indications for CS, frequency of ANC, perinatal outcome such as AGA, SGA, IUD, APGAR score of neonates at 1<sup>st</sup> min and at 5<sup>th</sup> min, mean birth weight, mean gestational age, postnatal death), (c) confounding variable or demographic variables (age, parity, educational status, occupation, socioeconomic status, residence).

### 2.8 Procedures of Preparing and Organizing Materials

Sample selection was done on the basis of inclusion and exclusion criteria.

After explaining the objectives of the study, written informed consent was obtained from the women who agreed to participate. Once a viable intra-uterine pregnancy was confirmed, Uterine Artery (UA) spectral Doppler assessment was performed in 22 weeks and 24 weeks of gestation on a GE Vivid 3 ultrasound unit, using a trans abdominal approach. Here 2 Uterine Artery Doppler Velocimetry (UADV) were done in each patient as abnormalities of imaging like notching is usually disappear at 22<sup>nd</sup> week in maximum cases. Even in those where it persists after 22<sup>nd</sup> week were disappeared at 24<sup>th</sup> week in majority cases. To ensure consistency of results, the consultant Radiologist was the only person

performing the scans and the ultrasound unit was serviced and calibrated on a regular basis. The probe was placed lateral to the uterus and the transducer gently tilted medially until the UA was identified where it crossed over the external iliac artery. The sample gate was placed over the entire diameter of the artery and pulsed wave Doppler was used to obtain three consecutive UA waveforms. Pre-diastolic notching was observed recorded. The Doppler assessment was repeated during the 22nd and 24th week scan. Ultrasound criteria for demonstration of high resistance flow were guided by [25]. The presence of UA notching during the second trimester was considered indicative of increased vascular resistance in the placental bed. All the patient again examined at different gestational age at the time of delivery. Pre-eclampsia (PE) was diagnosed on the basis of blood pressure measurement and urine R/E. Fetal Growth Restriction (FGR) was determined by measuring birth weight and gestational age at the time of delivery. Biographical data, uterine artery Doppler pre-diastolic notching status, fetal gestational age and fetal birth weight was recorded and compared for each patient. Descriptive and inferential statistical analyses were performed with SPSS version 23.0. P-value was determined by student's t test. sensitivity, specificity, positive predictive value and negative predictive value were determined. P-value was significant at  $<0.05$ . Relative Risk (RR) for development of PE and FGR in relation to severity of UADV findings was determined. All the results were presented in tabular and figure form.

## 2.9 Equipment Used

There are certain equipment's which are used to conduct the study are observation of doppler images, questionnaires, clinical examination, relevant laboratory investigations etc.

## 2.10 Procedures of Data Analysis and Interpretation

The data were collected by active participation and by interviewing through preformed structured questionnaires, checked as well as edited after collection and created chart by spread sheet of Windows 7. Frequency distribution and normal distribution of all continuous variables were calculated. Cross tabulation was prepared and a comparison was made between the respondents from different age, sex, educational, occupational

status and knowledge of symptoms. Chi-square analysis, student's t test, odds ratio have been prepared using SPSS version 23. 'P' values  $<0.05$  was considered as statistically significant.

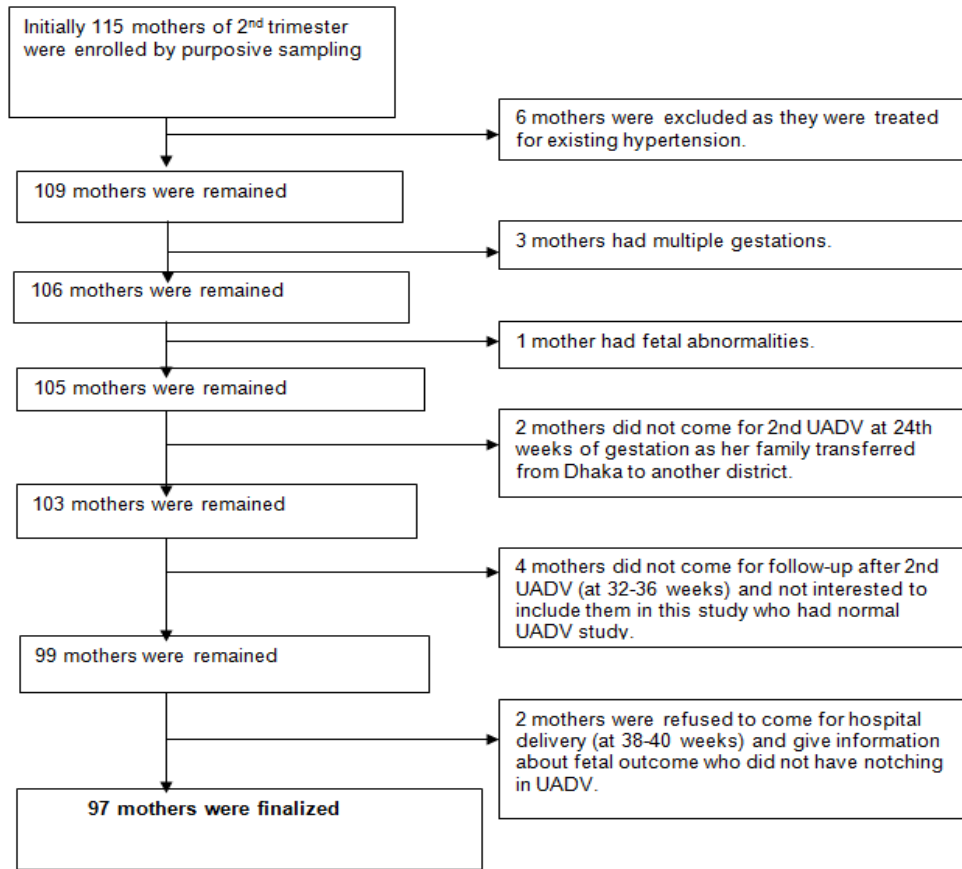
## 2.11 Ethical Issues

Ethical clearance for the study was taken from the department (department of Obs and Gynae) and concerned authority, DMCH (No: MEU-DMC/ECC/2017/190). The entire study subject was thoroughly appraised about the nature, purpose and implications of the study, as well as entire spectrum of benefits and risks of the study. There is minimum physical, psychological, social and legal risk during physical examinations; proper consent was taken. Interest of the study subjects was compromised to safeguard their rights and health. All study subjects were assured of adequate treatment of any complications developed in relation to purpose and freedom to withdraw themselves from the study any time. A signed informed consent was taken from the patient convincing that privacy of the patient was maintained and she was compensated for loss of work time if she wants. A data sheet was prepared for which a short interview of 15-30 minutes was required. No drug or placebo was used for this study.

## 3. RESULTS

A systematic flow diagram of the selection of participation of pregnant mothers of 2<sup>nd</sup> trimester of pregnancy are shown below:

Flow chart shows a total of 97 pregnant mothers of 2<sup>nd</sup> trimester of pregnancy were incorporated in this study. Initially 115 mothers were included. Multiple gestations, as these pregnancies are known to have a higher incidence of placental insufficiency, fetal abnormalities, as the possibility that those patients might opt for a pregnancy termination existed and data collection would thus be incomplete, patients on treatment for hypertensive disorders - results from those patients would not provide a true reflection as the patients were already on medication, patients having history of collagen vascular diseases before pregnancy, unwilling mothers to enroll in this study, to come for follow up and to come for hospital delivery were excluded from the study. The present study findings were discussed and compared with previously published relevant studies.



Flow chart 1. A systematic flow diagram of the selection of participation of pregnant mothers of 2<sup>nd</sup> trimester of pregnancy

Table 1. Distribution of the study subjects by age, para, BMI and socioeconomic status (n=97)

Age (in year)	Number of subjects n (%)	Mean±SD	Range (min, max)
≤20	23 (23.7)	23.4±3.4	18, 33
21-25	51 (52.6)		
26-30	19 (19.6)		
>30	4 (4.1)		
<b>Para</b>			
0	52 (53.6)	1.10.7	0, 3
1	27 (27.8)		
2	17 (17.5)		
3	1 (1.0)		
<b>BMI (Kg/m<sup>2</sup>)</b>			
<18.5 (Underweight)	17 (17.5)	20.1±1.8	16.2, 22.9
18.5-22.9 (Normal)	80 (82.5)		
<b>Socioeconomic status</b>			
Low	55 (56.7)		
Lower middle	31 (32.0)		
Upper middle	9 (9.3)		
Higher	2 (2.1)		

Low income= ≤15,000/- per month; Middle income= 16,000/- to 30,000/- per month, Higher income= >30,000/- per month (Overview of Bangladesh, [http:// azamoverseasbd.com/index.php/overview-of-Bangladesh?showall=&limitstart=](http://azamoverseasbd.com/index.php/overview-of-Bangladesh?showall=&limitstart=))



Table 1 shows age, para, BMI and socioeconomic status of the study subjects and it was observed that more than half (52.6%) of the subjects belonged to age 21-25 years. The mean age was found 23.4±3.4 years with ranged from 18 to 33 years. More than half (53.6%) subjects were nulli-para. Less than one fourth (17.5%) subjects had BMI <18.5 kg/m<sup>2</sup> (Underweight). The mean BMI was found 20.1±1.8 kg/m<sup>2</sup> with ranged from 16.2 to 22.9 kg/m<sup>2</sup>. More than half (56.7%) subjects came from low income group family.

Table 2 shows that 12(12.4%) patients had pre-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week.

Table 3 shows that 11(11.3%) patients developed pre-eclampsia and 15(15.5%) had FGR. Among 97 pregnant mother 11 developed

PE and the rest were normal. Futhermore, 15 fetus showed FGR where the rest of the fetus had normal birth weight according to gestational age.

Table 4 shows Comparison of findings in 2<sup>nd</sup> UADV at 24<sup>th</sup> week with development of Pre-eclampsia, it was observed that, true positive 8 cases, false positive 4 cases, false negative 3 and true negative 82 cases are identified by pre-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week.

The validity test of presence of Pre-diastolic notch in 2<sup>nd</sup> UADV study at 24<sup>th</sup> week to predict pre-eclampsia has sensitivity 72.7%, specificity 95.4%, accuracy 92.8% and positive predictive values 66.7% and negative predictive value 96.5%.

**Table 2. Distribution findings of 2<sup>nd</sup> UADV at 24<sup>th</sup> week among the study subjects (n=97)**

Findings of 2 <sup>nd</sup> UADV at 24 <sup>th</sup> week	Number of subjects	Percentage
Pre-diastolic notch Present	12	12.4
Normal study	85	87.6

*UADV=Uterine Artery Doppler Velocimetry*

**Table 3. Development of pre-eclampsia and fetal growth restriction among the study subjects (n=97)**

	Number of subjects	Percentage
Pre-eclampsia	11	11.3
Normal Pregnancy	86	88.7
FGR	15	15.5
Normal fetus	82	84.5

*FGR=Fetal Growth Restriction*

**Table 4. Comparison of findings of 2<sup>nd</sup> UADV at 24<sup>th</sup> weeks with development of Pre-eclampsia**

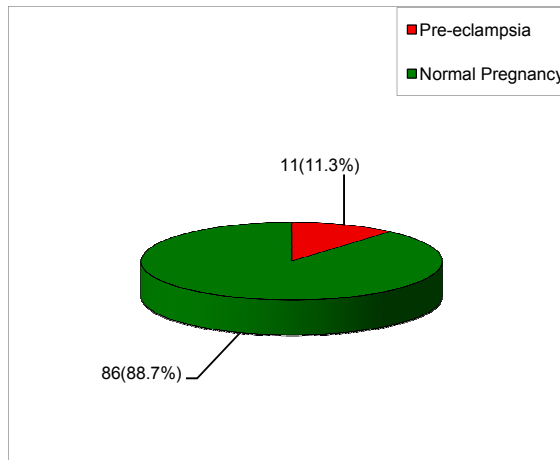
Findings in 2 <sup>nd</sup> UADV at 24 <sup>th</sup>	Pre-eclampsia	Normal	Total
Pre-diastolic notch present	8(true positive)	4(false positive)	12
Normal study	3(False negative)	82(true negative)	85
<b>Total</b>	<b>11</b>	<b>86</b>	<b>97</b>

*UADV=Uterine Artery Doppler Velocimetry*

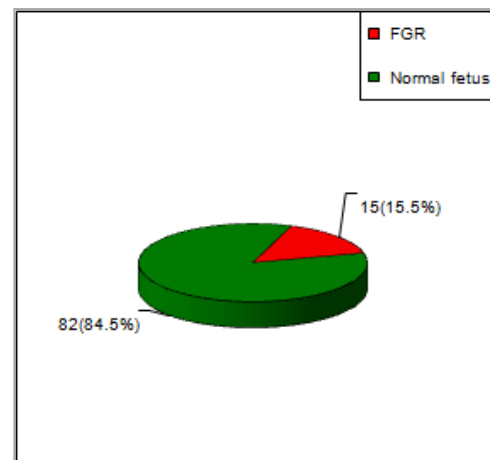
**Table 5. Sensitivity, specificity, accuracy, positive and negative predictive values of Pre-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week to predict pre-eclampsia**

Validity test	Percentage
Sensitivity	72.7
Specificity	95.4
Accuracy	92.8
Positive predictive value	66.7
Negative predictive value	96.5

*UADV=Uterine Artery Doppler Velocimetry*



**Fig. 3. Pie chart shows development of pre-eclampsia of the study subjects**



**Fig. 4. Pie chart shows development of FGR of the study subjects**

Table 6 shows that in UADV at 22<sup>nd</sup> weeks out of 16 patients having unilateral Pre-diastolic notch 2(12.5%) had pre-eclampsia. Out of 4 patients having bilateral Pre-diastolic notch 3(75.0%) had pre-eclampsia. Out of 77 normal patients 1(1.3%) had pre-eclampsia. In UADV at 24<sup>th</sup> weeks out of 7 patients having unilateral Pre-diastolic notch 3(42.9%) had pre-eclampsia. Out of 5 patients having bilateral Pre-diastolic notch 5(100.0%) had pre-eclampsia. Out of 85 normal patients 3(3.5%) had pre-eclampsia.

Table 7 shows Comparison of findings in 2<sup>nd</sup> UADV at 24<sup>th</sup> weeks with development FGR, it was observed that, true positive 3 cases, false positive 9 cases, false negative 12 and true negative 73 cases are predicted by pre-diastolic notch in 2<sup>nd</sup> UADV notching at 24<sup>th</sup> week.

The validity test of presence of Pre-diastolic notch in 2<sup>nd</sup> UADV study at 24<sup>th</sup> week to predict FGR has sensitivity 20.0%, specificity 89.0%,

accuracy 78.4% and positive predictive values 25.0% and negative predictive value 85.9%.

Table 9 shows that in 22<sup>nd</sup> weeks out of 16 patients having unilateral Pre-diastolic notch 1(6.3%) had FGR. Out of 4 patients having bilateral Pre-diastolic notch 1(25.0%) had FGR. Out of 77 normal patients 8(10.4%) had FGR. In 24<sup>th</sup> weeks out of 7 patients having unilateral Pre-diastolic notch 1(14.3%) had FGR. Out of 5 patients having bilateral Pre-diastolic notch 2(40.0%) had FGR. Out of 85 normal patients 12(14.1%) had FGR.

Table 10 shows that the mean age was 28.69±7.81 years who had per-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week and 24.13±6.11 years who had normal UADV study. The mean para was 1.29±0.33 who had per-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week and 1.77±0.29 who had normal UADV study. The mean BMI was 23.59±1.09 Kg/m<sup>2</sup> who had per-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week and 21.57±0.47 Kg/m<sup>2</sup> who had normal UADV study.

**Table 6. Development of Pre-eclampsia according to severity of UADV findings (n=97)**

Pre-diastolic notch	Pre-eclampsia	Normal	RR 95% CI	P -value
<b>UADV at 22<sup>nd</sup> weeks</b>				
Unilateral notch (n=16)	2 (12.5%)	14 (87.5%)	2.53 (0.51-12.67)	0.256 <sup>ns</sup>
Bilateral notch (n=4)	3 (75.0%)	1 (25.0%)	23.25 (6.67-81.05)	0.001 <sup>s</sup>
Normal study (n=77)	1 (1.3%)	76 (98.7%)	-	-
<b>UADV at 24<sup>th</sup> weeks</b>				
Unilateral notch (n=7)	3 (42.9%)	4 (57.1%)	4.82 (1.64-14.22)	0.030 <sup>s</sup>
Bilateral notch(n=5)	5 (100.0%)	0 (0.0%)	15.33 (7.07-33.24)	0.001 <sup>s</sup>
Normal study (n=85)	3 (3.5%)	82 (96.5%)	-	-

UADV=Uterine Artery Doppler Velocimetry; s= significant; ns= not significant; P-value was calculated by chi square test; P-value was significant P<0.05; P-value was not significant P>0.05

**Table 7. Comparison of findings in 2<sup>nd</sup> UADV at 24<sup>th</sup> weeks with development FGR**

Findings in 2 <sup>nd</sup> UADV at 24 <sup>th</sup>	FGR	Normal	Total
Pre-diastolic notch Present	3(true positive)	9(false positive)	12
Normal study	12(False negative)	73(true negative)	85
<b>Total</b>	<b>15</b>	<b>82</b>	<b>97</b>

*UADV=Uterine Artery Doppler Velocimetry; FGR=Fetal Growth Restriction*

**Table 8. Sensitivity, specificity, accuracy, positive and negative predictive values of Pre-diastolic notch in 2<sup>nd</sup> UADV at 24<sup>th</sup> week to predict FGR**

Validity test	Percentage
Sensitivity	20.0
Specificity	89.0
Accuracy	78.4
Positive predictive value	25.0
Negative predictive value	85.9

*UADV=Uterine Artery Doppler Velocimetry; FGR=Fetal Growth Restriction*

**Table 9. Development of FGR according to severity of UADV findings (n=97)**

Pre-diastolic notch	FGR	Normal	RR 95% CI	P -value
<b>UADV at 22<sup>nd</sup> weeks</b>				
Unilateral notch(n=16)	1 (6.3%)	15 (93.8%)	0.56 (0.08-4.14)	0.481 <sup>ns</sup>
Bilateral notch(n=4)	1 (25.0%)	3 (75.0%)	2.58 (0.42-15.71)	0.357 <sup>ns</sup>
Normal study(n=77)	8 (10.4%)	69 (89.6%)	-	-
<b>UADV at 24<sup>th</sup> weeks</b>				
Unilateral notch(n=7)	1 (14.3%)	6 (85.7%)	0.92 (0.14-6.00)	0.705 <sup>ns</sup>
Bilateral notch(n=5)	2 (40.0%)	3 (60.0%)	2.83 (0.86-9.27)	0.169 <sup>ns</sup>
Normal study(n=85)	12 (14.1%)	73 (85.9%)	-	-

*UADV=Uterine Artery Doppler Velocimetry; FGR=Fetal Growth Restriction; ns= not significant, P-value was calculated by chi square test; P-value was not significant P>0.05*

**Table 10. Comparison of age, para and BMI with presence of pre-diastolic notch (n=97)**

	2 <sup>nd</sup> UADV at 24 <sup>th</sup> week		P -value
	Pre-diastolic notch Present (n=12)	Normal study (n=85)	
Age (in year)	28.69±7.81	24.13±6.11	0.022 <sup>s</sup>
Para	1.29±0.33	1.77±0.29	0.001 <sup>s</sup>
BMI (Kg/m <sup>2</sup> )	23.59±1.09	21.57±0.47	0.001 <sup>s</sup>

*s= significant; P-value was calculated by unpaired t-test; P-value was significant P<0.05*

#### 4. DISCUSSION

This prospective observational study was carried out with an aim to detect the frequency of developing pre-eclampsia and Fetal Growth Restriction in relation to normal and abnormal doppler velocimetry and to observe development of Pre-eclampsia and Fetal Growth Restriction in relation to severity of Doppler findings.

In this present study, it was observed that 52.6% of the subjects belonged to age 21-25 years. The mean age was found 23.4±3.4 years with ranged from 18 to 33 years. In our country, early marriage is frequent practice event so the average age of 1<sup>st</sup> pregnancy is much lower.

Similarly, in our country Begum et al. found the mean age was 23.3 ± 6.7 years [26]. Akbari et al. found the mean age was 25.46±3.5 years [27]. Gupta et al. found women of <20years was 23.08% in their study patients [28]. In another study Todd et al. observation was supported with the present study [29]. On the other hand, Park et al. found the median age at delivery varied from 18-42 years [30]. Korevaar et al. had observed the median age in their study patients was 30.1 years [31]. Teixeira et al. found the mean age was 31.0 years with ranged from 27.7 – 33.6 years [32]. The higher mean age and age range maybe due to geographical variations, racial, ethnic differences and genetic causes.

One of the risk factors for pre-eclampsia is nulliparity, often women have no preexisting comorbidities. As a result, regular antenatal check-ups are advocated to detect hypertension and proteinuria until better widespread predictive tests is available, which may help stratify women into high- and low-risk groups. In this current study, it was observed that 53.6% subjects were nulli-para. Korevaar et al. found nulli-para were 60.9% and 52.80% respectively [31], which support with the present study. In Bangladesh a study done by Begum et al. found primigravida was 50.0% and multigravida 50.0% [26]. Nulliparity is a known risk factor for pregnancy induced hypertension as well as multiparity with an adverse obstetric history [33].

High BMI is known risk factors for pre-eclampsia. Among women with a high BMI ( $>25 \text{ kg/m}^2$ ), women with high FT4 (highest quintile) had a 2.9- fold higher risk of pre-eclampsia [31]. In this present study, it was observed that 17.5% subjects had BMI  $<18.5 \text{ kg/m}^2$  (Underweight). The mean BMI was found  $20.1 \pm 1.8 \text{ kg/m}^2$  with ranged from 16.2 to  $22.9 \text{ kg/m}^2$ . Begum et al. found the mean BMI was  $23.6 \pm 3.6 \text{ kg/m}^2$  [26]. Solanki and Maitra showed the mean BMI was found  $22.7 \pm 3.77 \text{ kg/m}^2$ , which is consistent with the current study [34]. On the other hand, Benoit and Rey (2011) showed the mean BMI was  $26.4 \pm 6.3 \text{ kg/m}^2$  based on first trimester weight [35].

Low Socio-economic factors act as multiple risk factors for pre-eclampsia. Low socio-economic factors are associated with nutritional issues, reduced ante-natal care and unsanitary hygienic conditions. In this current study, it was observed that 56.7% subjects came from low income group family. In Bangladesh it was found lower socioeconomic status was 50.0%, middle class 35.1% and rich class 14.9%, which is comparable with the current study [26].

Bangladesh is a developing country where about 16.0% prevalence of pre-eclampsia was reported [36]. An ideal predictive test for pre-eclampsia should be easy to perform early in the pregnancy, simple, reproducible and of high positive predictive value. In this present study, it was observed that 11.3% patients developed pre-eclampsia.

Stegers et al. reported that around 2–8% of pregnancies are affected by pre-eclampsia [37]. Early-onset pre-eclampsia results from impaired trophoblast invasion into the spiral arteries, causing placental ischemia and oxidative stress.

Placental histology in early-onset pre-eclampsia or FGR often demonstrates thrombotic changes in the villous trees, lending support to this theory Visser et al. [38]. In this present study, it was observed 15.5% had FGR. Figueras and Gratacos (2014) mentioned in this study that Fetal growth restriction (FGR) that develops in the absence of pre-eclampsia may also have its origin in defective placentation [39]. Velauthar et al. study reviewed the accuracy of uterine artery Doppler analysis in the first trimester in the prediction of FGR and pre-eclampsia [40]. Park et al. study showed the incidences of FGR were 8.0%, 10.2%, and 26.1%, and the incidences of PIH were 0.1%, 3.6%, and 14.5%, respectively [30].

Konchak et al. study showed that an elevated uterine resistance index and a uterine artery notch both were associated with increased relative risk of pre-eclampsia [41]. In this current study, it was observed that 12.4% patients had notching status. Gupta et al. study observed that uterine notch was found in 9.6% women [28].

In this present study, it was observed that, true positive 8 cases, false positive 4 cases, false negative 3 and true negative 82 cases are identified as pre-eclampsia. Similarly, in this study, it was observed that validity test of presence of pre-diastolic notch in UADV at 24<sup>th</sup> week has sensitivity 72.7%, specificity 95.4%, accuracy 92.8% and positive predictive values 66.7% and negative predictive value 96.5% to predict pre-eclampsia. The above findings indicate that the sensitivity is higher and it is a good predictor for future pregnancy related complications. Additionally, specificity suggests that there is minimum possibility to find the false negativity in this test. As the specificity is also at standard level for UADV test; it can be clearly claimed that it is a good screening test. We found quite a high NPV of 85.9% which indicates negative findings in UADV at 24th week have a low risk of development of FGR. Konchak et al. showed that an elevated uterine resistance index and a uterine artery pre-diastolic notch both were associated with increased relative risk of pre-eclampsia [41]. The sensitivity 83.3%, specificity 95.6%, PPV 55.65% and NPV 98.9% of a uterine notch in their study. In Gupta et al study, in low risk group, the sensitivity and specificity of increased uterine artery RI for prediction of pre-eclampsia were 70.0% and 94.87% respectively [28].

In this present study, it was observed that in UADV at 22<sup>nd</sup> weeks out of 16 patients having

unilateral notching 12.5% had pre-eclampsia having relative risk 2.53 with 95% CI 0.51-12.67%. Out of 4 patients have bilateral notching 75.0% had pre-eclampsia having relative risk 23.25 with 95% CI 6.67-81.05%. Out of 77 normal patients 1.3% had pre-eclampsia. Similarly Park et al. found in their study that patients having unilateral notching in 1<sup>st</sup> stage and 2<sup>nd</sup> stage having relative risk 2.10 with 95% CI 0.27-16.5% to developed pre-eclampsia [30]. Patients with unilateral notching 1<sup>st</sup> stage and 2<sup>nd</sup> stage bilateral notching having relative risk 87.3 with 95% CI 19.1-100.0%. On the other hand, in this series, it was observed that in UADV at 24<sup>th</sup> weeks out of 7 patients having unilateral notching 42.9% had pre-eclampsia having relative risk 4.82 with 95% CI 1.64-14.22%. Out of 5 patients have bilateral notching 100.0% had pre-eclampsia having relative risk 15.33 with 95% CI 7.07-33.24%. Out of 85 normal patients 3.5% had pre-eclampsia. Park et al. also found in their study that patients having bilateral notching in 1st stage and 2nd stage unilateral notching having relative risk 5.24 with 95% CI 0.63-43.6% to developed pre-eclampsia [30]. Patients with bilateral notching 1st stage and 2nd stage also bilateral notching having relative risk 26.2 with 95% CI 7.98-86.0%, which support with the present study. Gupta et al study showed that relative risk of developing pre-eclampsia with abnormal Doppler study in high risk and low risk group were 5.427(95% CI 2.272-12.958) and 13.65 (95% CI 5.669-32.865) respectively [30].

Park et al. mentioned in their study that it is relatively low sensitivity and positive predictive values regarding IUGR and delivery prior to the 34th week of gestation sensitivities: 36.5% and 48.6%, PPV: 14.3% and 6.4% preclude its usage as a screening test. In another study Khong et al. mentioned that an abnormal uterine artery PI in the first trimester was predictive of pre-eclampsia and early-onset pre-eclampsia with sensitivities of 26.4% and 47.8%, respectively [42], which are lesser with the present study, may be due to they enrolled different types of patients according to their inclusion criteria.

In this current study, it was observed that, true positive 3 cases, false positive 9 cases, false negative 12 and true negative 73 cases are identified by fetal outcome. Similarly, in this present study, it was observed that the validity test of fetal outcome has sensitivity 20.0%, specificity 89.0%, accuracy 78.4% and positive predictive values 25.0% and negative predictive value 85.9%. Khong et al. found that fetal growth

restriction was predicted at 15.4%, whereas early-onset FGR was associated with a higher sensitivity of 39.2% [42]. The sensitivity achieved for placental abruption was 44.4%. First-trimester Doppler indices showed a low predictive accuracy for stillbirth, with a sensitivity of 14.5%. However, combined parameters has highest sensitivity and positive predictive value of 96.3% and 50% respectively.

In this current series, it was observed that at 22<sup>nd</sup> weeks out of 16 patients having unilateral notching 6.3% had FGR having relative risk 0.56 with 95% CI 0.08-4.14%. Out of 4 patients have bilateral notching 25.0% had FGR having relative risk 2.58 with 95% CI 0.42-15.71%. Out of 77 normal patients 10.4% had FGR. In 24<sup>th</sup> weeks out of 7 patients having unilateral notching 14.3% had FGR having relative risk 0.92 with 95% CI 0.14-6.0%. Out of 5 patients have bilateral notching 40.0% had FGR having relative risk 2.83 with 95% CI 0.86-9.27%. Out of 85 normal patients 14.1% had FGR. Park et al. study found unilateral patients 10.2% had FGR and bilateral patients 26.1% had FGR [30], which is comparable with the present study.

## 5. CONCLUSION

This study was undertaken to predict the future probability of developing pre-eclampsia of pregnant mothers and fetal growth restriction in relation with normal and abnormal doppler velocimetry of uterine artery at 2<sup>nd</sup> trimester of pregnancy. We found quite a high NPV for both PE and FGR. The pregnant women who have negative UADV finding at their 2nd trimester possess less chance of development of both PE and FGR. The study of 2<sup>nd</sup> trimester uterine artery Doppler velocimetry is not sensitive enough to predict pre-eclampsia but has a strong association. Unilateral notch in UADV at 24 weeks is almost alike with normal UADV, which cannot predict FGR. However bilateral notch had strong association with fetal growth restriction but it had less positive predictive value. Therefore this is not a good screening test for prediction of fetal growth restriction.

## 6. RECOMMENDATION

Further research should focus on combining uterine artery Doppler velocimetry with other studies that can be performed during the 1st trimester to predict trophoblastic dysfunction and placental insufficiency. If this can be accomplished, the positive predictive value of

this test will be greatly enhanced Further studies can be done for long study period and by including large number of patients.

### CONSENT AND ETHICAL APPROVAL

Ethical clearance for the study was taken from the department (department of Obs and Gynae) and concerned authority, DMCH (No: MEU-DMC/ECC/2017/190). A questionnaire and a consent form have been prepared.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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