Original article

Second Trimester Uterine Artery Doppler Velocimetry and Serum Lipids for Prediction of Pre-Eclampsia

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Abstract

<u>*Background:*</u> Reliable markers for prediction and prevention of pre-eclampsia to reduce its associated maternal and perinatal morbidity are lacking. <u>*Aim and objectives:*</u> To evaluate uterine artery doppler velocimetry and serum lipids in second trimester of pregnancy for prediction of gestational hypertension and pre-eclampsia. <u>*Methods:*</u> One hundred healthy and normotensive women were enrolled in 2nd trimester of pregnancy. Presence of notching in uterine artery doppler on USG and serum lipid levels were recorded. All women were followed till term/delivery to see development of pre-eclampsia / gestational hypertension later. <u>*Results:*</u> Absence of diastolic notch in 2nd trimester USG, serum triglycerides levels of <150 mg/dL and serum LDL levels of <100 mg/dL in 2nd trimester of pregnancy were found to have a good negative predictive value of 96.6%, 96.3%, 92.7% for later development of GH/PE. <u>*Conclusion:*</u> Absent diastolic notch, serum triglycerides <150mg/dL and LDL <100 mg/dL in 2nd trimester of pregnancy can be used to stratify women with low risk pregnancy.

<u>*Keywords:*</u> risk of pre-eclampsia, prediction, diastolic notch, serum lipids, endothelial dysfunction, hypertriglyceridemia in pre-eclampsia

Introduction

Pre-eclampsia, complicates up to 10% of pregnancies worldwide[1] and constitutes one of the greatest causes of maternal and perinatal morbidity and mortality[2]. If incipient pre-eclampsia can be diagnosed, intensive obstetric care can be utilized more effectively for women who are at greater risk to improve maternal and fetal prospects. Early diagnosis, close antenatal surveillance and timely intervention are key for the management of pregnancy induced hypertension. Various biological, biochemical markers and imaging studies are implicated for prediction of gestational hypertension (GH), pre-eclampsia (PE) and eclampsia during the last two decades. Despite advances in medical research reliable screening tests for prediction of this pregnancy specific disease are still lacking.

The fundamental cause of pregnancy induced hypertension is thought to be abnormal uteroplacental circulation resulting from failure of second wave of trophoblastic invasion into spiral arterioles. This results in increased resistance of blood flow within the uterine arteries and decreased placental perfusion. The increased resistance of blood flow results in an abnormal waveform represented by an exaggerated diastolic notch which can be detected by Doppler uterine velocimetry[3]. Therefore, uterine artery velocimetry during 2nd trimester may be useful for prediction of hypertensive disorders specific to pregnancy.

Hormonal and metabolic changes that occur in the mother contribute to the changes in lipid profile in healthy, gestating women. Total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol increases in both second and third trimester of pregnancy[4]. Initially between 10-30 weeks, there is an anabolic phase with an increase in lipid synthesis and fat storage in preparation for the increase in fetal energy requirement in late pregnancy. The anabolic condition present in during early pregnancy in adipose tissue switches to a net catabolic condition in the third trimester due to insulin insensitivity resulting in breakdown of maternal lipids which is coincident with the highest rate of fetal growth[5].

Studies, indicate that dyslipidemia, particularly hypertriglyceridemia, precedes the clinical recognition of pre-eclampsia[6,7]. Increased serum lipids or dyslipidemia when found in early pregnancy causes more oxidative stress by formation of lipid peroxides and reactive

oxygen species, causing endothelial dysfunction[8] and predisposing to pre-eclampsia[9]. Staff et al and Serdar Z et al[10,11] have reported increased total cholesterol, phospholipids and lipid peroxides in decidua basalis of pre-eclamptic samples as compared to samples from normotensive controls.

Thus, serum lipid levels in early pregnancy can be a good predictor of development of pre-eclampsia.

Therefore, in this study, we have evaluated serum lipids and diastolic notch in Doppler ultrasonography for prediction of pre-eclampsia. As trophoblastic invasion of the maternal arterioles occurs in second trimester, hence, this gestation period was chosen for our study.

Aims and Objectives

To evaluate uterine artery Doppler velocimetry for presence of diastolic notch and serum lipid profile (triglyceride, LDL, total cholesterol and HDL) in second trimester of pregnancy for prediction of gestational hypertension and pre-eclampsia.

Material and Methods

This is a prospective study, conducted over a period of 2 years in Obstetric and Gynecology Department of Hindu Rao Hospital and associated NDMC Medical College, Delhi. Women attending antenatal OPD between 16-24 weeks of gestation, were enrolled after written consent and were followed up till delivery.

Inclusion Criteria- normotensive pregnant women in second trimester (16-24 weeks of gestational age) with single fetus without any fetal anomaly

Exclusion Criteria- refusal to give consent, multiple pregnancy, molar pregnancy, chronic hypertension, renal disease, epilepsy, diabetes, thyroid disease, any other medical disorder, history of pre-eclampsia in previous pregnancies.

One hundred normotensive pregnant women fulfilling inclusion and exclusion criteria were enrolled after informed consent. A detailed history; general, systemic and obstetric examination was done. Uterine artery Doppler examination was done at the time of enrollment. With patient in dorsal position and the table tilted at 45°, after emptying bladder, the right and left uterine arteries with respective ascending branches were evaluated by the Doppler ultrasonography using 3.5 MHz convex probe. A diastolic notch, was defined as the presence of a clear upswing in the waveform at the beginning of diastole, on any waveform. Presence of bilateral or unilateral notch was considered as abnormal flow velocimetry.

Serum lipid profile (total cholesterol, triglycerides, LDL, VLDL and HDL) were estimated in a fasting blood sample the next day. Samples were incubated and centrifuged to separate serum. Serum lipids were estimated by enzymatic method with the help of accurex diagnostic kit (manufactured by Accurex Biomedical Pvt. Ltd., India) and the tests were analyzed on Selectra-E random access analyzer. Serum LDL was calculated by Frederickson-Friedwald's formula.

Women were followed up in antenatal OPD monthly till 28 weeks, twice weekly till 36 weeks and weekly till term/delivery for development of gestational hypertension or pre-eclampsia. Blood pressure measurement, testing for proteinuria was done at every scheduled visit.

Women who could not be followed up till term were excluded from the study. Those women who were followed up till term (n=100) were divided into three groups depending on development / non-development of gestational hypertension (GH) or pre-eclampsia (PE).

> Group 1 comprised of women who remained normotensive.
> Group 2 comprised of women who developed GH
> Group 3 comprised of women who developed PE

Diagnosis of GH: The diagnosis of gestational hypertension was made when blood pressure recorded was > 140/90 mm of Hg on two occasions four hours apart after 20 gestational weeks[12]

Diagnosis of pre-eclampsia: When hypertension was associated with significant proteinuria (1+ on urine dipstick) or any severe feature of preeclampsia observed[12]

1. Hypertension: systolic >160 or diastolic >110 on two occasions at least 4 hours apart while the patient was on bed rest (unless antihypertensive therapy is initiated before this time).
2. Thrombocytopenia (platelet count <1,00,000 / mL)
3. Impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both.
4. New development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL, or doubling of serum creatinine in the absence of other renal disease).
5. Pulmonary edema.
6. New-onset cerebral or visual disturbances.

Statistical Analysis

Data was analyzed by using SPSS 20.0.1 software. Data was summarized as mean and standard deviation for numerical variables and counts and percentages for categorical variables. The median and the interquartile range have been stated for numerical variables that are not normally distributed. Student's t-test was applied to compare normally distributed numerical variables between groups; Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Numerical variables between three groups were compared by One-Way ANOVA. P value ≤ 0.05 was considered for statistically significant.

Results

Out of 100 pregnant women, 90 women remained normotensive during follow up (Group A), 5 developed gestational hypertension (Group B) and 5 developed pre-eclampsia (Group C). Various maternal parameters like age, BMI, gravidity, parity, systolic, diastolic blood pressure (at the time of enrolment in 2nd trimester) were found to be comparable in group A, B and C (Table 1).

Table 1: Maternal characteristics

Variable (n-=100)		Normotensive Group 1 (n=90)	Gest HTN Group 2 (n=5)	Preeclampsia Group 3 (n=5)	*p value
Age		24.4 ± 3.75	25.6 ± 3.05	25.8 ± 5.12	0.594
BMI		24.27 ± 4.01	23.24 ± 1.88	23.30 ± 3.39	0.744
Gravida	Primi	38	2	1	
	Second	40	3	3	0.755
	>2	12	0	1	
Parity	Nulliparity	39	2	2	0.881
	Parity1	40	3	2	
	Parity2	11	0	1	
BP mean (Baseline)	SBP mmHg	120.02 ± 6.95	122.40 ± 3.58	117.60 ± 7.67	0.545
	DBP mmHg	76.93 ± 4.94	76 ± 5.48	74± 5.48	0.418
BP mean at diagnosis	SBP mmHg	120.11±7.27	145.60±3.85	155.60±10.14	<0.0001
	DBP mmHg	77.1556±5.65	94.00±3.162	100.00± 7.071	<0.0001

*p value < 0.05 is significant

A significant difference was observed in the 3 groups in terms of presence of diastolic notch (p value <0.0001) during ultrasonography, serum triglyceride (p value 0.001) and serum LDL (p value 0.005) done at the time of enrolment (Table 2).

Table 2: Uterine Artery Doppler and lipid profile for prediction of GH / PE

Parameter		Normotensive Group 1(N=90)	Gest HTN Group 2 (N=5)	Preeclampsia Group 3 (N=5)	p value*
Uterine artery Doppler	Notching present (n=10)	3	3	4	<0.0001
	Notching absent (n=90)	87	2	1	
Triglyceride (mg/dL) mean		164.37 ± 51.75	245.20 ± 37.90	239.60±183.36	0.001
Median		166	267	198	
T.Cholesterol (mg/dL)mean		181.74 ± 37.98	203.2 ± 69.57	171.8 ± 52.50	0.433
Median		183	212	183	
HDL (mg/dL) mean		55.12 ± 10.34	51.6 ±9.6	50.6± 16.77	0.523
Median		55	52	53	
LDL (mg/dL) mean		93 ± 24.19	121.8± 34.11	117.8 ± 13.77	0.005
Median		96.5	116	121	

*p value < 0.05 is significant

Table 3: Sensitivity and specificity of significant parameters for prediction of GH / PE

Parameter	Sensitivity	Specificity	PPV	NPV
Diastolic notch present, uni/bilateral	70%	96.6%	70%	96.66%
S. Triglycerides (cut off < 150mg/dL)	90%	28.88%	12.31%	96.3%
S. LDL (cut off < 100mg/dL)	60%	56.67%	13.33%	92.7%

Discussion

One hundred women underwent evaluation for diastolic notch in uterine artery Doppler study and estimation of serum lipids in 2nd trimester of pregnancy. Women who had notching (n=10), 70% of them (n=7) developed pregnancy related hypertension and only 30% (n=3) remained normotensive. In women without notching (n=90), only 3.3% women (n=3) developed gestational hypertension / preeclampsia and other 96.7% remained normotensive (n=87). The difference was found to be statistically significant (p value <0.0001) (Table 2). Thus, presence of uterine artery notching in 2nd trimester of pregnancy was found to be a strong predictor of development of gestational hypertension and pre-eclampsia in our study.

In our study sensitivity for presence of diastolic notching to detect hypertensive disease was estimated to be 70% and specificity as 96.66%. The positive predictive value of diastolic notch was found to be 70% and negative predictive value 96.66% in our study.

Pedroso et al in a review of thirty articles has concluded that uterine artery Doppler detects less than 50% of the cases of PE[13] though, bilateral uterine notching in late 2nd trimester gestation was reported to be an independent risk factor for the development of early-onset pre-eclampsia and gestational hypertension by Espinoza et al[14]. A low sensitivity of 57.14% in low risk women for diastolic notch to predict GH/PE[15] was found by Bhattacharyya et al. A much lower sensitivity has been reported in various other studies[16,17]. The high specificity reported by these authors corroborates with observations of our study[15,16,17]. Also, a high (97.82%) negative predictive value of diastolic notch to predict pregnancy hypertension by Nagar T et al was similar to our study[17].

Thus, absence of diastolic notch in 2nd trimester can be used as a negative predictor for development of GH or PE.

Regarding lipid profile, various studies have shown that total cholesterol, LDL, VLDL and triglycerides were significantly increased. However, serum HDL was found to be decreased in pre-eclampsia when compared to normal pregnancy[18,19,20]. In a study severity of preeclampsia was found to have a positive correlation

with serum triglycerides, cholesterol, LDL and VLDL, and a negative correlation with serum HDL[18].

A systematic review and meta-analysis demonstrated that pre-eclampsia was associated with elevated total cholesterol, non-HDL-C, and triglyceride levels, regardless of gestational age at the time of blood sampling, and with lower levels of HDL-C in the third trimester. A marginal association was found with LDL-C levels[21].

In our study, we observed that median and mean serum TG levels and serum LDL levels were higher in women who developed GH and PE compared to women who remained normotensive. (p value 0.001). Thus, serum triglyceride and LDL levels were found to be strong predictors for development of hypertension in pregnancy.

Significant rise of serum triglyceride concentrations in our study has been corroborated in various other studies[20,22-25]. A 4.15-fold increase in the risk of pre-eclampsia among women with triglyceride levels >133 mg/dL (95% CI 1.50 to 11.49) has been reported by Enquobahrie DA et al[20].

The principle modulator of this hypertriglyceridemia is estrogen, as pregnancy is associated with hyperestrogenaemia. Estrogen induces hepatic biosynthesis of endogenous triglycerides, which is carried by VLDL[26]. This process may be modulated by hyperinsulinism found in pregnancy[27]. Increased TG, found in pregnancy induced hypertension, is likely to be deposited in predisposed vessels, such as the uterine spiral arteries and contributes to the endothelial dysfunction, both directly and indirectly through generation of small, dense LDL[28,29], predisposing to pre-eclampsia. Moreover, this hypertriglyceridemia may be associated with hypercoagulability[30].

In our study the sensitivity of serum triglycerides to detect GH or PE has been evaluated to be 90%, though its specificity was found to be low 28.88%. Its NPV was quite high 96.3%, and PPV very low 12.31% (Table 3). Thus, maternal triglycerides in 2nd trimester of pregnancy can be used as a negative predictor for development of GH or PE.

Serum LDL was also found to be significantly elevated (p value 0.005) in women who developed GH or PE in later pregnancy (p value 0.005) in our study (Table 2). This observation of our study is in corroboration with other studies[19,31,32]. Sensitivity of LDL to detect hypertensive disease was estimated to be 60% and specificity 56.66% in our study. The positive predictive value of LDL was 13.33% and negative predictive value to predict hypertensive disease of pregnancy was found to be 92.72% (Table 3). Thus serum LDL can also be used as a negative predictor for development for GH or PE.

Serum total cholesterol and HDL were found to be comparable in the 3 groups in our study (p value 0.433, 0.523 respectively) (Table 2), therefore cannot be used for predicting GH / PE. Jayanta De, Sattar et al[24,28] also reported comparable cholesterol levels in normotensive and hypertensive women. In some studies, cholesterol was significantly found to be higher who developed pregnancy related hypertension[19,33,20,29]. Similar to our study insignificant difference was found in HDL levels in normotensive and hypertensive women in pregnancy by Yadav et al and Anuradha et al[34,35], though Jayanta

De reported a significant decrease in HDL in pre-eclamptic and eclamptic pregnant women[24,20].

Conclusions

We conclude from the results of our study that presence of diastolic notch at mid-trimester uterine artery doppler on USG can be used to predict development of GH/PE. These women should be considered high risk and should be delivered in a health care facility where neonatal intensive care unit is available. Absence of diastolic notch in uterine artery Doppler ultrasonography, serum TG levels below 150 mg/dL, LDL levels below 100 mg/dL, done in mid-trimester of pregnancy, can be used as negative predictors for development of GH or PE and these women may be considered low risk and can be delivered at primary / secondary level health care facilities. Thus, these markers can be used for risk triaging in women with regard to development of pregnancy hypertension.

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