e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(10); 757-763

Original Research Article

Does Left Ventricular Diastolic Dysfunction Predict Outcomes in Patients with Pre-Eclampsia

Sushmita Varshney[1], Seema Hakim[2], Raghav Bansal[3], Mohammad Azharuddin Malik[4], Preeti Yadav[5]

[1]Junior Resident, Department of Obstetrics & Gynaecology, JN Medical College, AMU, Aligarh

[2]Professor, Department of Obstetrics & Gynaecology, JN Medical College, AMU, Aligarh

[3]Assistant Professor, Department of Cardiology, UN Mehta Institute of Cardiology and Research Centre, Ahmedabad

[4]Professor, Department of Cardiology, JN Medical College, AMU, Aligarh

[5]Consultant Obstetrician and Gynaecologist, Sant Parmanand Hospital, New Delhi

Received: 28-08-2022 / Revised: 30-09-2022 / Accepted: 18-10-2022

Corresponding author: Raghav Bansal

Conflict of interest: Nil

Abstract

Background: Left ventricular diastolic dysfunction has been shown to be associated with pre-eclampsia. Whether presence of diastolic dysfunction acts as a prognostic marker for adverse maternal and fetal outcomes, remains unknown.

Methods: This was a single centre prospective observational cohort study. 100 patients with pre-eclampsia presenting to the antenatal clinic were enrolled. Age and gestational age matched pregnant females were enrolled in the control group. All subjects received routine evaluation and standard of care in addition to transthoracic echocardiography for evaluation of diastolic dysfunction. Patients were followed up for outcomes of pregnancy and all the adverse events during follow-up were recorded.

Results: 100 patients with mean age of 25.9 ± 4.0 years and mean gestational age of 36.2 ± 2.5 weeks were included in the study and control groups each. Left ventricular diastolic dysfunction was noted in 43 patients (43%) in the study group as compared to none in the control group. Severe pre-eclampsia was noted in 47 patients (47%). Adverse maternal and fetal outcomes were noted more frequently in the pre-eclampsia group as compared to the control group (44% vs 24%, $p = 0.003$; and 53% vs 25%, $p < 0.001$ respectively). Left ventricular diastolic dysfunction was not associated with any adverse maternal or fetal outcomes. However, features suggestive of pre-eclampsia predicted adverse maternal and fetal outcomes.

Conclusion: In patients with pre-eclampsia, left ventricular diastolic dysfunction was found in 43% of the patients. Presence of left ventricular diastolic dysfunction did not predict adverse maternal or fetal outcomes.

Keywords: Diastolic dysfunction, maternal outcome, pre-eclampsia, fetal outcome

Introduction

Pre-eclampsia affects 2-8% of pregnancies worldwide and is a major cause of maternal morbidity and mortality, causing approximately 46,000 maternal and 500,000 fetal/ newborn deaths annually [1,2]. The disease burden is significantly

higher in low- and middle-income countries [2]. Pre-eclampsia is associated with profound effects on the cardiovascular system with endothelial dysfunction leading to vascular hyper-reactivity, cardiomyocyte hypertrophy, LV remodelling and diastolic dysfunction. These effects may then precipitate heart failure and portend a poorer prognosis in these patients. It has been shown on echocardiographic studies that pre-eclampsia is associated with diastolic dysfunction [3-6].

But whether, diastolic dysfunction has prognostic implications for maternal outcomes is not clearly defined. This study intends to determine the effect of diastolic dysfunction on prognosis of pre-eclampsia in a prospective manner. Further, there is meagre data on echocardiographic parameters in the Indian population, where maternal age tends to be younger, and the pre-eclampsia is often detected later and less well managed due to resource constraints. As a secondary objective, the study is also designed to estimate the prevalence of diastolic dysfunction in pre-eclamptic mothers and its corelation with severity of pre-eclampsia.

Methods

The study is an observational prospective single centre cohort study conducted over a period of 3 years from 2019 to 2021. All consecutive mothers presenting to the ante-natal clinic clinically diagnosed with pre-eclampsia were included for the study. Patients whose echocardiography could not be done due to any reason; or with pre-existing medical illness like diabetes mellitus, thyroid disorders, known structural heart disease, renal dysfunction and connective tissue diseases; or with pre-existing hypertension; or those presenting labour; or with intrauterine death were excluded. All patients received routine ante-natal care and management of hypertension as per standard institutional protocols. Maternal and gestational age matched controls were chosen from the healthy mothers with no known medical illness presenting to the ante-natal clinic.

A detailed history and physical examination were recorded for each subject. Blood pressure (BP) measurement was done on each visit, in sitting position after 5 minutes rest in a quiet room with a standard size blood pressure cuff and a calibrated BP instrument. Patients were classified with gestational hypertension if systolic BP was ≥140 mmHg; or diastolic BP was ≥ 90 mmHg on 2 readings 20 minutes apart after 20 weeks of gestation without any history of hypertension before.

Proteinuria was defined as excretion of more than 300 mg of protein in 24-hour urinary collection; or protein/creatinine ration of at least 0.3 mg/dL; or when quantitative tests were not available 1+ reading on dipstick test. Based on presence of thrombocytopenia (platelet count <100,000/ul), renal insufficiency (serum creatinine > 1.1 or doubling of creatinine without any renal disease), epigastric pain, elevated liver enzyme, cerebral and visual symptoms patients were classified as severe preeclampsia. Routine blood investigations, standard 12 lead electrocardiogram and transthoracic 2D echocardiography was done for all patients.

Echocardiography was done with GE Vivid E95 machine with a cardiac probe. Standard M-Mode, 2D and Doppler Echocardiography evaluation was performed in all patients in all the standard views (i.e. parasternal long axis, short axis and apical views) in left lateral recumbent position. Assessment of valvular lesions and left ventricular systolic/diastolic functions and chamber dimensions were recorded as per standard echocardiography procedure described in the American Society of Echocardiography guidelines. [7,8] Following parameters were particularly recorded at mitral valve level: (i) Peak E and A Velocity; (ii) E/A Ratio; (iii) E deceleration time (DT), (iv) E wave velocity time integral (EVTI) and A wave velocity time integral (AVTI);

isovolumetric relaxation time (IVRT); (v) TDI: medial e' with E/e' ratio; (vi) atrial electromechanical delay. The time from the onset of the P-wave on the surface ECG and the delayed diastolic wave (a') on tissue Doppler is considered PA interval (atrial electromechanical delay). Atrial electromechanical delay (EMD) is the time from the earliest onset of P wave on surface ECG to the onset of a' wave on tissue doppler imaging. Patients with E/e' ratio of more than 10 were considered to have diastolic dysfunction, for ease of classification.

All the data was compiled on IBM SPSS 26 software, and it was subjected to statistical analysis with the help of same. Statistical comparison among the groups was performed using independent sample t test for the quantitative variables. Chi square test was used for quantitative analysis of data. Statistical significance was accepted when the p value was less than 0.05.

Results

100 patients with pre-eclampsia were included in the study group. 100 Age and gestational age matched controls were recruited in the control group. The baseline demographic and clinical data is presented in table 1. As both cohorts were matched for patient age and gestational age; mean age of subjects in both the groups was 25.9 ± 4.0 years. Mean gestational age was 36.2 ± 2.5 weeks. 56 patients (56%) in the study group and 44 subjects (44%) in the control group were primigravida (p = <0.05). Mean systolic BP in the study group was 157.62 ± 11.54 mmHg and mean systolic BP in the control group was 119.02 ± 6.86 mmHg (p = 0.001). Mean diastolic BP was 98.42 ± 6.81 and 76.96 ± 7.89 mmHg in the study and the control group respectively (p < 0.001). In the study group, 50 patients had 1+ proteinuria, 32 patients had 2+ proteinuria and 18 patients had 3+ proteinuria. No patient in the control group had proteinuria. 34% of the study group while only 9% of the control group complained of dyspnoea (<0.001). Edema was found amongst 38% of the study group and 23% of the control group participants (p 0.021). Features of severe pre-eclampsia were seen in 47 patients in the study group (47%) (Table 2). Altered sensorium and convulsions were seen in 4 pre-eclamptic patients. While 13 patients with pre-eclampsia developed jaundice, interestingly 5 patients in the control group also developed jaundice. Diminution of vision was noted in 11 patients in the pre-eclampsia group.

Ante-partum haemorrhage complicated the pregnancy in 14 patients with pre-eclampsia while only 2 patients in the control group. Pre-term labor was more common in the study group (21%) as compared to the control group (11%) but the difference was not statistically significant; p 0.122). HELLP (Hemolysis Elevated Liver Enzymes & Low Platelets) syndrome complicated the pregnancy in 7 patients in the study group, while none of the patients in the control group were affected. Overall, adverse maternal outcomes were noted in 44 patients (44%) in the study group and 24 subjects (24%) in the control group (p = 0.003). Adverse fetal outcomes including intra-uterine death, pre-term birth, intra-uterine growth retardation and birth asphyxia were more common in the study group (53%) as compared to the control group (25%); p < 0.001 (table 3).

The echocardiographic parameters recorded amongst the two groups are presented in table 4. 43 patients (43%) in the study group, while none in the control group had LV diastolic dysfunction (p<0.001). The comparison of clinical features, maternal and fetal outcomes in the groups with diastolic dysfunction vs no diastolic dysfunction is presented in table 5. Interestingly, LV diastolic dysfunction on echocardiography was not associated with adverse maternal or fetal outcomes. However, severity of pre-eclampsia was associated with adverse maternal and fetal outcomes (Table 6).

Table 1: Baseline clinical characteristics

Parameter	Study Group (100)	Control Group (100)	P value
Age (mean ± SD) in years	25.91 ± 4.03	25.91 ± 4.03	1.0
Gestational age (mean ± SD) in weeks	36.24 ± 2.45	36.24 ± 2.45	1.0
Primi-gravida	56	41	0.048
Heart rate (mean ± SD) bpm	97.39 ± 13.37	90.26 ± 8.64	<0.001
SBP (mean ± SD) mmHg	157.62 ± 11.54	119.02 ± 6.86	<0.001
DBP (mean ± SD) mmHg	98.42 ± 6.81	76.96 ± 7.89	<0.001
Mean BP (mean ± SD) mmHg	137.86 ± 9.15	105.04 ± 6.47	<0.001
Hb (g/dL)	11.00 ± 1.29	11.08 ± 1.08	0.603
TLC	9806.50±2864.80	7832.10 ± 2219.54	<0.001
Creatinine	0.80 ± 0.48	0.59 ± 0.23	<0.001
Total Bil	0.83 ± 0.62	0.65 ± 0.34	0.015
ALT	54.58 ± 46.14	31.52 ± 23.42	<0.001
AST	66.32 ± 49.73	42.24 ± 25.26	<0.001
ALP	291.52 ± 110.82	251.46 ± 75.00	0.003
Dyspnoea	34%	9%	<0.001
Edema	38%	23%	<0.05
Mode of delivery (LSCS%/ Normal vaginal delivery%)	55%/45%	27%/73%	<0.001

SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb" Hemoglobin, Bil: Bilirubin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline Phosphatase, LSCS: Lower Segment Caesarean Section

Table 2: Features of severe pre-eclampsia

Parameter	Study Group (100)	Control Group (100)	P value
Altered sensorium	4	0	0.043
Convulsions	4	0	0.043
Jaundice	13	5	0.120
Diminution of vision	11	0	0.001
HELLP	7	0	0.007
Oliguria	14	1	<0.001

HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets

Table 3: Adverse maternal and fetal outcomes

Parameter	Study Group (100)	Control Group (100)	P value
Adverse Maternal outcomes			
Antepartum Haemorrhage	14	2	0.002
Preterm labor	21	11	0.122
Sepsis	20	12	0.123
Stroke	0	0	1
Postpartum Haemorrhage	17	14	0.558
ARDS	2	0	0.155
Adverse Fetal Outcomes			
Intrauterine Death	8	0	0.037
Intrauterine Growth Restriction	11	12	0.825
Preterm Birth	42	8	<0.001
Birth Asphyxia	19	11	0.113

Table 4: Echocardiographic parameters for assessment of left ventricular diastolic function

Parameter	Study Group (100)	Control Group (100)	P value
E/A ratio	1.63 ± 1.53	1.45 ± 0.44	0.257
Deceleration time	160.66 ± 29.82	146.15 ± 9.49	<0.001
E/e'	9.58 ± 3.05	6.35 ± 1.13	<0.001
Atrial electromechanical delay	84.12 ± 14.73	75.11 ± 7.83	<0.001

Table 5: Stratification of clinical features and outcomes based on presence or absence of LV diastolic dysfunction

Parameter		LV diastolic dysfunction (n = 43)	No LV diastolic dysfunction (n = 57)	P value
Age		26.30	25.61	0.401
Gestational age		36.19	36.28	0.849
Systolic BP		156.19	158.70	0.292
Diastolic BP		97.86	98.84	0.469
Primigravida		20 (46.5%)	36 (63.2%)	0.035
Dyspnoea		16(37.2%)	18(31.5%)	0.556
Edema		17(39.5%)	21(36.8%)	0.784
Jaundice		4(9.3%)	9(15.7%)	0.514
Oliguria		4(9.3%)	10(17.5%)	0.240
Diminution of vision		6(13.9%)	5(8.7%)	0.672
Altered sensorium		1(2.3%)	3(5.2%)	0.458
Convulsions		1(2.3%)	3(5.2%)	0.458
Proteinuria	1+	24(55.8%)	26(45.6%)	0.144
	2+	15(34.8%)	17(29.8%)	
	3+	4(9.3%)	14(24.5%)	
Severe Pre-eclampsia		18(41.8%)	29(50.8%)	0.371
HELLP		2(4.6%)	5(8.7%)	0.424
ARDS		2 (4.6%)	0	0.100
Sepsis		9 (20.9%)	11(19.2%)	0.840
Ante-partum Haemorrhage		3 (6.9%)	11 (19.2%)	0.079
Post-partum Haemorrhage		5 (11.6%)	12 (21%)	0.214
Intra Uterine Death		4 (9.3%)	8 (14%)	0.471
Intrauterine Growth Restriction		2 (4.6%)	9 (15.7%)	0.078
Birth Asphyxia		9 (20.9%)	10 (17.5%)	0.669
Preterm birth		19 (44.1%)	23 (40.3%)	0.700

BP: Blood Pressure, HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets; ARDS: Acute Respiratory Distress Syndrome

Table 6: Association of adverse maternal and fetal outcomes with severity of pre-eclampsia

Parameter	Severity of pre-eclampsia		P value
	Non-severe (53)	Severe (47)	
Adverse maternal outcomes	14	30	<0.001
Adverse Fetal outcomes	16	33	<0.001

Discussion

Pre-eclampsia is one of the world's leading causes of maternal morbidity and mortality with significant effects of fetal outcomes [1,2]. Pre-eclampsia, a multi-system disorder associated with pregnancy centred on placental pathogenesis, is characterized by new onset hypertension after 20 weeks of gestation and proteinuria. These women have abnormal cardiac adaptation to pregnancy and have altered cardiovascular hemodynamic, and the development of pre-eclampsia may be a risk factor for development of long-term cardiovascular disorders [9]. The hemodynamics are shifted towards low cardiac index, high systemic vascular resistance and reduced venous reserve capacity. Abnormal left ventricular remodelling patterns including concentric left ventricular hypertrophy and diastolic dysfunction associated with increased afterload may also be noted [10]. The consequent increased left atrial filling pressures leading to left atrial dilatation and altered contraction has also been noted. Abnormal cardiac remodelling predisposes to heart failure and other adverse cardiovascular events including stroke and myocardial infarction.

Diastolic dysfunction has been shown to occur in one quarter to half of the patients with pre-eclampsia. In a small study, Hamad *et al* reported a high septal and lateral wall E/e' ratio, suggesting a diastolic dysfunction in pre-eclamptic patients as compared to normal pregnancies. This was associated with a raised level of cardiac biomarkers [3]. In a case control study of 50 patients each by Melchiorre *et al*, global diastolic dysfunction was found in 40% patients with pre-eclampsia as compared to only 14% of the controls. Mean maternal age was 32 years in the pre-eclampsia arm in this study [4]. Rizwana *et al* reported an increased left ventricular mass in a small Indian cohort with pre-eclampsia. However, they did not specifically study diastolic dysfunction. With a mean age of 25.75 years, this cohort had younger patients as compared to western data [5]. In a similar aged Indian cohort of 120 patients with pre-eclampsia, left ventricular diastolic dysfunction was found in 20.8% patients with direct association with severity of hypertension and pre-eclampsia. In this study diastolic dysfunction was much more common in patients with severe pre-eclampsia (38.9%) as compared to mild pre-eclampsia (3%) [6]. The present study studied 100 patients with pre-eclampsia with mean age of 25.9 years which is similar to previous Indian cohorts, left ventricular diastolic dysfunction was found in 43% of the patients. 47% of the patients had features of severe pre-eclampsia. However, there was no correlation of left ventricular diastolic dysfunction with severity of hypertension or features of severe pre-eclampsia as reported by Muthyala *et al* [6]. Our study was novel in including atrial electro-mechanical delay as a marker of left atrial and left ventricular diastolic function in addition to E/A, E/e' ratios and deceleration time recordings on doppler hemodynamics used in previous studies. Although it may seem intuitive that the presence of diastolic dysfunction may predict worse clinical outcomes, this was not found in our study. This suggests that the propensity to develop diastolic dysfunction may have a different predisposition and pathophysiology as compared to that of severe pre-eclampsia. The adverse maternal and fetal outcomes were associated with clinical features of severe pre-eclampsia. Thus, at present assessment of left ventricular diastolic dysfunction cannot be suggested for prediction of adverse maternal or fetal outcomes.

There are several limitations of the study which need to be noted. Blinding was used during echocardiography due to logistic reasons. Echocardiography was done at the presentation when the diagnosis of pre-eclampsia was made. Follow-up echocardiograms were not done. Presence and severity of left ventricular dysfunction may change according to the duration of

pre-eclampsia. Also, simplistic criteria were used based on E/e' which may be flawed. Lastly, there was no long-term follow-up to study the effect on long term maternal outcomes.

Conclusion

Diastolic dysfunction of left ventricle as determined by echocardiography is highly prevalent in preeclampsia patients. In our study prevalence of diastolic dysfunction was found to be 43%. In line to what is known, preeclampsia patients had worse maternal and foetal outcomes as compared to normotensive patients. No correlation was however, established between diastolic dysfunction and maternal and foetal outcomes in patients with preeclampsia. Greater Left Atrial Electro-Mechanical Delay was also seen in preeclampsia patients as compared to normotensive pregnant females; however clinical implication of this finding warrants further investigation.

References

1. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009; 33:130–137.
2. Magee LA, Nicolaides KH, von Dadelszen P. Preeclampsia. N Engl J Med. 2022; 386(19): 1817-32.
3. Rafik Hamad R, Larsson A, Pernow J, Bremme K, Eriksson MJ. Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. J Hypertens. 2009; 27(11): 2257-64.
4. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. Hypertension. 2011 Jan; 57(1): 85-93.
5. Solanki R, Maitra N. Echocardiographic assessment of cardiovascular hemodynamics in preeclampsia. J Obstet Gynaecol India. 2011; 61(5): 519-22.
6. Muthyala T, Mehrotra S, Sikka P, Suri V. Maternal Cardiac Diastolic Dysfunction by Doppler Echocardiography in Women with Preeclampsia. J Clin Diagn Res. 2016; 10(8): QC01-3.
7. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29(4):277-314.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1-39. e14.
9. Guirguis GF, Aziz MM, Boccia Liang C, Williams SF, Apuzzio JJ, Bilinski R, Mornan AJ, Shah LP. Is preeclampsia an independent predictor of diastolic dysfunction? A retrospective cohort study. Pregnancy Hypertens. 2015 Oct;5(4):359-61.
10. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. Hypertension. 1991; 17: 1072–1077.