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A study on mid gestational maternal cardiovascular profile in pre term and term pre-eclampsia: A prospective study

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Abstract
Background: Pre-eclampsia (PE) is associated with maternal cardiac remodelling and biventricular diastolic dysfunction. Preterm PE alone can also be associated with severe left ventricular hypertrophy and biventricular systolic dysfunction.
Aim & Objectives of the study: The aim of this study was to assess whether the maternal cardiovascular profile at mid-gestation in nulliparous normotensive women differs in women destined to develop preterm PE versus those who will develop PE at term.
Results: The study includes only nulliparous women with singleton pregnancy and at increased risk of developing PE. Risk for developing PE is determined by uterine artery Doppler assessment at the routine ultrasound assessment at 20-23 weeks of gestation. In order to achieve the aims and objective of study, 115 cases of mid gestational pregnant women were taken in the sample for study. These cases were classified into 4 groups i) low risk women with uneventful outcome (59 No's), ii) high risk women with uneventful outcome (35 No's), iii) high risk women who developed Term PE (13 No's) and iv) high risk women who developed preterm PE (8 No's). As per the protocol of the study data were collected on demographic profile, clinical profile and analyzed following appropriate statistical tools and techniques. The distribution of age among the four groups of patients were found to be more or less homogeneous as per the chi square test of association (p=0.411). Among the low risk women with uneventful outcome, all were having normal BMI. Among the high risk women with uneventful outcome 11.4% were overweight. The pair wise comparison of MAP by groups with the help of Mann-Whitney U test. It was clearly revealed that high risk women irrespective of status of event were having more or less the same MAP value with p=0.727, p=0.731, p=0.8 respectively. High risk women with or without uneventful outcome have clearly higher value of MAP than the low risk women with uneventful outcome (p=0.000). The Kruskal Wallis test revealed no significant difference in heart rate of the 4 groups of pregnant women (p=0.224). The stroke volume of each of the 3 groups of HRW with uneventful outcome, term PE and preterm PE was significantly lower than LRW with uneventful outcome with p value=0.000 for each of them. HRW with preterm PE have significantly lower stroke volume index than HRW with uneventful outcome (p=0.003). HRW with preterm PE and term PE do not differs significantly in stroke volume index (p=0.638). The comparison of cardiac output by groups is presented in table 10. The lowest median value of 3.79 L/min (3.67 L/min-3.96 L/min) was observed among HRW with preterm PE which gradually increased to 4.9 L/min (4.6 L/min-5.12 L/min) among LRW with uneventful outcome and the difference was found to be significant (p=0.000). The frequency distribution of cardiac index gradually shift to right from HRW with preterm PE to LRW with uneventful outcome signifying lower stroke volume index for HRW with uneventful outcome, with term PE and preterm PE in descending order. The frequency distribution of LVMi depicted that the distribution of LRW with uneventful outcome is more or less symmetrical whereas in case of 3 HRW groups the distribution is right screwed. The frequency distribution of left ventricular wall thickness, It clearly emerged that the distribution of LRW with uneventful outcome is relatively towards the left of the axis than the other three HRW groups. There is a significantly higher prevalence of LV remodelling /hypertrophy at mid-gestation in both preterm PE and term PE women. Asymptomatic cardiac diastolic dysfunction, impaired relaxation, altered geometry at mid gestation is only seen in high risk pregnant women with pre term preeclampsia but not in those with term preeclampsia.
Conclusion: It is now evident that women who developed preterm PE in pregnancy have a much higher incidence of developing symptomatic heart failure many years after delivery. Although it is not possible to distinguish pre-existing cardiac dysfunction from that acquired as a result of pregnancy, these cardiac findings may be useful in understanding the cardiovascular pathophysiology of PE.

Keywords: Pre-eclampsia, cardiac output, left ventricle wall, heart rate, mid-gestation

Introduction

Pre-eclampsia (PE) a serious hypertensive pregnancy disorder complicating 2% to 5% of all pregnancies is characterized by new onset hypertension along with denovo proteinuria after 20 weeks of gestation [1] or new onset protienuria that develops after 20 weeks in women with pre-

existing hypertension. Women with history of PE have an increased risk to develop chronic hypertension and related cardiovascular morbidity and mortality [2].

Therefore, characterization of biological pathways common to both pre-eclampsia and cardiovascular disease may provide novel insights into both conditions [3].

The problem of overlapping risk factors (Exemplified by the strong association between PE & IUGR) is ubiquitous in investigations of the association between PE and cardiovascular disease. Traditional risk factors for cardiovascular disease, such as increased body mass index and pre-existing hypertension, are also known to be associated with increased risk of PE. Such overlapping risk factors continue to provoke a multitude of questions about independence and confounding.

There is monitoring data showing an increased risk of cardiovascular disease (CVD) and mortality, especially coronary artery disease, in women with a history of pre-eclamptic pregnancy [4-6]. This risk seems to be even more increased when associated with early onset of pre-eclampsia and fetal growth restriction [7-8]. Pre-eclampsia & fetal growth restrictions are known to be associated with altered cardiac geometry, impaired myocardial relaxation and biventricular diastolic dysfunction. Preterm but not term PE, is also associated with severe left ventricular hypertrophy and biventricular dysfunction in a significant proportion of women. Postpartum follow up of women whose pregnancies were complicated by PE has shown persistence of altered cardiac geometry and left ventricular diastolic dysfunction in those who had preterm PE, but not for women who developed PE at term [9-11, 13, 15, 18].

The long term cardiovascular system morbidity of women who developed PE in pregnancy is well characterized and is worse for those who developed preterm PE. These findings suggest that maternal cardiovascular susceptibility may play an important role in the pathogenesis of preterm more than term PE.

The aim of this study was to assess whether the maternal cardiovascular profile at mid-gestation in nulliparous normotensive women differs in women destined to develop preterm PE versus PE at term.

Materials and Methods

The study includes only nulliparous women with singleton pregnancy and at increased risk of developing PE. Risk for developing PE is determined by uterine artery Doppler assessment at the routine ultrasound assessment at 20-23 weeks of gestation. Women with a mean uterine artery pulsatility index (PI) greater than the 95th percentile (Screen positive women) are to be asked to take part in the study. Nulliparous women with normal uterine artery Doppler PI are to be recruited consecutively during the same period matched for gestational age at assessment.

Patients to be categorized accordingly to mid gestation uterine artery Doppler screening test and pregnancy outcome in one of the following mutually exclusive groups:

1. Screen negative (normal uterine artery PI) women with uncomplicated pregnancy delivering at term (control).
2. Screen positive(high uterine artery PI)women with uneventful pregnancy
3. Screen positive women who required delivery before 37 weeks because of the severity of PE (preterm PE).
4. Screen positive women who developed PE at or after 37 weeks (term PE).

PE is classified according to the international society for the study of hypertension in pregnancy guidelines. Women recruited into the study are normotensive and normoproteinuric at mid gestation with complete recovery within 12 weeks postpartum. Women with postpartum persistent hypertension or proteinuria (essential hypertension or nephropathy) are excluded from the analysis.

The study assessment includes weight, height, blood pressure profile, 12-lead echocardiogram and echocardiography. All women are to be studied by standard two-dimensional and Doppler transthorasic echocardiography. Echocardiography is performed within 1 week of the mid-gestational uterine Doppler assessment by one investigator blinded for pregnancy outcome.

Left sided cardiovascular system assessment

Left ventricular (LV) global diastolic dysfunction-the inability of the heart to fill to a normal volume without an increase in chamber filling pressures. The LV diastolic function and left heart chamber filling pressures are assessed and graded using standard diagnostic algorithms with the recommended adjustments reflecting the concomitant systolic function and maternal age and further adjustments reflecting the pregnancy state.

Normal LV geometry: Defined as normal LV mass index (LVMI <95g/sq m) and relative wall thickness (LV wall thickness). Altered cardiac geometry was defined according to the following three mutually exclusive categories

- **Concentric remodeling:** Normal LVMI with increased RWT (>0.42)
- **Eccentric hypertrophy**: Increased LVMI (>95g/sqm) with normal RWT
- **Concentric hypertrophy**: Increased LVMI (>95g/sqm) and RWT (>0.42)
- **LV radial systolic dysfunction**: Average peak systolic velocity at the level of the left and septal sites of mitral valve annulus index two standard deviations (SDs) below the expected mean for age.
- **LV global systo-diastolic dysfunction**: LV global diastolic dysfunction in the presence of ejection fraction less than 55%. The severity of LV systolic dysfunction and remodeling/hypertrophy is graded according to the American society and European association of echocardiography guidelines.

Study design: Prospective study

Setting: Dept. of O&G & Dept. of Cardiology, S.C.B Medical College & Hospital, Cuttack.

Inclusion criteria: Nulliparous normotensive women at 20-23 weeks of gestation.

Exclusion criteria: Women with medical co-morbidities, smokers, on medication or with fetal abnormalities

Results and Observation

In order to achieve the aims and objective of study, 115 cases of mid gestational pregnant women were taken in the sample for study. These cases were classified into 4 groups i) low risk women with uneventful outcome (59 No's), ii) high risk women with uneventful outcome (35 No's), iii) high risk women who developed Term PE (13 No's) and iv) high risk women who developed preterm PE (8 No's). As per the protocol of the study data were collected on demographic profile, clinical profile and analyzed following appropriate statistical tools and techniques.

Analyses are presented in the forms of tables and graphs along with interpretation in this chapter.

Demographic profile and their association

Table 1: Age distribution of subjects by groups

Group	20 - 24		25 - 29		>= 30		Total		χ2,p
	No	%	No	%	No	%	No	%	
Low-risk women with uneventful outcome	27	45.8	26	44.1	6	10.2	59	100	χ2=6.112 p=.411
High-risk women with uneventful outcome	13	37.1	18	51.4	4	11.4	35	100	
High-risk women who developed term PE	8	61.5	5	38.5	0	0	13	100	
High-risk women who developed preterm PE	6	75.0	2	25	0	0	8	100	
Total	54	47	51	44.3	10	8.7	115	100	

The age profile of the study subjects is presented in table 1 and fig. 1 and 2. Out of 115 subjects 54 (47%) belonged to 20-24 years age group, 51 (44.3%) to 25-29 years age group and 10 (8.7%) belonged to more than equal to 30 years. The distribution of age among the four groups of patients were found to be more or less homogeneous as per the chi square test of association (p=0.411).

BMI

Table 2: BMI distribution of subjects by groups

Group	Normal		Overweight		Total		χ2,p
	No	%	No	%	No	%	
Low-risk women with uneventful outcome	59	100	0	0	59	100	χ2=45.923 p=.000
High-risk women with uneventful outcome	31	88.6	4	11.4	35	100	
High-risk women who developed term PE	7	53.8	6	46.2	13	100	
High-risk women who developed preterm PE	2	25	6	75	8	100	
Total	99	86.1	16	13.9	115	100	

Distribution of subjects by BMI is presented in table 2 and figure 3. Among the low risk women with uneventful outcome, all were having normal BMI. Among the high risk women with uneventful outcome 11.4% were overweight. The proportion of overweight increased to 46.2% among the high risk women who developed term PE and to 75% among the high risk women who developed preterm PE. This indicated the overweight pregnant women have higher risk of developing into term PE and preterm PE. The chi square test of association also confirms significant association of BMI and term and preterm PE (P=0.000).

Comparison of hemodynamic parameters

MAP

Comparison of MAP of different groups of women is presented in table 3. The results clearly indicated that the MAP of HRW group with uneventful outcome, term PE, preterm PE distributed at a higher value than the LRW with uneventful outcome. The lowest median value of 83 mm Hg (80.6 mm Hg-86 mm Hg) was observed among low risk women with uneventful outcome. Among the groups significant difference was observed through Kruskal Wallis test with a p value 0.000. There is a little difference in median value of MAP among the high risk women with or without eventful outcome. The pair wise comparison of MAP by groups with the help of Mann-Whitney U test is presented in table 4. It was clearly revealed that high risk women irrespective of status of event were having more or less the same MAP value with p=0.727, p=0.731, p=0.8 respectively (table 4). High risk women with or without uneventful outcome have clearly higher value of MAP than the low risk women with uneventful outcome (p=0.000).

Table 3: Comparison of MAP by groups

Group	Mean arterial pressure					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	83	80.6	86	35.82	0.000
High-risk women with uneventful outcome	35	93.3	90.6	96	81.33	
High-risk women who developed term PE	13	94	87	96.6	80.58	
High-risk women who developed preterm PE	8	91.65	90.3	96.25	82.81	
Total	115	87	82.6	93.3		

Table 4: Pair wise comparison of MAP by group

Group	Mean arterial pressure	N	Mean Rank	Mann-Whitney Up value
1	Low-risk women with uneventful outcome	59	33.59	0.000
	High-risk women with uneventful outcome	35	70.94	
	Total	94		
2	Low-risk women with uneventful outcome	59	31.84	0.000
	High-risk women who developed term PE	13	57.65	
	Total	72		
3	Low-risk women with uneventful outcome	59	30.39	0.000
	High-risk women who developed preterm PE	8	60.62	

	Total	67		
4	High-risk women with uneventful outcome	35	24.07	0.727
	High-risk women who developed term PE	13	25.65	
	Total	48		
5	High-risk women with uneventful outcome	35	22.31	0.731
	High-risk women who developed preterm PE	8	20.62	
	Total	43		
6	High-risk women who developed term PE	13	11.27	0.8
	High-risk women who developed preterm PE	8	10.56	
	Total	21		

Heart rate

Table 5 furnished the comparison of heart rate by groups. The median heart rate ranges from 70/min (70/min-74/min) among HRW who developed pre term PE to 76/min (70/min-78/min) among LRW with uneventful outcome. The median along with quartiles for the two HRW groups were the same {74/min (72/min-76/min)}. The Kruskal Wallis test revealed no significant difference in heart rate of the 4 groups of pregnant women (p=0.224).

Table 5: Comparison of heart rate by groups

Group	Heart rate					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	76	70	78	62.35	0.224
High-risk women with uneventful outcome	35	74	72	76	55.49	
High-risk women who developed term PE	13	74	72	76	57.62	
High-risk women who developed preterm PE	8	70	70	74	37.56	
Total	115	74	70	76		

Stroke volume

Analysis of stroke volume by groups is presented in table 6, fig. 6 and 7. The histogram in fig. 6 depicted clearly that lower value of stroke volume is noticed for HRW with preterm PE which gradually increases for HRW with term PE, HRW with uneventful outcome and LRW with uneventful outcome in sequential order. The box plot in fig. 7 clearly indicated lower value for 3 groups of HRW than LRW. The distribution of stroke volume is skewed for HRW. The median value of stroke volume for HRW with preterm PE was 52 ml (52 ml-54 ml) which gradually increased to 66 ml (63 ml-68 ml) for LRW with uneventful outcome. The difference in stroke volume among the groups was found to be significant (p=0.000).The pair wise comparison of stroke volume is presented in table 7.The stroke volume of each of the 3 groups of HRW with uneventful outcome, term PE and preterm PE was significantly lower than LRW with uneventful outcome with p value=0.000 for each of them. Besides HRW with uneventful outcome has significantly higher stroke volume than HRW with preterm PE (p=0.001). HRW who developed preterm PE have lower value of stroke volume than HRW with term PE. But the difference was not statistically significant (p=0.106).

Table 6: Comparison of Stroke volume by groups

Group	Stroke volume (ml)					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	66	63	68	75.86	0.000
High-risk women with uneventful outcome	35	58	55	64	46.36	
High-risk women who developed term PE	13	54	52	64	35.73	
High-risk women who developed preterm PE	8	52	52	54	13.44	
Total	115	64	56	66		

Stroke volume index

The comparison of median stroke volume index with quartile values in table 8 indicated significant difference among the groups (p=0.000). The lowest stroke volume index was observed among HRW with preterm PE {32 ml/m^2 (31.1 ml/m^2-34.1 ml/m^2)} and highest among LRW with uneventful outcome with median value 43.2 ml/m^2 (40.5 ml/m^2-45.3 ml/m^2). The pair wise comparison of stroke volume index (table 9) by groups indicated that each of the HRW groups have lower stroke volume index than LRW with uneventful outcome (p=0.000). HRW with preterm PE have significantly lower stroke volume index than HRW with uneventful outcome (p=0.003). HRW with preterm PE and term PE do not differs significantly in stroke volume index (p=0.638).

Table 7: Comparison of Stroke volume Index by groups

Group	Stroke volume Index (ml)					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	43.2	40.5	45.3	77.59	0.000
High-risk women with uneventful outcome	35	37.4	33.9	41	44.1	
High-risk women who developed term PE	13	32.3	31.1	40.7	32.27	
High-risk women who developed preterm PE	8	32	31.1	34.1	16.12	
Total	115	40.7	35.2	43.8		

Cardiac output

The comparison of cardiac output by groups is presented in table 9.The lowest median value of 3.79 L/min (3.67 L/min-3.96 L/min) was observed among HRW with preterm PE which gradually increased to 4.9 L/min(4.6 L/min-5.12 L/min) among LRW with uneventful outcome and the difference was found to be significant (p=0.000). HRW who developed preterm PE have significantly lower cardiac output than HRW with term PE (p=0.032). Similarly HRW with preterm PE have significantly lower cardiac output than HRW with uneventful outcome (p=0.003). However HRW with term PE and HRW with uneventful outcome have more or less similar cardiac output (p=0.371). Each of the 3 groups of HRW has lower cardiac output than LRW with uneventful outcome with $p< 0.05$ (table 10).

Table 8: Comparison of Cardiac output by groups

Group	Cardiac output					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	4.9	4.6	5.12	75.03	0.000
High-risk women with uneventful outcome	35	4.33	3.96	4.8	46.19	
High-risk women who developed term PE	13	4.2	3.92	4.6	38.42	
High-risk women who developed preterm PE	8	3.79	3.67	3.96	15.88	
Total	115	4.7	4.2	4.94		

Cardiac Index

Table 10 analyzed the cardiac index. Lowest median value of cardiac index was 2.28 L/min/m^2 (2.18 L/min/m^2-2.51 L/min/m^2) for HRW with preterm PE and the highest value was 3.23 L/min/m^2 (2.95 L/min/m^2-3.37 L/min/m^2) for LRW with uneventful outcome. The difference among the groups was significant with p=0.000. Each of the other 3 groups of HRW have lower cardiac index than LRW with uneventful outcome ($p< 0.05$). HRW with preterm PE have significantly lower median value than HRW with uneventful outcome (p=0.005). HRW with preterm PE have lower median than HRW with term PE with p=0.059.However this difference is not conclusive as p is closely around the cut off value of 0.05.

Table 9: Comparison of Cardiac index by groups

Group	Cardiac index					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	3.23	2.95	3.37	77.61	0.000
High-risk women with uneventful outcome	35	2.7	2.48	3.01	43.54	
High-risk women who developed term PE	13	2.47	2.32	2.92	34.35	
High-risk women who developed preterm PE	8	2.28	2.18	2.51	15.06	
Total	115	2.98	2.59	3.31		

Comparison of left ventricular geometry

LVMi

The analysis of left ventricular mass index (LVMi) in table 11 revealed that the median value of LVMi was highest for HRW with term PE {68 gm/m^2 (66 gm/m^2-70 gm/m^2)} and was lowest for LRW with uneventful outcome {61 gm/m^2 (58 gm/m^2-65 gm/m^2)}. Group medians are found to be significantly different with p=0.000. The pair wise comparison of groups in table 15 revealed that HRW with term PE or uneventful outcome have significantly higher median value than the LRW with uneventful outcome with p <0.05. For all other pairs of groups the medians do not differ significantly (p>0.05).

Table 10: Comparison of Left Ventricular Mass Index by groups

Group	Left ventricle mass index gm/m2					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	61	58	65	44.13	0.000
High-risk women with uneventful outcome	35	66	63	68	71.27	
High-risk women who developed term PE	13	68	66	70	81.58	
High-risk women who developed preterm PE	8	64	59	82	63.94	
Total	115	64	59	68		

Table 11: Comparison of Left Ventricular Mass Index by groups - Pair wise comparison of group mean

Group	Left ventricle mass index gm/m2	N	Mean Rank	Mann-Whitney Up value
1	Low-risk women with uneventful outcome	59	38.93	0.000
	High-risk women with uneventful outcome	35	61.94	
	Total	94		
2	Low-risk women with uneventful outcome	59	32.45	0.000
	High-risk women who developed term PE	13	54.88	
	Total	72		
3	Low-risk women with uneventful outcome	59	32.75	0.151
	High-risk women who developed preterm PE	8	43.25	
	Total	67		
4	High-risk women with uneventful outcome	35	22.93	0.2
	High-risk women who developed term PE	13	28.73	

	Total	48		
5	High-risk women with uneventful outcome	35	22.4	0.661
	High-risk women who developed preterm PE	8	20.25	
	Total	43		
6	High-risk women who developed term PE	13	11.96	0.363
	High-risk women who developed preterm PE	8	9.44	
	Total	21		

Left ventricular wall thickness

The comparative analysis of 4 groups is presented in table 13. The high risk women who developed preterm PE have the highest median value with value of 10 mm (8 mm-12 mm). The low risk women with uneventful outcome have the lowest median value of 6mm (5 mm-6 mm). Kruskal wallis test revealed significant difference among the group medians. The pair wise comparison of group medians in table 14 revealed that 3 HRW groups have significantly higher median than LRW with uneventful outcome (p<0.05).There is no significant difference between the medians of HRW with preterm PE and term PE (p=0.581).

Table 12: Comparison of left ventricular wall thickness by groups

Group	Left ventricle wall thickness (mm)					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	6	5	6	31.68	0.000
High-risk women with uneventful outcome	35	9	8	10	83.83	
High-risk women who developed term PE	13	9	9	10	87.69	
High-risk women who developed preterm PE	8	10	8	12	90.88	
Total	115	7	6	9		

Table 13: Pair wise comparison of group medians - Left ventricle wall thickness

Group	Left ventricle wall thickness	N	Mean Rank	Mann-Whitney Up value
1	Low-risk women with uneventful outcome	59	30.62	0.000
	High-risk women with uneventful outcome	35	75.96	
	Total	94		
2	Low-risk women with uneventful outcome	59	30.84	0.000
	High-risk women who developed term PE	13	62.19	
	Total	72		
3	Low-risk women with uneventful outcome	59	30.22	0.000
	High-risk women who developed preterm PE	8	61.88	
	Total	67		
4	High-risk women with uneventful outcome	35	22.8	0.153
	High-risk women who developed term PE	13	29.08	
	Total	48		
5	High-risk women with uneventful outcome	35	21.07	0.296
	High-risk women who developed preterm PE	8	26.06	
	Total	43		
6	High-risk women who developed term PE	13	10.42	0.581
	High-risk women who developed preterm PE	8	11.94	
	Total	21		

Comparison of left sided cardiac chamber function

E/A ratio

The analysis of group medians in table 15 indicated that HRW with preterm PE have the lowest median value of 0.95 (0.93-1.25) and the LRW with uneventful outcome have the highest median value of 1.7 (1.6-1.8). The group median were significantly different (p=0.000).The pair wise comparison of E/A ratio by groups is presented in table 16. This revealed that HRW with preterm PE has significantly lower median value than the HRW with uneventful outcome (p=0.036). The HRW with term PE and preterm PE do not have any significant difference (p=0.154). The 3 groups of HRW have significantly lower E/A ratio than the LRW with uneventful outcome.

Table 14: Comparison of E/A ratio by groups

Group	Mitral valve E/A ratio					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	1.7	1.6	1.8	81.66	0.000
High-risk women with uneventful outcome	35	1.3	1.2	1.4	36.14	
High-risk women who developed term PE	13	1.2	1.1	1.4	32.46	
High-risk women who developed preterm PE	8	0.95	0.93	1.25	20.62	
Total	115	1.5	1.2	1.7		

Table 15: Pair wise comparison of E/A ratio by groups

Group	Mitral valve E/A ratio	N	Mean Rank	Mann-Whitney Up value
1	Low-risk women with uneventful outcome	59	62.13	0.000
	High-risk women with uneventful outcome	35	22.84	
2	Low-risk women with uneventful outcome	59	41.92	0.000
	High-risk women who developed term PE	13	11.92	
3	Low-risk women with uneventful outcome	59	37.62	0.000
	High-risk women who developed preterm PE	8	7.31	
	Total	67		
4	High-risk women with uneventful outcome	35	25.41	0.4
	High-risk women who developed term PE	13	22.04	
	Total	48		
5	High-risk women with uneventful outcome	35	23.89	0.036
	High-risk women who developed preterm PE	8	13.75	
	Total	43		
6	High-risk women who developed term PE	13	12.5	0.154
	High-risk women who developed preterm PE	8	8.56	
	Total	21		

LAVI

Comparison of LAVi by groups is presented in table 17. The combine median of all the groups was 34 ml/m^2 (33 ml/m^2-35 ml/m^2). The group medians are mostly similar to the combined median. The kruskal wallis test revealed no significant difference among the group median (p=0.732).

Table 16: Comparison of LAVI by groups

Group	Left atrial volume index					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	34	32	35	57.3	0.732
High-risk women with uneventful outcome	35	34	33	37	62.33	
High-risk women who developed term PE	13	33	32	35	50.69	
High-risk women who developed preterm PE	8	34	33	35	56.12	
Total	115	34	33	35		

Ejection fraction

The comparison of group median in table 18 clearly revealed that HRW who developed preterm PE have the lowest median value of 52% (49%-60%). The pair wise comparison (table 22) indicated that HRW with or without eventful outcome have significantly lower EF than the LRW with uneventful outcome ($p< 0.05$). HRW with term PE have significantly lower ejection fraction than HRW with uneventful outcome (p=0.000).

Table 17: Comparison of ejection fraction by groups

Group	Ejection fraction					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	62	58	65	75.85	0.000
High-risk women with uneventful outcome	35	58	56	59	46.1	
High-risk women who developed term PE	13	54	52	55	25.42	
High-risk women who developed preterm PE	8	52	49	60	31.38	
Total	115	58	56	62		

Comparison of birth weight

The comparison of birth weight by groups (table 19) implied that HRW with preterm PE have the lowest median of 1.72 kg (1.67 kg-1.92 kg) followed by HRW who developed term PE {2.4 kg (2.2 kg-2.6 kg)}. Kruskal Wallis test reveals that the group medians were significantly different (p=0.000). The pair wise comparison of birth weight by groups revealed that HRW who developed preterm PE have significantly lower birth weight than HRW with term PE (p=0.001) and HRW with uneventful outcome (p=0.000). HRW with term PE have significantly lower birth weight than HRW with uneventful outcome (p=0.000). HRW with or without PE have significantly lower birth weight than the LRW with uneventful outcome (p=0.000). HRW with uneventful outcome and LRW with uneventful outcome have no significant difference (p=0.363).

Table 18: Comparison of birth weight by groups

Group	Weight of baby in Kg.					
	No.	Median	Percentile 25	Percentile 75	Mean Rank	Kruskal Wallis Test p value
Low-risk women with uneventful outcome	59	2.8	2.7	2.9	63.98	0.000
High-risk women with uneventful outcome	35	2.9	2.8	3	70.03	
High-risk women who developed term PE	13	2.4	2.2	2.6	28.19	
High-risk women who developed preterm PE	8	1.72	1.67	1.92	9.69	
Total	115	2.8	2.6	2.9		

Cardiac abnormality

The association of cardiac abnormality by groups is analyzed in table 20 with help of chi square test of association. The abnormality under study includes altered geometry, myocardial function and chamber function.

Table 19: Cardiac Abnormality by groups

	Low-risk women with uneventful outcome		High-risk women with uneventful outcome		High-risk women with term PE		High-risk women with preterm PE	Total			χ^2,p
Altered Geometry	No.	%	No.	%	No.	%	No.	%	No.	%	
No abnormality	56	94.9	33	94.3	10	76.9	3	37.5	102	88.7	
Altered Geometry	3	5.1	2	5.7	3	23.1	5	62.5	13	11.3	
Concentric Remodelling	0	0	0	0	2	15.4	3	37.5	5	4.3	χ^2=44.976
Ecentric Hypertropic	3	5.1	2	5.7	1	7.7	1	12.5	7	6.1	p=0.000
Concentric Hypertropy	0	0	0	0	0	0	1	12.5	1	0.9	
Total	59	100	35	100	13	100	8	100	115	100	
Myocardial Function											
No abnormality	52	88.1	31	88.6	10	76.9	1	12.5	94	81.7	
Impaired relaxation	5	8.5	3	8.6	2	15.4	5	62.5	15	13	χ^2 = 28.666
Impaired Contractility	2	3.4	1	2.9	1	7.7	2	25.0	6	5.2	p = 0.000
Total	59	100	35	100	13	100	8	100	115	100	
Chamber Function											
No abnormality	54	91.5	32	91.4	10	76.9	1	12.5	97	84.3	
Diastolic Dysfunction	5	8.5	3	8.6	2	15.4	5	62.5	15	13	χ^2=41.202
Longitudinal systolic dysfunction	0	0	0	0	1	7.7	2	25	3	2.6	p=0.000
Total	59	100	35	100	13	100	8	100	115	100	

Altered geometry

Abnormality in geometry was found among 11.3% of cases overall. Among the HRW with preterm PE the corresponding percentage was 62.5% which was the highest followed by HRW with term PE (23.1%) and HRW with uneventful outcome (5.7%). There was high association of altered geometry with HRW with term PE and preterm PE (p=0.000).

Myocardial function

Among the HRW with preterm PE, 5 out of 8 (62.5 %) had impaired relaxation and 2 out of 8 (25%) had impaired contractility. Among the HRW with term PE, 2 cases were having impaired relaxation and 1 case was with impaired contractility constituting 15.4% and 7.7% respectively.

Chamber function

Among the HRW with preterm PE, 5 out of 8 (62.5 %) had diastolic dysfunction and 2 out of 8 (25%) had longitudinal systolic dysfunction. Among the HRW with term PE, 2 cases were having diastolic dysfunction and 1 case was with longitudinal systolic dysfunction constituting 15.4% and 7.7% respectively.

Discussion

High risk women who developed preterm PE exhibit more severe cardiovascular impairment at mid-gestation compared with high risk women who developed term preeclampsia and with uneventful outcome.

Demographic profile

BMI

The proportion of overweight increased to 46.2% among the high risk women who developed term PE and to 75% among the high risk women who developed preterm PE. This indicated the overweight pregnant women have higher risk of developing into term PE and preterm PE. This is Consistent with study of Tara E. O'Brien, *et al.*, 2003 [15] who demonstrated that there is a consistently strong positive association between maternal pregnancy body mass index and the risk of preeclampsia [16] and Sara Sohlberg *et al.*, 2011 [17] who found that a short maternal stature and a high BMI increase risks of preeclampsia of all severities. The associations seem especially strong between short stature and severe types of preeclampsia, and high BMI and mild types of preeclampsia [18]. Maternal BMI is an important risk factor of preeclampsia. Women with an above normal body mass index had a higher incidence of pre-eclampsia than women with a normal body mass index (controls).

Hemodynamic parameters

High risk women with or without uneventful outcome have clearly higher value of MAP than the low risk women with uneventful outcome (p=0.000). There is a little difference in median value of MAP among the high risk women with or without eventful outcome. The median value of MAP was 94 mm Hg {87 mm Hg (25^{th} percentile)-96.7 mm Hg (75^{th} percentile)} for high risk women who developed term PE. This was highest among all. The lowest median value of 83 mm Hg (80.6 mm Hg-86 mm Hg) was observed among low risk women with uneventful outcome. Measurement of blood pressure in the first or second trimesters can predict which women will develop problems later on. Increased diastolic blood pressure is associated with an increased risk of pre-eclampsia [19] Study depicted clearly that lower value of stroke volume is noticed for high risk women who developed preterm PE which gradually increases for high risk women who developed term PE, high risk women with uneventful outcome and low risk women with uneventful outcome in sequential order.

The difference among the groups was significant with p=0.000. High risk women who developed pre term preeclampsia demonstrated significantly lower stroke volume index, lower cardiac index at mid gestation than low risk women with uneventful outcome. This finding is consistent with that of K Melchiorre *et al.*, 2012 [20]. This high impedance/low volume hemodynamic state seen in women destined to develop preterm preeclampsia suggests that there is an increased LV after load and contracted circulating volume even at mid gestation. But my study is in contrast when compared in between high risk group women who developed term preeclampsia, term preeclampsia

and high risk group women with uneventful outcome. So this is not consistent with that of K Melchiorre *et al.*, 2012 [20]. This is in contrast to the finding of Valensise *et al.* and Hibbard *et al.* who presented that there is unchanged cardiac index hemodynamic state in between high risk group who developed term preeclampsia and low risk group women with uneventful outcome.

Left ventricle geometry

The frequency distribution of LVMi depicted that the distribution of LRW with uneventful outcome is more or less symmetrical whereas in case of 3 HRW groups the distribution is right screwed. The pair wise comparison of groups in table 15 revealed that HRW with term PE or uneventful outcome have significantly higher median value than the LRW with uneventful outcome with $p < 0.05$. There is a significantly higher prevalence of LV remodelling /hypertrophy at mid-gestation in both preterm PE and term PE women. This finding is likely to represent a compensatory response to the increased after load that is evident from the higher mid-gestational mean arterial pressures seen in women with PE. Left ventricular remodelling is required to minimize wall stress in the presence of increased after load as a recognized mechanism for preserving the balance between myocardial oxygen demand and supply. In women destined to develop PE it seems to be an effective response, as wall stress indices remain unaltered between cohorts. Our results are in agreement with those of previous authors who have similarly demonstrated compensatory altered LV geometry in the preclinical phase of both preterm and term PE.

Left-sided cardiac chamber function

The LRW with uneventful outcome have the centre relatively to the right. This gives an impression that HRW with preterm PE have relatively lower E/A ratio than the other 2 HRW groups and LRW group. HRW with preterm PE has significantly lower median value than the HRW with uneventful outcome (p=0.036). The HRW with term PE and preterm PE do not have any significant difference (p=0.154). The 3 groups of HRW have significantly lower E/A ratio than the LRW with uneventful outcome. The histogram of ejection fraction (fig.14) depicted an indication that HRW with preterm PE have the relatively lower median than HRW with term PE and HRW with uneventful outcome. LRW with uneventful outcome indicated higher value of ejection fraction than all other groups. The comparison of group median in table 21 clearly revealed that HRW who developed preterm PE have the lowest median value of 52% (49%-60%).

Maternal haemodynamic and heart geometry to assess cardiac function demonstrated a very high prevalence (33%) of LV diastolic dysfunction at mid-gestation in women who subsequently developed preterm PE compared with the women with term PE or uneventful pregnancy. There was no significant difference in mid-gestational LV diastolic function between women with term PE and control women. This is a novel finding as no previous study has systematically assessed diastolic function in the preclinical stages of PE. Diastolic dysfunction is related to increased after load and LV stiffness, as demonstrated by significantly higher mean arterial pressure, TVRI, RWT and LV concentric hypertrophy noted in women destined to develop preterm PE. Preterm PE, but not term PE, also exhibited longitudinal systolic dysfunction at the level of the lateral LV free wall with preserved radial function. This pattern of systolic impairment affecting only the longitudinal function is similar to that seen in early essential hypertension in nonpregnant women and is indicative of after load-induced impairment of subendocardial myocardial fibres. 18 Our findings of significant LV diastolic dysfunction in preterm PE suggest that there is exhaustion of cardiac reserve by midgestation in these women. This may favour the subsequent deterioration of cardiac function seen with the diagnosis of preterm PE and the higher long-term cardiac morbidity/ mortality seen in preterm versus term PE and controls. The only other study that assessed cardiac function in the preclinical phase of the disease in early and late PE was performed by Valensise *et al.* [14].

Cardiac abnormality

Abnormality in geometry was found among 11.3% of cases overall. Among the HRW with preterm PE the corresponding percentage was 62.5% which was the highest followed by HRW with term PE (23.1%) and HRW with uneventful outcome (5.7%). High risk Pregnant women destined to develop preterm preeclampsia exhibit more severe type of altered geometry like concentric remodelling, eccentric hypertrophy, concentric hypertrophy at midgestation in comparison to high risk pregnant women destined to develop term preeclampsia. Impaired relaxation was more found in high risk group pregnant women than impaired contractility. In terms of myocardial function high risk pregnant women destined to develop preterm preeclampsia exhibit significant abnormality in comparison to pregnant women destined to develop term preeclampsia, uneventful outcome. Diastolic dysfunction was more evident at mid gestation in high risk pregnant women destined to develop pre term preeclampsia.

This study finding is consistent with Esther F. Davis *et al.*, 2012 [21] which depicted in women with preeclampsia, hypertension is associated with exaggerated ventricular hypertrophy, but LV systolic function is unchanged [22]. My study is also in agreement with the study of Karen Melchiorre, *et al.* 2012 [20] who depicted that women with preterm preeclampsia have a more severe cardiac impairment than those with term preeclampsia. This finding may explain the increased long-term cardiovascular risk associated with preterm preeclampsia. The cardiac assessment of women with preterm preeclampsia may be of relevance in identifying women at higher risk of developing cardiovascular morbidity and mortality in later life [23].

Conclusion

High risk pregnant women with preterm preeclampsia, term preeclampsia, uneventful outcome and low risk pregnant women with uneventful outcome demonstrate different cardiovascular profile at mid gestation. There is a significantly higher prevalence of LV remodelling /hypertrophy at mid-gestation in both preterm PE and term PE women. Asymptomatic cardiac diastolic dysfunction, impaired relaxation, altered geometry at mid gestation is only seen in high risk pregnant women with pre term preeclampsia but not in those with term preeclampsia. It is now evident that women who developed preterm PE in pregnancy have a much higher incidence of developing symptomatic heart failure many years after delivery. Although it is not possible to distinguish pre-existing cardiac dysfunction from that acquired as a result of pregnancy, these cardiac findings may be useful in understanding the cardiovascular pathophysiology of PE.

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Conflict of interest

The authors declare that they have no conflict of Interest.

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