Original Article

Mid-term maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective analysis

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Abstract

Aims and Objectives: Maternal cardiovascular system is largely affected in the pathogenesis of preeclampsia. In other words, those women who are destined to develop preeclampsia, severe cardiovascular remodeling with ventricular dysfunction starts during the mid gestational age which differs those who develop preterm preeclampsia than those of term eclampsia. The aim of this study to differentiate what cardiovascular changes occur between these two high risk pregnancy groups during mid gestation who were normotensive during then.

Materials & Methods: This is a prospective analysis taking totally 115 women, including 56 high risk women tend to develop PE as determined by mid-gestational uterine artery Doppler assessment. All women underwent blood pressure monitoring, echocardiography and Doppler assessment between 20-23 weeks of gestation and there cardiovascular profile in women with normal pregnancy and those that subsequently developed preterm preeclampsia and term preeclampsia were compared.

Results: Out of 56 high risk women, 13 women developed PE and 8 developed preterm PE. Irrespective of gestation, 23% preeclamptic women had evidence of concentric left ventricular remodeling which was not found in control women group. 1 out of 8 preterm PE women (12.5%) developed concentric hypertrophy which was not seen in term preeclamptic group also. Only women who developed preterm PE exhibited a high resistance low volume haemodynamic state at mid gestation. They also have evidence of left ventricular diastolic and systolic dysfunction.

Conclusion: Asymptomatic cardiac diastolic dysfunction is evident at mid gestation in women who subsequently develop preterm PE but not in those who develop term PE. Also concentric hypertrophy of LV is mainly associated with preterm PE than term PE group. These cardiovascular changes support preeclampsia is not a single disorder, but a cluster of symptoms that have several different etiologies.

Keywords: PE – preeclampsia, LV – left ventricle, }

Introduction

Approximately 20% of patients with preeclampsia at term have more evident myocardial dysfunction. Diastolic dysfunction usually precedes systolic dysfunction in the evolution of hypertensive cardiac diseases.\(^1\)
As preeclampsia develops, the cardiac output significantly drops that coincides with increases in total vascular resistance. The earlier the onset of symptoms the greater and the earlier the decline in systolic function.2

Maternal systolic function is reduced to a similar degree in both IUGR and pre-eclamptic IUGR, while there is a greater impairment in diastolic function in pre eclamptic IUGR.3

In pregnancy, left ventricular mass and dimensions increase. This eccentric hypertrophy is a healthy physiological response that reverses within few weeks postpartum. In contrast, during preeclampsia, women show more pronounced increase in LVM, but with less pronounced LV widening. This concentric hypertrophy develops secondary to the increased LV workload that accompanies the elevated blood pressure.3

Concentric Cardiac remodeling is also accompanied by a decline in diastolic function, reflected in larger values for left atrial diameter and circulating atrial natriuretic peptide levels.4,5,6 Global diastolic dysfunction was seen in 52% of women with PE, and half of them also presented increased left chamber filling pressures. The cardiovascular findings were either more prevalent or more severe in women with PE pregnancies, with features of impaired myocardial contractility and systolic chamber dysfunction.6

The long term cardiovascular morbidity of women who developed PE in pregnancy is well characterized. 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
This is a prospective study conducted in a tertiary hospital over a period of 2 years from Aug 2014 to Aug 2016. Study includes only nulliparous women with single tone pregnancy & at increased risk of developing PE which was determined by uterine artery (UA) Doppler assessment at 20-23 weeks of gestation. Women with a mean UA pulsatility index (PI) greater than the 95th centile (screen positive) were asked to take part in the study. Women with medical comorbidities, smokers, on medication or with feto-maternal anomalies were excluded from the study.

Patients were categorized accordingly to mid gestation UA Doppler screening test into these four categories. 1. Screen negative (normal uterine artery PI) women with uncomplicated pregnancy delivering at term as controls. 2, screen positive (high UA PI) women with uneventful pregnancy. 3, screen positive women who require delivery before 37 weeks because of severe PE (Preterm PE). 4, screen positive women who develop PE at or after 37 weeks (term PE).

The study assessment includes weight, height, blood pressure profile, 12-lead electrocardiogram and echocardiography. Echocardiography were performed within 1 week of the mid gestational UA 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 were 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 normal relative wall thickness (RWT < 0.42). Altered cardiac geometry was defined according to the following three mutually exclusive categories

- CONCENTRIC REMODELLING–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 was defined as ejection fraction less than 55%.
• Left ventricular longitudinal 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.

Myocardial function was assessed using tissue colour Doppler derived strain and strain rate technique. Peak systolic strain rate was considered abnormal if it was two SDs below the expected mean for the age. If at least one myocardial segment was affected, it was termed impaired myocardial contractility. Regional diastolic dysfunction was defined as early to late strain rate ratio below or equal to one. If at least one myocardial segment was affected, it was termed impaired myocardial relaxation.

Results

Table 1-Parameters

| Parameter                         | Low-risk women with uneventful outcome (n=59) | High-risk women with uneventful outcome (n=35) | High-risk women who developed term PE (n=13) | High-risk women who developed preterm PE(n=8) |
|----------------------------------|---------------------------------------------|-----------------------------------------------|---------------------------------------------|---------------------------------------------|
| Avg Maternal age (years)         | 30.5                                        | 31.3                                          | 31                                          | 29.8                                       |
| Pre-pregnancy BMI (Kg/m²)        | 22                                          | 24.2                                         | 25.6                                        | 26.2                                       |
| BMI at assessment (kg/m²)        | 23.3                                        | 25.1                                         | 26.2                                        | 27                                         |
| Gestational age at delivery (in weeks) | 39.3                                    | 39                                           | 38.5                                        | 32.2                                       |
| Birth weight (kg)                | 2.8kg                                       | 2.9kg                                        | 2.4kg                                       | 1.72kg                                     |
| Haemodynamics                    |                                             |                                               |                                             |                                             |
| HR (beats/min)                   | 80                                          | 78                                           | 82                                          | 81                                         |
| MAP (mm Hg)                      | 83                                          | 93.3                                         | 94                                          | 91.65                                      |
| SV (ml)                          | 66                                          | 58                                           | 54                                          | 52                                         |
| SVI (ml/m²)                      | 43.2                                        | 37.4                                         | 32.3                                        | 32                                         |
| CO (L/min)                       | 4.9                                         | 4.33                                         | 4.2                                         | 3.78                                       |
| CI (L/min/m²)                    | 3.23                                        | 2.7                                          | 2.48                                        | 2.28                                       |
| TVR (dynes/s/cm⁵)                | 1012                                        | 1229                                         | 1372                                        | 1458                                       |
| LV geometric indices             |                                             |                                               |                                             |                                             |
| Relative wall thickness (RWT in mm) | 6                                        | 9                                            | 9                                           | 10                                         |
| LVMI (g/m²)                      | 61                                          | 66                                           | 68                                          | 64                                         |
| Systolic Function                |                                             |                                               |                                             |                                             |
| Ejection Fraction (%)            | 62                                          | 58                                           | 54                                          | 52                                         |
| Altered Geometry                 |                                             |                                               |                                             |                                             |
| Concentric remodeling            | 0                                           | 0                                            | 2                                           | 3                                          |
| Ecentric hypertrophy             | 3                                           | 2                                            | 1                                           | 1                                          |
| Concentric hypertrophy           | 0                                           | 0                                            | 0                                           | 1                                          |
| Myocardial Function              |                                             |                                               |                                             |                                             |
| Impaired relaxation              | 5                                           | 3                                            | 2                                           | 5                                          |
| Impaired contractility           | 2                                           | 1                                            | 1                                           | 2                                          |
| Chamber Function                 |                                             |                                               |                                             |                                             |
| Diastolic dysfunction            | 1                                           | 1                                            | 2                                           | 3                                          |
| Longitudinal systolic dysfunction | 0                                           | 0                                            | 1                                           | 2                                          |
Out of 115 patients, 59 (LRW, low risk women) patients were having normal UA pulsatility index (PI) and rest 56 patients whose PI were above 95 percentile, 13 developed preeclampsia (PE) and 8 developed preterm PE leading to delivery before 37 weeks of gestation. So 4 groups were considered 59 patients were LRW (low risk women), 35 out of 56 were termed as HRW (high risk women) who have normal pregnancy outcome with PI more than 95 percentile, then 8 were PT PE (preterm preeclampsia) leading to early delivery before 37 weeks due to severe preeclampsia and rest 13 were termed as term preeclampsia (term PE) who delivered after 37 weeks. (table 1) There was no significant demographic differences between the controls and women who developed PE. Women who developed PT PE were significantly heavier than those with normal pregnancy outcomes i.e control and high risk uneventful groups.

**Haemodynamic parameters**

Women who subsequently developed term and preterm PE had significantly higher mean arterial pressure and total vascular resistance at mid gestation than those with normal pregnancy outcomes. Women who subsequently developed PT PE but not those who developed term PE had lower SV index and cardiac index than controls (fig 1).

**Left ventricular geometry**

Women who subsequently developed term and preterm PE has higher LV RWT and unchanged LV mass and wall stress indices at mid-gestation compared with women with normal pregnancy outcomes (fig 1). The prevalence of altered geometry was significantly higher in both PE groups at mid-gestation compared with women with normal pregnancy outcomes. (PT PE -62.5 %, term PE -23 %, High risk uneventful outcome – 5.7%, LRW – 5%).

**LV diastolic function**

3 out of 8 women (37.5%) who went on to develop preterm PE demonstrated LV global diastolic dysfunction at mid gestation compared with one in the control and one in the high-risk uneventful groups (1.7% & 2.9% respectively). Five out of 8 (62.5%) PT PE women exhibited impaired myocardial relaxation compared with 8.4% of controls & 8.5% of HRW with uneventful outcomes.

**LV Systolic function**

LV systolic function is too affected most in case of PT PE group, then term PE and HRW and LRW in descending order as suggested by the ejection fraction 52%, 54%, 58% & 62% respectively.

**Discussion**

Women with PT PE exhibit more severe cardiovascular impairment at mid-gestation compared with those who are delivered at term with PE or with an uneventful pregnancy. The women who went on to develop PT PE showed significantly higher TVR (total vascular resistance) and lower CI cardiac index) at mid-gestation than both control women & PE women. These findings are consistent with that of Valensise et al. This high-impedance/low-volume haemodynamic state seen in women destined to develop preterm PE suggests that there is an increased LV after load and contracted circulating volume even at mid-gestation.

There is a significantly higher prevalence of LV remodeling/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 remodeling is required to minimise 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.10
In particular, Valensise et al.\textsuperscript{11} demonstrated altered midgestational cardiac geometry in women who subsequently developed fetal growth restriction and gestational hypertension. In another study, the authors demonstrated that third-trimester concentric remodeling in women affected by early mild gestational hypertension was an independent predictor for the development of PE.\textsuperscript{10} they also showed that LVMI and RWT were significantly higher at 24 weeks of gestation in women who subsequently developed PE compared with control women.

The combined use of tissue Doppler and conventional echocardiography taking into account maternal hemodynamic 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 non-pregnant women and is indicative of after load-induced preclinical phase of the disease in early and late PE was performed by Valensise et al.\textsuperscript{11}

**Conclusion**

Preterm and term PE exhibit different cardiovascular profiles at mid-gestation of pregnancy, before the onset of overt disease. Asymptomatic cardiac diastolic dysfunction and impaired myocardial relaxation at mid-gestation is only seen in women who subsequently develop preterm PE but not term PE. 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\textsuperscript{8,9} Although it is not possible to distinguish preexisting 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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