Original Article

Association of sympathovagal imbalance with arterial stiffness indices in women with risk factors for pregnancy-induced hypertension in first and third trimesters of gestation

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Abstract

Background and Aim: Though contribution of sympathovagal imbalance (SVI) to arterial stiffness indices (ASI), and markers of CV risk in pregnancy-induced hypertension (PIH) has been reported, their association during early trimesters of gestation in PIH has not been studied. Therefore, in the present study, we have investigated the association of SVI with ASI in pregnant women with risk factors for PIH during their first and third trimesters of gestation.

Methods: Blood pressure (BP), rate-pressure product (RPP), spectral analysis of heart rate variability (HRV), and arterial stiffness indices (ASI) were assessed in subjects of control group (normal pregnant women without having risk for PIH, *n* = 50) and study group (pregnant women with risk factors for PIH, *n* = 50). Independent association of LF:HF ratio to the various parameters were determined using multiple regression analysis.

Results: It was observed that the ratio of low-frequency to high-frequency power (LF-HF ratio) of HRV, the sensitive indicator of SVI was significantly high in study group subjects starting from first trimester of pregnancy. SVI could be due to both sympathetic activation and vagal withdrawal. ASI was found to be significantly high in study group subjects compared to that of controls. LF-HF ratio had significant correlation and independent association with RPP (the marker of CV risk) and ASI.

Conclusion: SVI is associated with arterial stiffness in pregnant women having risk factors for PIH. SVI and increased arterial stiffness could contribute to CV risks in pregnant women with risk factors for PIH.

Key words: Arterial stiffness indices, cardiovascular risks, heart rate variability, pregnancy-induced hypertension, sympathovagal imbalance

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INTRODUCTION

Pregnancy-induced hypertension (PIH) is a serious complication of pregnancy that affects 3-8%[1] of all pregnancies and accounts for about 12% of maternal deaths in developing countries of south-east Asia.[2] It has been reported recently that PIH is associated with arterial stiffness (AS),[3] which is a marker of increased cardiovascular (CV) disease risk.[4] Also, there are reports of CV diseases in preeclamptic women during and years after pregnancy.[5,6] It has been observed that both preeclampsia and CV disease share common risk factors.[7] Therefore, repeated screening of women with risk factors for PIH in the early part of pregnancy is essential for proper management and prevention of PIH.

Though the etiology of PIH is still elusive, it has been documented that the disease is characterized by low circulating volume and high vascular resistance.[8] The

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vascular resistance in PIH has been reported due to the increased sympathetic tone.[9,10] Recently, we reported that along with sympathetic overactivity, there is vagal withdrawal in PIH.[11-13] From our earlier studies, we observed that women who develop PIH in later part of pregnancy, had some degree of sympathetic overactivity from the early trimester of pregnancy.[11] With the progress of pregnancy, vagal withdrawal occurs in later part of pregnancy in addition to the sympathetic overactivity that contributes to the development of SVI and PIH.[13] However, till date, no study has been conducted to assess the degree of SVI in women with risk factor for PIH. SVI has recently been reported to be associated with CV morbidity and mortality.[14,15] Studies have demonstrated that sympathetic overactivity is implicated in the stiffening of arteries and diastolic dysfunction, which might contribute to development and progression of hypertension and its complications.[16] There are reports of increased arterial stiffness indices (ASI) in PIH[3,4,17] and increase in arterial stiffness is an independent predictor of CV mortality.[18,19] Although there are evidence to suggest that arterial stiffness contributes to CV outcomes,[20,21] studies in pregnant women in their early trimester are lacking. To the best of our knowledge, no study has been conducted till date to assess the association of SVI with ASI comparing the early trimester with late trimester of pregnancy. Therefore, in the present study we have assessed the link between arterial stiffness and SVI during early and late trimesters in pregnant women with risk factors for PIH.

MATERIALS AND METHODS

The present study was conducted in the department of physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India. After obtaining approval of the project plan from research and ethics committees of JIPMER, 100 subjects (50 in control group, 50 in study group) were recruited from the out-patient unit of the obstetrics and gynecology department of JIPMER. Written informed consent was obtained from all the participants prior to initiation of the study. Subjects of study group included pregnant women who had risk factors for PIH and of control group included normal pregnant women without any risk factor for PIH.

Inclusion criteria for the study group were established risk factors for PIH,[8] such as family history of preeclampsia, preeclampsia in previous pregnancy, extremes of reproductive age, body mass index (BMI) >35, diastolic blood pressure (DBP) >80 mmHg at the first visit, first pregnancy, multiple pregnancy, underlying medical conditions (diabetes mellitus, renal disease, pre-existing hypertension), etc. Subjects of control group included normal pregnant ladies who had none of the above-mentioned risk factors for PIH. Subjects receiving oral contraceptives prior to pregnancy were excluded from both the groups.

Subjects attended obstetrics OPD for their regular check-ups and also reported to polygraph laboratory of physiology department for recording of various parameters at all the three trimesters of pregnancy. The subjects reported to polygraph laboratory about two hours after a light breakfast devoid of coffee or tea. Height and weight were measured to calculate body mass index (BMI). Blood pressure (BP) was recorded using the automatic non-invasive BP monitor, (Omron, HEM 7203 model, Omron Healthcare Co., Kyoto, Japan). Heart rate, systolic BP and DBP were noted from the display screen of BP monitor, and mean arterial pressure (MAP) was calculated. Rate pressure product (RPP) was calculated.[22]

HRV recording

Following 10 minutes of supine rest in polygraph laboratory (room temperature maintained at 25°C), basal heart rate (BHR) and BP (diastolic and systolic) were recorded. For recording of short-term HRV, recommendation of the Task Force on HRV was followed.[23] For this purpose, electroencephalogram (ECG) electrodes were connected and Lead II ECG was acquired at a rate of 1000 samples/second during supine rest using BIOPAC MP 100 data acquisition system (BIOPAC Inc., USA). The data was transferred from BIOPAC to a windows-based PC with AcqKnowledge software version 3.8.2. Ectopics and artifacts were removed from the recorded ECG. RR tachogram was extracted from the edited 256-s ECG using the R wave detector in the AcqKnowledge software and saved in ASC-II format, which was later used offline for short term HRV analysis. HRV analysis was done using the HRV analysis software version 1.1 (Bio-signal Analysis group, Finland). Among the frequency-domain indices of HRV, ratio of low-frequency to high-frequency power (LF-HF ratio) was recorded.

Assessment of arterial stiffness

Arterial stiffness was assessed by measuring pulse wave velocity (PWV), following the standard procedures and the ASI was computed.[24] PWV was determined by PeriScope (M/S Genesis Medical System, Hyderabad, India) in an 8-channel real-time personal computer-based simultaneous acquisition and analysis system with an acquisition rate of 200 samples/second. In this method, BP is measured by detecting pulsation of the artery as the pressure oscillation in the cuff caused by ventricular ejection. The entire recording was carried out following 10-15 minutes of supine rest. For this purpose, electrodes were placed on the proximal end of the limbs and BP cuffs were wrapped on both upper arms 2.5 cm above the cubital fossae for recording from the brachial artery, and on both

legs above the ankle for recording from the tibial artery. The cuffs were connected to a plethysmographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures BP volume waveforms from the brachial and tibial arteries. Cuff pressure was controlled by a microcomputer, which activates the cuff inflation and deflation system during the measurement cycle. PWV is the speed at which the pressure pulse wave travels from the heart to the peripheral artery, after blood rushes out during contraction assesses the stiffness of the artrial wall.

Statistical analysis of data

SPSS version 13 (SPSS Software Inc., Chicago, IL, USA) was used for statistical analysis. All data were expressed as mean ± SD. Normality of data was tested by Kolmogorov Smirnov test. For parametric data, the level of significance between the groups was tested by Student's unpaired *t*-test and for nonparametric data Welch's corrected *t*-test was used. The association of LF-HF ratio with HRV, and ASI parameters were assessed by Pearson's correlation analysis. The independent contribution of various parameters to SVI (alteration in LF-HF ratio) were assessed by multiple regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

There was no significant difference in age, body weight, and BMI between the subjects of control group and study group at first trimester recordings [Table 1]. In the third trimester, the body weight ($P = 0.0371$) and BMI ($P = 0.0425$) of study group subjects was more than that of the control group. BHR of study group subjects was significantly more compared to the control group from early trimesters. SBP, DBP, MAP, and RPP of study group subjects were significantly more ($P < 0.0001$) compared to the respective values of control group both in first and third trimesters. Among the frequency-domain indices, LF-HF ratio was significantly more in study group compared to the control group in both the first and third trimester recordings [Table 1 and Figure 1].

All brachial artery PWV parameters and ASI were significantly increased in study group compared to control group in both the trimester recordings [Table 2 and Figure 2a and b]. In study group, BMI was not correlated with LF-HF ratio in first and third trimester recordings [Table 3]. Though BHR, MAP, RPP, PWV, and ASI were not correlated with LF-HF ratio in first trimester recordings of the study group, they demonstrated a significant correlation in third trimester [Table 3]. In third trimester, in the study group, RPP, PWV, and ASI, had significant independent contribution to the LF-HF ratio as demonstrated by multiple regression analysis [Table 4].

Table 1: Age, body weight, BMI and cardiovascular parameters in subjects of control and study group

Parameters	Control group (*n*=50)	Study group (*n*=50)	*P* value
First trimester			
Age (year)	25.33±2.79	26.41±3.22	0.2131
Body weight (kg)	53.42±6.12	55.47±7.19	0.1279
BMI (kg/m^2)	23.87±3.94	25.00±3.97	0.1563
BHR (per min)	82.37±8.68	90.87±9.65	0.0003
SBP (mmHg)	97.90±8.99	116.95±11.65	<0.0001
DBP (mmHg)	63.87±8.42	82.93±7.99	<0.0001
MAP (mmHg)	75.21±7.75	94.27±7.09	<0.0001
RPP (mmHg/min)	80.70±11.79	106.54±20.96	<0.0001
LF:HF ratio	0.82±0.21	1.08±0.28	<0.0001
Third trimester			
Body weight (kg)	60.34±9.49	64.38±9.62	0.0371
BMI (kg/m^2)	26.38±5.39	28.59±5.36	0.0425
BHR (pm)	89.67±12.28	100.77±6.62	<0.0001
SBP (mmHg)	100.05±9.20	119.41±9.40	<0.0001
DBP (mmHg)	70.55±12.77	84.79±9.54	<0.0001
MAP (mmHg/min)	80.38±9.93	96.33±8.23	<0.0001
RPP (mmHg/min)	89.95±16.07	120.37±12.63	<0.0001
LF:HF ratio	1.17±0.33	1.47±0.42	<0.0001

The data presented are mean±SD. *P* value<0.05 was considered statistically significant. BMI: Body mass index, BHR: Basal heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, RPP: Rate-pressure product, LF:HF ratio: Ratio of low-frequency to high-frequency power

Table 2: Arterial stiffness indices in control and study groups in the first and third trimester

Parameters	Control group (*n*=50)	Study group (*n*=50)	*P* value
First trimester			
RB-PWV	978.51±91.20	1118.77±190.32	<0.0001
LB-PWV	946.35±129.98	1074.13±162.23	<0.0001
RA-BI	1.03±0.06	1.10±0.21	0.0256
LA-BI	1.04±0.06	1.09±0.07	0.0002
Third trimester			
RA-PWV	963.85±119.50	1194.28±121.83	<0.0001
LB-PWV	878.65±122.68	1128.56±139.26	<0.0001
RA-BI	1.08±0.05	1.21±0.21	<0.0001
LA-BI	1.05±0.08	1.26±0.05	<0.0001

The data presented are mean±SD. *P* value<0.05 was considered statistically significant. PWV: Pulse wave velocity. B-PWV: Right brachial PWV, LB-PWV: Left brachial PWV, RA-BI: Right ankle-brachial index, LA-BI: Left ankle-brachial index

DISCUSSION

In the present study, significantly high BHR, SBP, DBP, MAP, and RPP were seen in study group (pregnant women with risk factors for PIH) compared to the control group (women with normal pregnancy) [Table 1], which suggest that subjects having risks of developing PIH have altered CV parameters even in the early part of pregnancy. Heart rate (HR) at rest is the function of vagal tone and increase in HR represents decreased vagal activity.[23] Recently, it has been reported that increase in resting HR is a cardiometabolic risk and risk factor for all cause

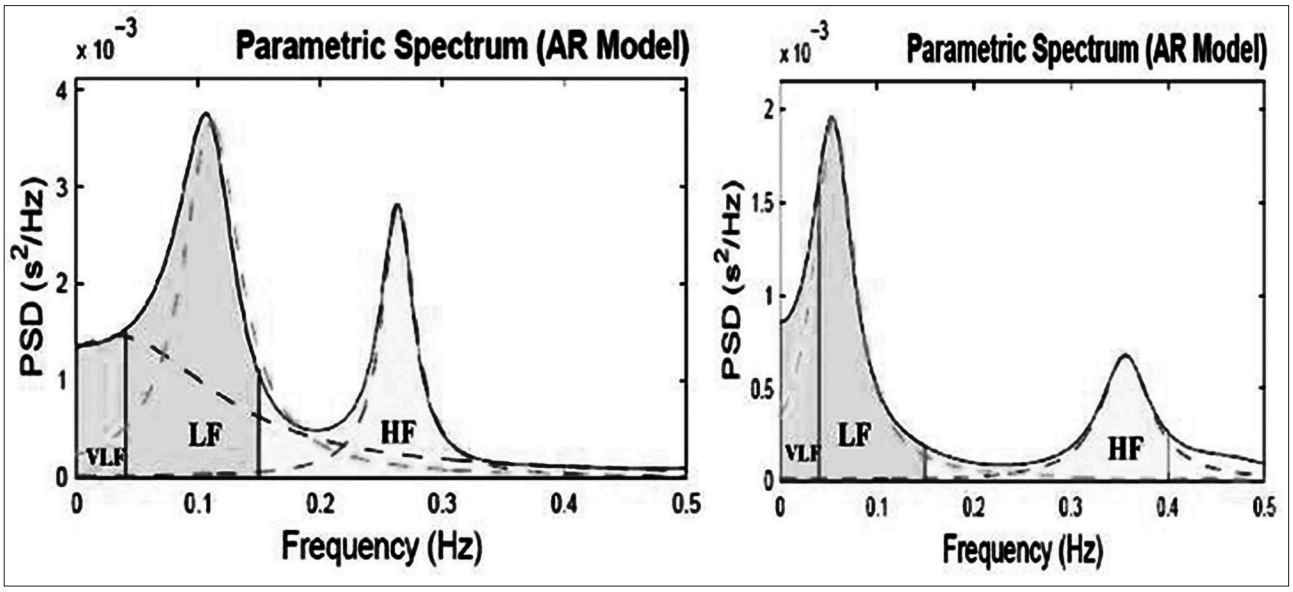

Figure 1: Power spectral analysis (Auto Regression model) of heart rate variability (from one of the subject for sample) depicts the ratio of low-frequency to high-frequency power (sympathovagal imbalance) in women with risk factors for pregnancy-induced hypertension in the first trimester and third trimesters of gestation. VLF: Very low-frequency power, LF: Low-frequency power, HF: High-frequency power, PSD: Power spectrum density

Table 3: Correlation of LF/HF ratio with BMI, BHR, SBP, DBP and ASI of subjects with risk factors for PIH

	First trimester		Third trimester	
	r	*P*	*r*	*P*
BMI	0.018	0.590	0.025	0.445
BHR	0.064	0.297	0.272	0.020
MAP	0.088	0.144	0.265	0.022
RPP	0.044	0.366	0.307	0.008
RB-PWV	0.039	0.483	0.256	0.038
LB-PWW	0.041	0.458	0.260	0.035
RA-BI	0.158	0.092	0.402	0.001
LA-BI	0.152	0.089	0.405	0.001

The *P* values less than 0.05 was considered significant. BMI: Body mass index, BHR: Basal heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, RPP: Rate-pressure product, LF:HF ratio: Ratio of low-frequency to high-frequency power, ASI: Arterial stiffness indices, PWV: Pulse wave velocity, RB-PWV: Right brachial PWV, LB-PWV: Left brachial PWV, RA-BI: Right ankle-brachial index, LA-BI: Left ankle-brachial index, PIH: Pregnancy induced hypertension

Table 4: Multiple regression analysis of LF-HF ratio (as dependable variable) with various parameters (as independent variables) in subjects of PIH risk group in the third trimester

Independent variables	Standardized regression coefficient beta	Confidence interval		*P* values
		Lower limit	Upper limit	
RPP	0.240	0.007	0.065	0.035
RB-PWV	0.262	0.002	0.035	0.015
LB-PWW	0.225	−0.020	0.003	0.052
RA-BI	0.332	0.045	0.120	0.006
LA-BI	0.315	0.030	0.110	0.007

P values<0.05 considered significant. RPP: Rate-pressure product, PWV: Pulse wave velocity, RB-PWV: Right brachial PWV, LB-PWV: Left brachial PWV, RA-BI: Right ankle-brachial index, LA-BI: Left ankle-brachial index, PIH: Pregnancy induced hypertension

mortality.[25,26] The level of BP is the function of vascular resistance that reflects the sympathetic tone.[27] Thus, the increase in HR and BP in study group subjects indicated decreased vagal tone and increased sympathetic tone in pregnant women with risk factors for PIH. RPP is a measure of myocardial work load and oxygen utilization.[28] Increased RPP, especially in individuals with high BP has been reported as a potential CV risk.[28]

LF-HF ratio is the index of SVI and increase in this ratio reflects increased sympathetic activity.[29] LF-HF ratio was significantly high in study group in comparison to the control group [Figure 1], which confirms the presence of sympathetic overactivity in subjects with risks for PIH since early part of pregnancy, that may lead to the development of hypertension in the later part of pregnancy.

Since sympathetic overactivity is involved in the stiffening of large arteries, assessment of sympathetic activity should be considered as a measure of arterial function. Increased arterial stiffness and elevated BP could be mutually and causally related, and it appears that the significance of this relationship may increase with the increase in BP, even in subjects without hypertension.[16]

MAP has been shown to be a measure of pulsatile component of BP and is a marker of increased large artery stiffness. Sympathetic overactivity may have a stiffening influence on arterial mechanical properties.[16,20]

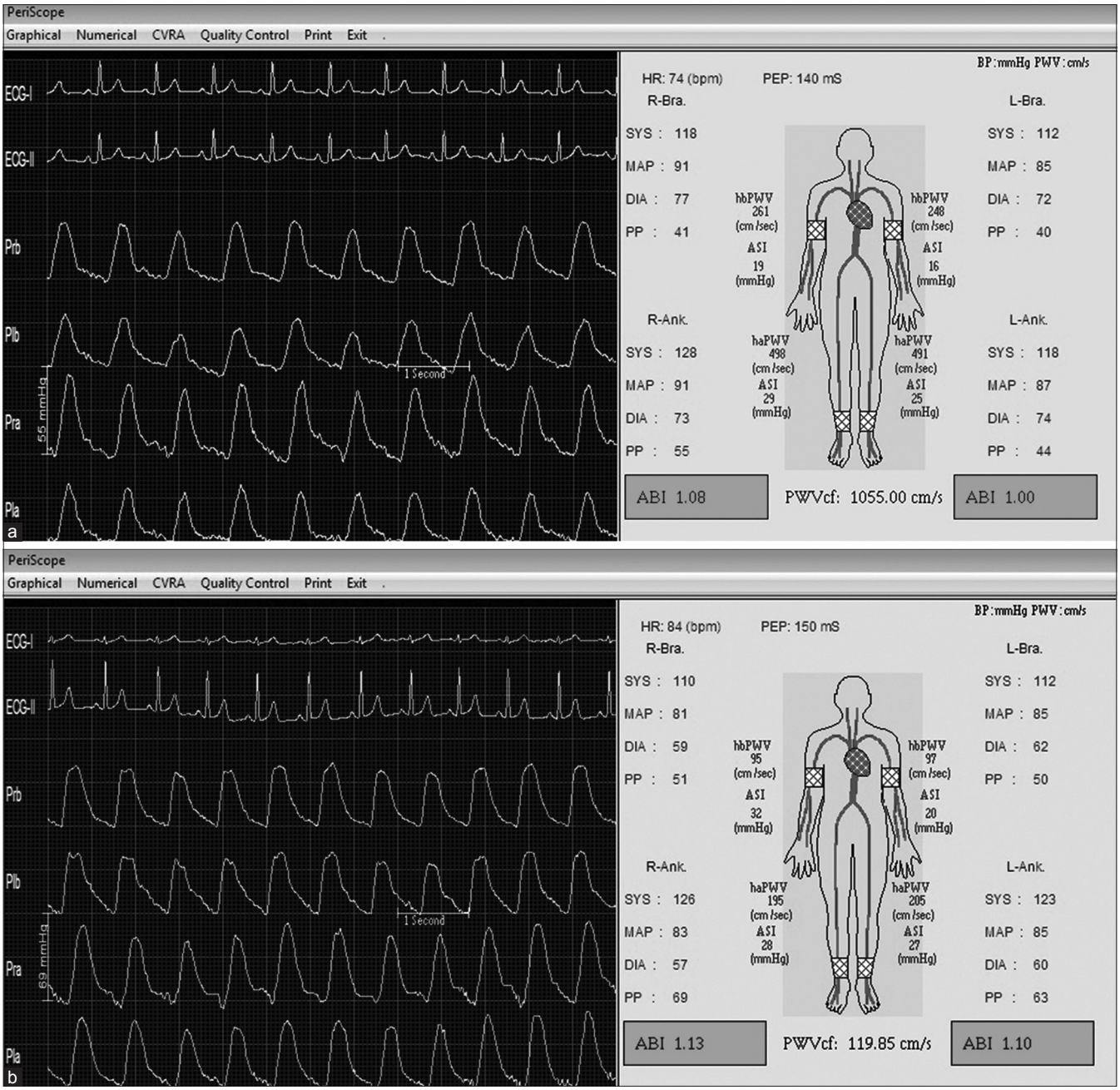

Figure 2: This picture depicts the numerical data recordings of the (a) Normal pregnant women and (b) In pregnant women with risk factors for pregnancy induced hypertension obtained using periscope. HR: Basal heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PP: Pulse pressure, PWV: Pulse wave velocity, ASI: Arterial stiffness index, ABI: Arterial brachial indices, RB: Right brachial artery; LB: Left brachial artery, RA: Right ankle; LA: Left ankle, ECG: Electroencephalogram, Prb: PWV in right brachial artery, Plb: PWV in left brachial artery, Pra: PWV in right ankle, Pla: PWV in left ankle

Increased RPP, especially in individuals with high BP has been reported as a potential CV risk.[28] Thus, increased BP, resting tachycardia, and increased RPP in study group subjects could predispose them to CV risk throughout their pregnancy. There is an experimentally well-defined and physiologically plausible mechanism linking increased arterial stiffness to cardiac risk via raised pulse pressure. Prior studies have reported that MAP and pulse pressure reflects increased large artery stiffness and is a risk factor for both CV and cerebrovascular events.[20,21]

Brachial artery PWV and ASI were significantly higher in study group compared to the control group [Figure 2a and b], indicating that there is increased arterial wall thickness and stiffness in PIH risk subjects, which was progressively more from the first trimester. As indices of PWV and ASI were significantly correlated with

LF-HF ratio in third trimester in the study group, arterial stiffness could be associated with SVI. Furthermore, all these indices had independent contribution to LF-HF in third trimester in PIH risk subjects, as demonstrated by multiple regression analysis [Table 4]. Thus, SVI appears to contribute to ASI in PIH risk subjects. Persistent increase in sympathetic tone in subjects with PIH risk subjects could be the cause of increased arterial stiffness, as chronic sympathetic stimulation has been reported to produce increase in arterial wall thickness and promote vascular resistance.[30,31] As increased arterial stiffness is an established CV risk,[32] SVI in PIH risk women further contribute to CV risks in these subjects. PWV in women with risk factors for PIH was higher compared with that in normotensive controls.

Furthermore, studies in women with a history of PIH have demonstrated increased PWV (carotid femoral)[33] and the persistence of maternal endothelial dysfunction for several months following the index pregnancy.[34] The increased arterial stiffness and SVI[18] in PIH risk factor women observed in our study, could provide a plausible link between this condition and the increased risk of CV events that these women could experience later on in life.[35] In the present study, SVI in the form of increased LF-HF ratio and increased arterial stiffness indices were noted in the first trimester of pregnancy. Our study is the first report to assess the association of SVI with arterial stiffness in the early part of pregnancy. However, though SVI and arterial stiffness were noted in the first trimester, there was no significant correlation of LF-HF ratio with arterial stiffness indices. Therefore, it appeared that in early part of pregnancy, arterial stiffness was not directly linked to the SVI, which was not significant but marginally increased. In the later part of pregnancy, i.e. in the third trimester, SVI was more intense and was found to be significantly correlated with arterial stiffness indices. Moreover, LF-HF ratio had independent contribution to ASI as demonstrated by multiple regression analysis in the third trimester. Therefore, it is likely that SVI has to be more intense to be directly associated with the arterial stiffness. Further studies should be done to assess what factors contribute to arterial stiffness in the initial part of pregnancy, which is accentuated by increased SVI in later part of pregnancy.

Therefore, future studies should evaluate the association of maternal endothelial dysfunction to CV risks attributed by SVI during and after pregnancy in women with risk factors for PIH. Furthermore, findings of the present study demonstrate the presence of ASI in women at high risk for PIH; we suggest that all pregnant women with risk factors for PIH should be screened for SVI and ASI. Moreover, a long term follow up study measuring both ASI and SVI in all three trimesters is necessary to establish the exact mechanism of these alterations. As pregnant women with risk for PIH are at greater risk of cardiac morbidities and mortalities, studies should evaluate if sympathovagal stability by various non-pharmacological means such as yoga and relaxation therapy,[36,37] can prevent development of PIH in these high-risk subjects.

CONCLUSION

Our study suggests that SVI is associated with arterial stiffness in pregnant women having risk factors for PIH. Though arterial stiffness persistsed in those women in mild form in the early trimester, it was found to be very prominent in third trimester and it significantly correlated with SVI in third trimester of the women with risk factors for PIH. Therefore, from our study it was found out that SVI and increased arterial stiffness were associated with each other and might contribute to the CV risks in pregnant women with risk factors for PIH.

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