Indian J Physiol Pharmacol 2011; 55 (2) : 128–138

ASSOCIATION OF ALBUMIN-GLOBULIN RATIO WITH SYMPATHOVAGAL IMBALANCE IN PREGNANCY-INDUCED HYPERTENSION

G. K. PAL[1]*, P. SHYMA[1], S. HABEEBULLAH[2], P. SHYJUS[2], PRAVATI PAL[1] AND NIVEDITA NANDA[3]

[1]*Department of Physiology,* [2]*Obstetrics & Gynecology,*
Jawaharlal Institute of Medical Education and Research (JIPMER),
Puducherry – 605 006 and
[3]*Department of Biochemistry,*
Pondicherry Institute of Medical Sciences (PIMS),
Puducherry – 605 014

(Received on Maty 10, 2010)

Abstract : The early prediction of pregnancy-induced hypertension (PIH) is based on the demonstration of increased sympathetic activity in early part of pregnancy. However, the mechanisms that increase sympathetic activity in PIH have not yet been fully elucidated. Therefore, in the present study we have investigated the link of albumin-globulin ratio (AGR) to sympathovagal imbalance in PIH patients. Spectral analysis of HRV was performed in three groups of subjects (Group I: normal pregnant women; Group II: pregnant women with risk factors for PIH, but did not develop PIH; Group III: pregnant women with risk factors and developed PIH) and their biochemical parameters including AGR were recorded. It was observed that LF-HF ratio, the most sensitive indicator of sympathovagal balance was significantly high ($P<0.01$) since early pregnancy in group III compared to other groups, which was considerably correlated with AGR in group III (PIH subjects). It was suggested that alteration in AGR could have direct contribution to the sympathovagal imbalance that plays a critical role in the genesis of PIH.

Key words : pregnancy-induced hypertension, heart rate variability, spectral analysis of HRV, LF-HF ratio, albumin-globulin ratio

INTRODUCTION

In developing countries of south-east Asia, pregnancy-induced hypertension (PIH) accounts for about 12% of maternal deaths, which is mainly due to its late diagnosis and inadequate treatment (1, 2). The clinical and laboratory characteristics of hypertension induced by pregnancy are difficult to differentiate from those of hypertension present during but independent of pregnancy (3). PIH usually develops late in pregnancy

*Corresponding Author : Dr. G. K. Pal, MD, Professor, Department of Physiology, JIPMER, Pondicherry – 605 006; E-mail : gopalpravati@sify.com; Fax : 0-91-413 – 2272067; Phone : 0-91- 93442 91160

and in some, the dysfunction progresses rapidly (4). Hence, in the absence of meticulous and repeated screening at short intervals, early diagnosis of PIH is missed and patient reports in the advanced stage of the disease; and therefore, this usually creates difficulty in the management of the dysfunction. PIH has been proposed to be a state of sympathetic overactivity in which placenta is believed to play an important role as only removal of the placenta following delivery usually cures the disease (5). It was suggested that some vasoconstrictors released from abnormal placenta increases sympathetic activity in PIH, nevertheless the exact nature of these chemicals is yet to be identified (5). Though the etiology of PIH is not exactly known, it has been clearly documented that the disease is characterized by low circulating volume and high vascular resistance (5, 6). The vascular resistance primarily depends on basal sympathetic tone, as systemic blood vessels have exclusively sympathetic innervation (7). It was observed that sympathetic activity slowly increases in third trimester in normal normotensive pregnancy (8), which is exaggerated in PIH, and therefore, it was suggested that changes in baroreceptor sensitivity and sympathovagal tone in early pregnancy can be used to predict the development of PIH (9).

Recently, it has been proposed that determination of sympathovagal balance is the most important autonomic function test and spectral analysis of heart rate variability (HRV) is a very sensitive indicator of sympathovagal balance for establishing diagnosis and assessing prognosis of diseases that occur due to autonomic dysfunctions (10). A study by Sasika et al has proposed that serial assessment of cardiovascular control in the form of baroreflex gain, HRV and blood pressure variability shows early signs of pre-eclampsia (11). Other studies have also reported alterations in uterine perfusion, HRV and blood pressure variability as early predictors of PIH (12-14). Recent reports from our laboratory indicates reduction in total power of HRV, with increased low frequency (LF) power as percentage of total compared to high frequency (HF) power (15), indicating the increased sympathetic activity causing sympathovagal imbalance (SVI) in the early part of pregnancy in PIH, which is exaggerated to produce PIH in later part of pregnancy (16).

To best of our knowledge, no research has been conducted yet to understand the biochemical alteration in plasma due to placental abnormalities that lead to SVI in PIH. Therefore, in the present study we have assessed the association of biochemical parameters with the sympathovagal imbalance determined by spectral analysis of HRV and analyzed its importance in early prediction, pathophysiology and prevention of this dysfunction in Indian population.

MATERIALS AND METHODS

The present study was conducted in the clinical polygraph laboratory of 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, 230 subjects (50 in control group, 180 in study group) were recruited from the outpatient 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 included established risk factors for PIH (17) such as family history of preeclampsia, preeclampsia in previous pregnancy, extremes of reproductive age, BMI > 35, DBP > 80 mm Hg at the first visit, first pregnancy, multiple pregnancy, underlying medical conditions (diabetes mellitus, renal disease pre-existing hypertension) etc. Subjects of control group (group I), 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 control and study groups.

Twelve subjects in the control group and seven subjects in the study group did not turn up for second and third trimester recordings. Therefore, these subjects were excluded from the study. Rest all subjects (38 in the control group and 173 in the study group) attended obstetrics OPD for their regular check-ups and also reported to polygraph laboratory of physiology department for recording of various parameters at all three trimesters of pregnancy. Accordingly, three recordings were performed on all subjects at three different times; the 1st recording at completion of 1st trimester (towards end of 12th week), the 2nd recording at completion of 2nd trimester (towards end of 24th week), and the 3rd recoding at the end of 31st week (as previous records of obstetrics and gynecology department of JIPMER indicated that PIH usually occurs after 32nd weeks). 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 Colin PressMate 8800 (Colin Corporation, Japan) non-invasive blood pressure monitor.

Spectral analysis of HRV

Following 10 minutes of supine rest in polygraph laboratory (room temperature maintained at 25°C), basal heart rate (BHR) and blood pressures (diastolic and systolic) were recorded. For recording of short-term HRV, recommendation of the Task Force on HRV was followed (18). For the purpose, 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 Acqkowledge software version 3.8.2. Ectopics and artifacts were removed from the recorded ECG. RR tachogram was extracted from the edited 256 sec ECG using the R wave detector in the Acqkowledge 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). Mean RR was measured in second(s). Variance, defined as power in a portion of the total spectrum of frequencies was measured in milliseconds squared (ms^2). Different frequency domain indices such as low frequency component expressed as normalized unit (LFnu), high frequency component expressed as normalized unit

(HFnu) and LF/HF ratio, were calculated.

Estimation of biochemical parameters

After the recordings at the polygraph lab, the subject was taken to clinical biochemistry lab of biochemistry department for blood sample collection and estimation of following biochemical parameters. The biochemical parameters were estimated with Bayer's express plus random blood analyzer (Bayer's Co. USA) by collecting 2 ml of blood by venipuncture as part of the routine investigations at all trimesters of pregnancy.

The parameters studied were :

1. Random blood sugar
2. Total serum protein
3. Serum albumin
4. Serum globulin
5. Albumin-globulin (A:G) ratio
6. Serum urea

All subjects were followed up till term and any incidence of PIH was recorded. Out of 173 study subjects, 27 developed PIH during their course of pregnancy. Hence, at the end of the study, subjects of study group were divided into two groups; Group II: subjects who did not develop PIH (n=146), and Group III: subjects who developed PIH (n=27).

Statistical analysis of data

SPSS version 13 was used for statistical analysis. All the data were expressed as Mean±SD. One-way ANOVA with Tukey-Krammer post-hoc was used in analyzing the data across the three groups. Student's paired *t* test was used to detect the level of significance within the groups. The association between LF-HF ratio with biochemical parameters was assessed by Pearson correlation analysis. The P values less than 0.05 were considered significant.

RESULTS

211 subjects (n=38 in group I, n=146 in group II and n=27 in group III) attended obstetrics OPD regularly and also reported to polygraph laboratory at all three trimesters of pregnancy for recording of various parameters. However, two subjects of group III developed PIH before 31st week of pregnancy and therefore, they do not have 31st week recordings. Rest of the subjects of group III developed PIH between 32nd week and term. Out of 173 women having risk factors for PIH, 27 (15.6%) developed PIH.

General parameters

There was no significant difference in age between the subjects of control group and study groups. The body weight and BMI of subjects who developed PIH (group III) was significantly higher than the subjects who did not develop PIH (group II) and the subjects of control group (group I) at all the three recorded weeks of pregnancy (Table I). Though, the increase in BW and BMI was progressive from 12th week to 31st week of pregnancy in all the groups, the data were statistically highly significant ($P<0.001$) only in group II and only body weight was just significant ($P<0.05$) in group I at 31st week.

TABLE I: Comparison of age, body weight (BW), body mass index (BMI), basal heart rate (BHR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the subjects of different groups (Group I: control subjects with normal pregnancy; Group II: subjects with risk factors but did not develop PIH; Group III: subjects with risk factors and developed PIH;) at different weeks of pregnancy.

Parameters at diff. weeks	*Group I (n=38)*	*Group II (n=146)*	*Group III (n=27)*	*P value*
At 12th week:				
Age (yr)	24.21±3.12	23.82±4.50	25.14±3.94	0.318
BW (kg)	49.84±10.70	49.14±8.75	57.40±21.28**,##	0.003
BMI (Kg/m^2)	20.26±3.98	20.40±3.03	24.04±8.95**,##	0.0004
BHR (per min)	74.44±13.77	80.94±12.58*	90.14±17.89**,##	<0.0001
SBP (mm Hg)	103.60±9.32	106.58±9.77	113.03±11.55***,##	0.001
DBP (mm Hg)	59.34±7.78	60.45±7.64	65.66±7.19**,##	0.002
At 24th week:				
BW (kg)	52.81±10.81	51.69±8.84^{f}	60.59±21.78**,###	0.002
BMI (Kg/m^2)	21.47±4.01	21.47±3.06^{ff}	25.36±9.17**,###	0.000
BHR (per min)	78.92±13.72	87.90±11.39***,fff	91.18±16.78***	0.0001
SBP (mm Hg)	104.44±7.92	104.80±9.638	120.81±13.92***, ###	<0.0001
DBP (mm Hg)	59.89±6.14	59.80±6.920	72.296±10.167***,###,f	<0.0004
At 31st week:				
BW (kg)	56.28±10.81^{f}	54.77±8.90^{fff,aa}	64.46±22.19**,###	0.001
BMI kg/m^2	22.89±4.00	22.74±3.07^{fff,aa}	25.93±10.55*,##	0.008
BHR (per min)	87.08±14.40^{fff,a}	91.42±13.24^{fff,a}	96.15±14.09*	0.030
SBP (mm Hg)	104.77±8.26	107.14±10.63	128.55±11.73***,###,fff	<0.0001
DBP (mm Hg)	62.00±7.79	62.93±7.88^{f,a}	81.55±10.19***,###,fff,aa	<0.0001

The values are Mean±SD; Statistical analysis was done by one-way ANOVA and post-hoc by Tukey-Krammer multiple comparison test. The * mark indicates comparison with group I and the # mark indicates comparison with group II. *P<0.05; **P<0.01; ***P<0.001; #P<0.05; ##P<0.01; ###P<0.001. The ^{f} indicates comparison with 12th week and the ^{a} indicates comparison with 24th week. ^{f}P<0.05; ^{ff}P<0.01; ^{fff}P<0.001; ^{a}P<0.05; ^{aa}P<0.01. (n=25 in group III at 31st week).

At 12th week, BHR of groups II and III was significantly higher (P<0.05, P<0.01 respectively) than group I, and of group III was higher than group II (P<0.01). The difference in BHR of groups II and III with group I became more significant (P<0.001) at 24th week, when the difference between groups II and III ceased statistically. At 31st week, BHR of only group III was statistically significant (P<0.05) from group I. With advancement of pregnancy, though the increase in BHR of group I was statistically significant (P<0.001) at 31st week compared to 12th week value, and of group II was higher at 24th week (P<0.001) and 31st week (P<0.001) compared to its 12th week value, the increase was not significantly different in group III.

SBP of group III was significantly more than group I (P<0.001) in all the three recordings and group II (P<0.01) at 12th week, which became more significant (P<0.001), compared with group II at 24th and 31st weeks of pregnancy. Though the increase in SBP of group III at 31st week was significantly higher (P<0.001) compared to its 12th week recordings, the increase was not significant in groups I and II.

At 12th week, DBP of group III was significantly higher than group I and II

(P<0.01), which became more significant (P<0.001) at 24th and 31st weeks of pregnancy. Though, the increase in DBP at 31st week was not significant compared 12th week recording in group I, the increase was significant in group II (P<0.05) and group III (P<0.001).

HRV parameters

LFnu of group III was significantly higher than group I at 12th (P<0.05), 24th (P<0.001) and 31st (P<0.05) week recordings and the difference between group II and III was significant (P<0.05) only at 24th week (Table II). Though, the increase in LFnu of 31st week of groups I and II was significantly higher (P<0.05 and P<0.001 respectively) compared to their 12th week recordings, the increase was not significant for group III.

The decrese in HFnu in group III was significant (P<0.05) compared to group I (not group II) only at 12th week (not at 24th and 31st weeks). Moreover, the decrease in HFnu at 31st week compared to 12th week was significant (P<0.001) only in group II, not in group I and III.

The LF-HF ratio of group III at 12th week was significantly more (P<0.01) compared to group I and II. The significance between group I and III decreased at 24th and 31st week recordings, when the significance ceased between group II and III. Though, the LF-HF ratio of 31st week recording of groups I and II was significantly higher (P<0.01 and 0.001 respectively) compared to their 12th week recordings, the increase was not significant in group III.

Biochemical parameters

Though random blood sugar (RBS) in group III subjects was significantly high (P value <0.001) compared to group II and group

TABLE II: Comparison of HRV indices of the subjects of different groups (Group I: control subjects with normal pregnancy; Group II: subjects with risk factors but did not develop PIH; Group III: subjects with risk factors and developed PIH;) at different weeks of pregnancy

HRV indices at diff. weeks	*Group I (n=38)*	*Group II (n=146)*	*Group III (n=27)*	*P value*
At 12th week:				
LFnu	42.61±20.66	47.75±20.78	57.24±24.13*	0.0241
HFnu	55.64±20.90	52.05±20.73	42.76±21.13*	0.0435
LF/HF ratio	1.16±1.04	1.50±1.30	2.41±2.00**,##	0.0013
At 24th week:				
LFnu	45.92±20.37	52.34±20.34	64.91±20.76***,#	0.0013
HFnu	50.07±20.37	47.65±20.34	40.23±21.16	0.1411
LF/HF ratio	1.38±1.04	1.71±1.44	2.30±1.98*	0.0452
At 31st week:				
LFnu	54.51±22.83f	58.10±19.60fff,a	67.64±23.93*	0.0448
HFnu	45.48±22.83	41.75±19.61fff, a	36.35±18.93	0.2149
LF/HF ratio	2.01±1.20ff, a	2.24±1.42fff, aa	2.95±2.07*	0.0405

The values are Mean±SD; Statistical analysis was done by one-way ANOVA and post-hoc by Tukey-Krammer multiple comparison test. The * mark indicates comparison with group I and the # mark indicates comparison with group II. *P<0.05; ** P<0.01; ***P<0.001; #P<0.05; ##P<0.01; ###P<0.001. The f indicates comparison with 12th week and the a indicates comparison with 24th week. fP<0.05; ffP<0.01; fffP<0.001; aP<0.05; aaP<0.01. (n=25 in group III at 31st week).

I subjects, at all the three gestational weeks (Table III). RBS was significantly high in group II at 31st week compared to its own 12th and 24th week recordings.

Total protein content was significantly low (P value <0.01) in group III compared to group I at 12th week, which was reduced further at 24th and 31st week compared to groups I and II (P value <0.001). Total protein was significantly reduced in all the groups at 31st week compared to their own 12th recordings. In groups I and III the reduction at 31st week was significant compared to their 24th week recording and also, the reduction was significant at 24th week compared to their 12th week recording.

Though there was no statistically significant difference in albumin level between the groups at 12th and 24th weeks recordings, in group III at 31st week albumin level was significantly less (P value <0.01) compared with group II, and also compared to its own 12th week value. At 12th week, globulin was reduced significantly (P value <0.001) in groups II and III compared to the value of group I. At 24th and 31st weeks, the globulin content was reduced significantly (P value <0.001) in group III compared to the groups I and II, and also compared to its own 12th week value (P value <0.01).

At 12th week, the A:G ratio in group III

TABLE III : Comparison of biochemical parameters of the subjects of different groups (Group I: control subjects with normal pregnancy; Group II: subjects with risk factors but did not develop PIH; Group III: subjects with risk factors and developed PIH) at different weeks of pregnancy.

Parameters at diff. weeks	*Group I (n=38)*	*Group II (n=146)*	*Group III (n=27)*	*P value*
At 12th week:				
RBS (mg/dl)	65.92±16.32	73.96±15.03*	98.85±24.32***,###	0.000
TP (mg/dl)	7.616±0.73	7.012±0.64	7.20±0.76**	0.000
Albumin (mg/dl)	3.68±0.38	3.53±0.36	3.671±0.46	0.061
Globulin (mg/dl)	3.95±0.78	3.45±0.58***	3.33±0.85***	0.000
A: G Ratio	0.93±0.29	1.02±0.43	1.10±0.34***,#	0.020
Urea (mg/dl)	18.69±3.45	18.23±5.23	18.13±3.95	0.236
At 24th week:				
RBS (mg/dl)	66.12±15.32	73.61±13.20**	99.03±30.21***,###	0.000
TP (mg/dl)	7.21±0.63	6.71±0.48***,##	5.87±0.58***,###	0.000
Albumin (mg/dl)	3.52±0.35	3.45±0.51	3.35±0.35	0.547
Globulin (mg/dl)	3.64±0.67	3.22±0.62	2.45±0.59***,###	0.234
A: G Ratio	0.09±0.27	1.07±0.47***	1.36±0.31***,###	0.002
Urea (mg/dl)	18.96±3.65	18.23±5.23[f]	19.63±3.72	0.350
At 31st week:				
RBS (mg/dl)	70.11±16.62	92.81±15.62***	107.32±26.24***,###	0.000
TP (mg/dl)	6.61±0.50	6.88±0.46**	5.37±0.53***,###	0.000
Albumin (mg/dl)	3.26±0.36	3.46±0.42*	3.12±0.63##	0.003
Globulin (mg/dl)	3.34±0.85	3.42±0.62**	2.14±0.53***,###	0.000
A: G Ratio	0.97±0.36	1.01±0.48	1.45±0.42***,###	0.000
Urea (mg/dl)	18.52±3.78	18.65±6.12	20.65±4.85	0.219

The values are Mean±SD; Statistical analysis was done by one-way ANOVA and post-hoc by Tukey multiple comparison test. The * mark indicates comparison with group I and the # mark indicates comparison with group II. *P<0.05; **P<0.01; ***P<0.001; #P<0.05; ##P<0.01; ###P<0.001. RBS: random blood sugar; TP: total protein; A: G Ratio: albumin globulin ratio. (n=25 in group III at 31st week).

was significantly more compared to the values of group I (P value <0.001) and group II (P value <0.05). At 24th and 31st weeks, A:G ratio in group III was further increased (P value <0.001) compared to the values of group I and group II, and also compared to its own 12th week value.

The serum urea was not significantly different between groups at all the gestational weeks. However, serum urea was significantly high (P<0.05) in group III at 31st week compared to its own 12th week value.

LF/HF ratio was significantly correlated with A:G ratio at all trimesters of pregnancy in PIH subjects (group III) (Table IV).

TABLE IV: Correlation of LF/HF ratio with biochemical parameters of subjects of PIH group (n=27).

	12th week		*24th week*		*31st week*	
	r	*p*	*r*	*p*	*r*	*p*
RBS	0.010	0.210	0.015	0.180	0.032	0.102
TP	–0.230	0.086	–0.312	0.078	–0.352	0.059
AGR	0.380	0.042	0.416	0.013	0.486	0.008
Urea	0.011	0.210	0.020	0.160	0.031	0.108

The P values less than 0.05 was considered significant. RBS: random blood sugar; TP: total protein; AGR: albumin globulin ratio.

DISCUSSION

In the present study, significantly high BHR, SBP and DBP in group III compared to both group I and group II at all the three recordings suggest that subjects who developed PIH later in pregnancy had altered cardiovascular parameters from the first trimester of pregnancy. Significant increase in LFnu in group III in comparison to group I in recordings at all the three gestational weeks depicts sympathetic overactivity in PIH subjects throughout pregnancy starting from 12th week, as LFnu primarily reflects sympathetic modulation of heart functions (10). The increase in sympathetic activity in PIH group compared to control subjects was maximum in second trimester as the level of significance was highest (P<0.001; Table II) at 24th week recording and was also significant compared to group II. However, with progress of pregnancy, the progressive increase in sympathetic activity as reflected by increased LFnu was not significantly high in PIH subjects at 31st week compared to their 12th week value as the increase in sympathetic tone was already highly significant in these subjects from the first trimester itself, whereas the increase at 31st week was mildly high (P<0.05) in normal pregnant women and very high (P<0.001) in women with risk factors who did not develop PIH as these subjects had minimal sympathetic activity at 12th week. Though, others have already reported sympathetic overactivity in PIH by spectral analysis of HRV (1, 14, 15), their reports indicate that the sympathetic activation occurs mostly in second trimester of pregnancy, whereas the present study reveals a significant rise in sympathetic discharge from first trimester itself. This difference in the time of onset of sympathetic overactivity could be due to lack of adequate data of first trimester of pregnancy in the previous studies or the PIH subjects of the present study (Indian population) might have a different sympathetic sensitivity from others. The present study is the first report on spectral analysis of HRV in PIH from Indian subcontinent.

HFnu represents vagal modulation of SA nodal discharge (10), which was decreased in group III compared to group I at 12th week recording, depicting that there was some degree of vagal withdrawal in PIH subjects in 1st trimester in addition to sympathetic overactivity. However, decrease in vagal modulation in PIH group compared to other two groups was not significant in second and third trimesters, reflecting a less vagal modulation of cardiac activities compared to sympathetic modulation towards later part of pregnancy in PIH. However, similar to the pattern of sympathetic stimulation, vagal withdrawal was prominent in group II at 31st week in comparison to its 12th and 24th week recordings indicating that inhibition in vagal modulation contributes substantially to autonomic dysfunction in women with risk factors not developing PIH.

LF-HF ratio, the index of sympathovagal homeostasis (10) represents balance between sympathetic and parasympathetic activities of the individual at any given time in supine resting conditions. (18). Lesser values of this ratio indicate parasympathetic dominance and greater values indicate sympathetic dominance (18). LF-HF ratio was significantly high in group III in comparison to group I at all the three trimesters of recordings. As increase in LF-HF ratio reflects increased sympathetic activity (10), its maximum value ($P<0.01$) in group III in first trimester and also its significant difference from group II further confirms the presence of sympathetic overactivity in PIH subjects since early part of pregnancy that precedes development of hypertension. These findings suggest that sympathovagal imbalance is due mainly to the increased sympathetic activity than to the vagal withdrawal. Moreover, sympathovagal balance in group III was increased ($P<0.05$) in second and third trimesters in the absence of significant decrease in vagal tone as HFnu did not change significantly at 24th and 31st weeks. The LF-HF ratio in group I and II at 31st week was more in comparison to their 12th and 24th week recordings, indicating a progressive increase in sympathetic activity in these two groups, in which the increase was more in group II compared to group I. In group I, the increased sympathetic activity was not accompanied by proportionate vagal withdrawal, whereas in group II there was a significant decrease in vagal activity. Thus, the observation of increased sympathetic activity in normal pregnancy is in conformity with findings of earlier reports (1, 9). However, in the present study, findings of significant sympathovagal imbalance due to increased sympathetic discharge and decreased vagal tone in women with risk factors who did not develop PIH is a new observation as similar reports have not been documented earlier.

It was observed earlier that the immunological disturbances are prominent in PIH (19-21). However, the link of immunological factors to sympathetic overactivity has not yet been studied. In the present study, though there was significantly high random blood sugar, total protein and AG ration in PIH group compared to high risk and control groups in all trimesters of pregnancy (Table III), correlation of LF-HF ratio was significant only with AG ratio at all the three trimesters in PIH group. This strongly indicates the immunological association through the link of AG ratio with alteration in sympathovagal balance in PIH. Correlation of increased AG ratio with

increased SVI could be due to hepatic alteration in protein synthesis or alteration in production of plasma proteins from abnormal placenta in PIH. Further studies should be aimed at defining the role of placenta in the association of AG ratio with SVI in PIH.

It has also been reported that PIH is a temporary metabolic syndrome in which insulin resistance is associated with sympathetic overactivity, and though blood pressure normalizes after pregnancy, some degree of insulin resistance and higher sympathetic tone continues to persist (22). In a recent study, it has been investigated that persistence of insulin resistance and sympathetic overactivity predisposes women who formerly had PIH to cardiovascular diseases (23). Therefore, future studies should assess the association of lipid risk factors and insulin resistance with sympathovagal balance during and after pregnancy in women with PIH.

Conclusion

In summary, the present study clearly indicates the presence of sympathovagal imbalance mainly in the form of sympathetic overactivity since 12th week of pregnancy in Indian women who develop PIH in the later part of pregnancy, which suggests the use of spectral analysis of HRV as a an early predictive tool for this dysfunction. This study also reveals that the women having risk factor for PIH (but do not develop PIH) develop sympathovagal imbalance in the form of both sympathetic overactivity and vagal withdrawal in third week of pregnancy compared to their own early pregnancy values. AG ratio was significantly high in PIH group in comparison to risk group and control group subjects. Also, the LF-HF ratio was significantly correlated with AG ratio in PIH group at all the trimesters of pregnancy. Thus, it was concluded that AG ratio could have direct contribution to sympathovagal imbalance in PIH.

REFERENCES

1. Greenwood JP, Stoker JB, Walker JJ, Mary DA. Sympathetic nerve discharge in normal pregnancy and pregnancy-induced hypertension. *J Hypertens* 1998; 16: 617–624.
2. Gupta P, Ghai OP. Common complications of pregnancy. In: Preventive and social medicine. 2nd edition. New Delhi: CBS Publications, 2007; 358–361.
3. Steven JW, Snezana B, Vesna DG. Hypertensive pregnancy disorders. *J Clin Hypertens* 2007; 9: 560–566.
4. Joydev M, Subroto LS, Geeta BB. Current concepts in PIH. In: Current obstetrics and gynecology. Geeta GM (editor). 1st edition. New Delhi: Jaypee Publications, 2007; 93–100.
5. Hans PS, Thorsten F, Karsten H, Helmut G, Ronal ES. Preeclampsia: a state of sympathetic overactivity. *New Eng J Med* 1996; 335: 1480–1485.
6. Visser W, Wallenburg HC. Central hemodynamic observation in untreated preeclamptic patients. *Hypertension* 1991; 17: 1072–1077.
7. Ganong WF. Cardiovascular regulatory mechanisms. In: Review of Medical Physiology. 22nd ed. San Fransisco: McGraw Hill, 2005; 597–602.
8. Matsuo H, Inoue K, Hapsari ED, Kitano K, Shiotani H. Changes of autonomic nervous activity during pregnancy and its modulation of labor assessed by spectral heart rate variability analysis. *Clin Exp Obst Gyn* 2007; 34: 73–79.
9. Blake MJ, Martin A, Manktelow BN, et al. Changes in baroreceptor sensitivity for heart

rate during normotensive pregnancy and the puerperium. *Clin Sci (Lond)* 2000; 98: 259–268.

10. Alberto M. Heart rate variability: from bench to bedside. *Europ J Int Med* 2005; 16: 12–60.
11. Sasika R, Wolf H, Montfrans GA, Karemaker JM. Serial assessment of cardiovascular control shows early signs of developing preeclampsia. *J Hypertens* 2004; 22: 369–376.
12. Ekholm EM, Tahvanainen KU, Metsälä T. Heart rate and blood pressure variabilities are increased in pregnancy-induced hypertension. *Am J Obst Gyneccol* 1997; 177: 1208–1202.
13. Ursem NT, Clark EB, Keller BB, Hop WC, Wladimiroff JW. Do heart rate and velocity variability derived from umbilical artery velocity waveforms change prior toclinical pregnancy-induced hypertension? *Ultrasound Obst Gynecol* 1999; 14: 244–249.
14. Walther T, Wessel N, Malberg H, Voss A, Stephen H, Faber R. A combined technique for prediciting pre-eclampsia: concurrent measurement of uterine perfusion and analysis of heart rate and blood pressure variability. *J Hypertens* 2006; 24: 747–750.
15. Shyma P, Pal GK, Habeebullah S, Shyjus P, Pravati Pal. Decreased total power of HRV with increased LF power in early part of pregnancy predicts development PIH in Indian population. *Biomedicine* 2008; 28: 104–107.
16. Pal GK, Shyma P, Habeebullah S, Shyjus P and Pravati Pal. Spectral analysis of heart rate variability for early prediction of pregnancy-induced hypertension. *Clin Experiment Hypertens* 2009; 31: 330–341.
17. Duckitt K, Harrington D. Risk factors for preeclampsia at antenatal booking: systemic review of controlled studies. *Br Med J* 2005; 330: 565–571.
18. Task force of the European Society of Cardiology and the North American society of Pacing and Electrophysiology. Heart rate variability. Standard and measurement, physiological interpretation and clinical use. *Circulation* 1996; 93: 1043–1065.
19. Steck T, Würfel W. The role of immunologic factors in the etiology of pregnancy-induced hypertension. *Zentralbl Gynakol* 1995; 117: 3–10.
20. Chen G, Wilson R, Cumming G, Walker JJ, McKillop JH. Immunological changes in pregnancy-induced hypertension. *Eur J Obstet Gynecol Reprod Biol* 1994; 53: 21–25.
21. Marinoni E, De Pità O, Bresadola M, Ippoliti F, Di Iorio R. Cell-mediated immunity imbalance in pregnancy-induced hypertension. *Gynecol Obstet Invest* 1994; 38: 236–240.
22. Kaaja RJ, Pöyhönen-Alho MK. Insulin resistance and sympathetic overactivity in women. *J Hypertens.* 2006; 24: 131–141.
23. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol* 2007; 3: 613–622.