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Original Article

Physiology Section

Non Linear Heart Rate Variability Study During Pregnancy in Indian Women

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ABSTRACT

Introduction: Adaptation of Autonomic Nervous System (ANS) in pregnancy can be suitably assessed by Heart Rate Variability (HRV). Non linear methods of HRV better quantify the chaotic dynamics of HRV. However, non linear HRV studies are not found in literature for Indian pregnant women.

Aim: To investigate the adaptation of autonomic control during pregnancy based on non linear HRV analysis.

Materials and Methods: Twenty five normal healthy non pregnant volunteer women and 22 pregnant women underwent various analyses of HRV following a standard sampling. Time domain and frequency domain measures as well as non linear analysis parameters of HRV were compared between same pregnant women in first and third trimester by paired Student's t-test as well as with non pregnant women as controls by unpaired Student's t-test.

Results: Time domain, frequency domain and even non linear parameters of HRV showed no statistically significant differences in control group and pregnant women during first trimester. Comparison between control group and pregnant women in third trimester showed statistically significant alterations in absolute High Frequency (HF) power, Root of Mean Squared Standard Deviation (RMSSD) of RR intervals and some non linear parameters like Standard Deviation 1 (SD1) and correlation dimension D2, whereas almost all the parameters both linear and non linear showed statistically significant differences with progression of pregnancy from first to third trimester.

Conclusion: Normal pregnancy is characterised by enhancement of sympathetic component and attenuation of parasympathetic component of ANS. Decrease in non linear HRV parameters suggested decreased complexity of the autonomic control system. Non linear HRV parameters were altered to a larger extent than linear HRV parameters suggesting a need to study non linear parameters while doing HRV analysis. Further longitudinal studies with large sample size are needed to generate normative data of linear and non linear HRV parameters in pregnancy.

Keywords: Approximate entropy, Autonomic function, Correlational dimension, Sample entropy

INTRODUCTION

Adaptation of cardiovascular system to changing hemodynamic needs during pregnancy requires a well-controlled interaction between sympathetic and parasympathetic system [1]. This adaptation of ANS in pregnancy can be suitably assessed by HRV, a non invasive functional indicator of ANS. Non linear system analysis of HRV [2] has advantages over traditional time and frequency domain techniques as it measures the functional order and temporal unfolding of heart rate [3] by treating heart rate as an information generating source. It detects high-risk, abrupt autonomic changes better than conventional techniques [4,5]. Non linear methods better quantify the chaotic dynamics of HRV. However, non linear HRV parameters are not being studied may be due to complex statistical methods and non inclusion of these parameters in most of the HRV software in use.

HRV data in Indian pregnant women is very meagre [6-8]. Moreover, non linear HRV studies are not found in literature for Indian pregnant women though non linear HRV has been studied in pregnant women in some other population [9].

The aim of the current study was to study ANS adjustments during pregnancy by means of linear as well as non linear HRV analysis by a longitudinal study and to compare these analyses with HRV analyses of non pregnant women.

MATERIALS AND METHODS

A prospective cohort study was conducted for studying autonomic function responses during progress of pregnancy from first to third trimester. Also, the comparison of autonomic functions in pregnant and non pregnant females was done, making it a case-control study. Study duration was two years from January 2014 to December 2015. The study protocol was approved by the Institutional Ethics Committee and study was performed in accordance with the ethical standards as laid down inthe 1964 declaration of Helsinki and its later amendments.

Study participants were recruited into the study from Department of Obstetrics of a Tertiary Care Hospital attached to a medical college. Inclusion criteria for study group were pregnant females (age range of 24-30 years) of 12 to 14 weeks of gestation with parity 1 with single normotensive pregnancy, normal findings on physical examination, ECG, and routine blood tests including Hb% and blood sugar. Females with history, signs, or symptoms of cardiovascular, pulmonary, or endocrine diseases as assessed by detailed history taking and thorough clinical examination were excluded from the study.

Study participants were explained about the detailed plan of work and aim of the present research work. Written informed consent was obtained from all individual participants included in the study. HRV was measured in first trimester of pregnancy. Pregnant women were again subjected to HRV measurement in third trimester of pregnancy during 32-34 weeks of pregnancy. Those who dropped out of study were not included in the final analysis. Those who were diagnosed by obstetricians as having pregnancy induced hypertension later were also excluded.

From data obtained during pilot study on 15 pregnant women in first and third trimesters, effect size was calculated which was 0.67 and above for all the non linear parameters. Maintaining a power of 80% and level of significance at 0.05, this effect size suggested a sample size of 21 for two-tailed distribution for paired t-test. Considering possible attrition and exclusion criteria for women who turned hypertensive during follow-up, total 32 women were studied, out of which 8 could not be followed up for assessment in third trimester and 2 turned hypertensive in third trimester, who were excluded from the study group. Thus, study group comprised of 22 pregnant women. Twenty five healthy non pregnant subjects of the same age group were selected in the control group from amongst the healthy relatives of the study participants so as to match the socioeconomic status with similar inclusion criteria except pregnancy.

Resting supine Electrocardiogram (ECG) recordings for 10 minutes were obtained for all subjects in the same quiet room after the subject had 20 minutes of rest in supine position. The recordings were made between 10:00 am and 12:00 noon to obviate diurnal influences. ECG was recorded continuously on a computerised data acquisition and analysis system (Powerlab, AD Instruments).

The analogue to digital conversion of the ECG signal was done using A/D converter with the sampling frequency 5 kHz. In order to avoid interference of any artefacts, the ECG recordings and the corresponding event series were manually checked for artefacts and only artefact-free sections were included in analysis. RR text files (all RR intervals in milliseconds in a text file format) were generated with Lab Chart Pro and further HRV analysis i.e., frequency and time domain analysis and non linear analysis was done using HRV analysis software of Kubios HRV version 2.2.

For frequency domain analysis, fast fourier transformation was done using window width of 256 seconds and window overlap of 50%. Entire spectrum of frequencies was divided into three major bands, very low frequency (VLF, 0-0.04 Hz), low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz). For computing HRV indices during supine rest, recommendations of the task force on HRV were followed [10].

STATISTICAL ANALYSIS

Descriptive statistics like mean and standard error of mean was used to describe linear and non linear HRV parameters in both the groups. Normality of the data was tested by Kolmogorov-Smirnov test. As data distribution was normal for all parameters under consideration, Student's t-test was applied for between groups comparison. Paired t-test was used for comparison between first trimester and third trimester evaluation. Unpaired t-test was used for comparison between pregnant women and control group. Comparisons were made using two-tailed significance at probability less than 0.05.

RESULTS

As age is the confounding factor for HRV analyses, two groups were analysed and were found to be similar for age (Mean age±SD – control group 23.71±2.75 years, study group 23.16±2.28 years; t-test, p>0.05). Results of HRV parameters (both time domain and frequency domain) in pregnant and non pregnant groups for linear HRV and non linear HRV are noted in [Table/Fig-1,2] respectively whereas comparison of linear and non linear HRV analysis in different groups is given in [Table/Fig-3,4] respectively.

Time domain, frequency domain and even non linear parameters of HRV showed no statistically significant differences in control group and pregnant women during first trimester. Comparison between control group and pregnant women in third trimester showed statistically significant alterations in absolute HF power, RMSSD and some non linear parameters like SD1 and correlation dimension D2, whereas almost all the parameters both linear and non linear showed statistically significant differences with progression of pregnancy from first to third trimester.

Parameter	Non pregnant (Control Group) ±SEM	Pregnancy (First Trimester) ±SEM	Pregnancy (Third Trimester) ±SEM
Total power (ms^2)	3212.77±707.53	2989.48±568.31	2437.39±577.16
SDNN (ms)	53.07±5.52	51.82±4.83	45.45±5.34
RMSSD (ms)	40.92±4.19	37.50±2.57	24.80±3.59
PNN 50 (%)	24.35±4.65	15.70±3.70	8.59±3.63
HF (ms^2)	667.75±126.61	437.37±79.09	261.30±60.55
LF (ms^2)	699.79±131.75	500.08±79.90	413.49±82.11
LF nu (%)	52.80±4.72	55.57±3.13	62.82±3.96
HF nu (%)	47.19±4.72	44.42±3.13	37.17±3.96
LF/HF ratio	1.455±0.26	1.385±0.17	2.091±0.31

[Table/Fig-1]: Time domain and frequency domain variables of HRV in pregnant and non pregnant group.
SDNN: Standard deviation of normal to normal RR intervals; RMSSD: Root of mean squared standard deviation of RR intervals; PNN 50: Percentage of consecutive NN intervals with more than 50 m/sec difference; HF: High frequency power; LF: Low frequency power; nu: normalised units; SEM: Standard error of mean; ms: millisecond

Parameter	Non pregnant (Control Group) ±SEM	Pregnancy (First Trimester) ±SEM	Pregnancy (Third Trimester) ±SEM
SD1	29.028±2.98	23.794±2.444	17.562±2.539
SD2	68.585±7.483	66.997±7.612	61.198±7.491
Correlation dimension D2	3.052±0.354	2.305±0.369	1.703±0.373
ApEn	1.147±0.093	1.201±0.049	1.096±0.058
SampEn	1.692±0.072	1.666±0.121	1.464±0.128

[Table/Fig-2]: Non linear HRV parameters in pregnant and non pregnant group.
SD: Standard deviation; ApEn: Approximate entropy; SampEn: Sample entropy; SEM: Standard error of mean

Parameter	Non pregnant vs. First Trimester (Unpaired t-test)	Non pregnant vs. Third Trimester (Unpaired t-test)	First Trimester vs. Third Trimester (Paired t-test)
Total power (ms^2)	t=0.246 p=0.807	t=0.849 p=0.403	t=2.011 p=0.065
SDNN (ms)	t=0.1695 p=0.866	t=0.991 p=0.330	t=3.076 p=0.0088**
RMSSD (ms)	t=0.694 p=0.494	t=2.917 p=0.007**	t=5.54 p<0.001***
PNN 50 (%)	t=1.454 p=0.158	t=2.670 p=0.013	t=3.421 p=0.0045**
HF (ms^2)	t=1.543 p=0.137	t=2.89 p=0.009**	t=4.533 p<0.001***
LF (ms^2)	t=1.295 p=0.208	t=1.844 p=0.078	t=1.506 p=0.155
LFnu (%)	t=-0.487 p=0.630	t=-1.622 p=0.117	t=-5.27 p<0.001***
HF nu (%)	t=0.487 p=0.630	t=1.622 p=0.117	t=5.27 p<0.001***
LF/HF ratio	t=0.215 p=0.831	t=-1.544 p=0.134	t=-4.259 p<0.001***

[Table/Fig-3]: Comparison of time domain and Frequency domain linear HRV parameters in different groups.
** highly significant (p<0.01), *** Very highly significant (p<0.001)

DISCUSSION

The aim of this study was to examine cardiac autonomic imbalance in pregnant subjects by means of linear and non linear HRV parameters and comparing their HRV measures with those of healthy non pregnant subjects. Changes in both linear and non linear HRV parameters were not significant in first trimester of pregnancy as compared to control non pregnant group. However, statistically significant differences were observed in some of the HRV parameters in third trimester as compared to control group. SDNN, which reflects a blend of sympathetic and parasympathetic influences, was lower in pregnant women compared with non

Parameter	Non pregnant vs. First Trimester (Unpaired t-test)	Non pregnant vs. Third Trimester (Unpaired t-test)	First Trimester vs. Third Trimester (Paired t-test)
SD1	t=1.357 p=0.186	t=2.928 p=0.007**	t=8.903 p<0.001***
SD2	t=0.148 p=0.882	t=0.697 p=0.491	t=7.877 p<0.001***
Correlation Dimension D2	t=1.458 p=0.156	t=2.619 p=0.014*	t=8.879 p<0.001***
ApEn	t=-0.506 p=0.617	t=0.461 p=0.649	t=4.986 p<0.001***
SampleEn	t=0.181 p=0.858	t=1.549 p=0.136	t=11.98 p<0.001***

[Table/Fig-4]: Comparison of non linear HRV parameters in different groups.
* significant (p<0.05), ** highly significant (p<0.01), *** Very highly significant (p<0.001)

pregnant controls though statistically significant level was not reached for these differences. RMSSD, a representative of parasympathetic activity, was statistically lowered in third trimester pregnancy. HF power was significantly lower in third trimester pregnant women than in non pregnant women indicating reduced parasympathetic control in pregnancy. Alterations in absolute Low Frequency (LF) power and LF (normalised units) were not statistically different in pregnancy (both first trimester and third trimester) as compared to control group. However, parasympathetic reduction as suggested by reduced RMSSD and absolute HF power was obvious in third trimester as compared to non pregnant women. Non linear HRV parameters viz., SD1 and correlation dimension D2 were significantly reduced in third trimester pregnancy as compared to non pregnant females.

Progression of pregnancy from first to third trimester in the follow-up of study subjects showed very highly significant alterations in both linear and non linear HRV parameters. Moreover, significance level was very high for reduction of all the non linear HRV parameters studied as compared to linear parameters [Table/Fig-3,4].

Results of present study suggest that normal pregnancy is associated with a facilitation of sympathetic regulation as shown by increase in LF nu and increased LF/HF ratio [11] and an attenuation of parasympathetic influence of heart rate characterised by decreased RMSSD, pNN50, and HF [12]. Similar results have been obtained in Indian population as measured by linear HRV parameters [7,8]. Attenuation of parasympathetic control to a larger degree than facilitation of sympathetic control in the present study is similar to a major finding in a study by Yang CC et al., [12] who have proposed that "under supine conditions advancing gestation leads to a decrease in baroreceptor sensitivity for heart rate, most likely due to a decrease in vagal, rather than to an increase in sympathetic tone". According to Schobel H, alterations in autonomic nervous system function may be a result of mechano-electrical feedback due to volume related stretch of the sino-atrial node [13].

SD1 describes short-term variability which is mainly caused by respiratory sinus arrhythmia. SD2, on the other hand, describes long-term variability [14]. Approximate Entropy (ApEn) measures the complexity or irregularity of the signal [15]. Large values of ApEn indicate high irregularity and smaller values of ApEn more regular signal. Sample Entropy (SampEn) also measures the complexity or irregularity of the signal however, it reduces the bias of ApEn [16]. Correlation dimension measures the complexity or strangeness of the time series [17]. It is expected to give information on the minimum number of dynamic variables needed to model the underlying system, thus it gives idea about complexity of control system. More is the complexity, better is the control system. Non linear data obtained from the current study suggest a very highly significant reduction of the complexity of time series as judged by statistically significant reduction of SD1, SampEn and low complexity of the control system suggested by highly reduced correlation dimension.

An important finding of the present study was the maximum change in non linear HRV parameters compared to linear HRV parameters as assessed by the probability values for different parameters, particularly in comparison of first and third trimester of pregnancy in a cohort study. This was suggestive of earliest change detection potential of non linear parameters for altered autonomic response to advancing pregnancy. In one cross-sectional observational study [9], HRV changes at the time of full term pregnancy were compared with non pregnant healthy volunteers and the authors found that frequency domain HRV parameters remain unaffected while non linear HRV parameters decreased in pregnant women as compared to non pregnant healthy female volunteers. Though linear HRV parameters have been studied and are found to be useful predictors of Pregnancy Induced Hypertension (PIH) [7,18,19], non linear HRV parameters may be more useful in early detection and prediction of pregnancy induced hypertension and needs to be studied with larger sample size.

LIMITATION

Major limitation of the present study was small sample size. At the same time strength of the study was the longitudinal study design and use of non linear HRV parameters for autonomic function studies in pregnancy.

CONCLUSION

The present study clearly demonstrates that advancing pregnancy is associated with cardiac autonomic imbalance of a large extent, which can be best evaluated by non linear HRV parameters. This finding clearly demonstrates the need for study of non linear HRV parameters, which at present is not being studied in clinical set ups. Further studies with large sample size are needed to clarify and substantiate the complex dynamics of cardiac autonomic imbalance in advancing pregnancy and its clinical significance. At the same time, an urgent need is felt for generation of normative data of both linear and non linear HRV parameters in Indian population as well as for pregnancy, which we aim to undertake in our future research work.

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