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Original Article

Physiology Section

Pattern of Cardiac Autonomic Modulation Assessed by Heart Rate Variability in Normal Pregnancy: A Longitudinal Cohort Study

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ABSTRACT

Introduction: Normal pregnancy is associated with adaptive maternal haemodynamics, viz., increase in blood volume, Heart Rate (HR), cardiac output, and fall in blood pressure. Alterations in hormones and plausible autonomic modulation may regulate these haemodynamic changes and failure of such alterations could have clinical consequences like pregnancy-induced hypertension and preeclampsia. Heart Rate Variability (HRV), a non-invasive measure of cardiac autonomic activity may provide insights in pattern of cardiac autonomic modulation during pregnancy, and tracking it may be useful clinically.

Aim: To evaluate the pattern of cardiac autonomic modulation assessed by HRV during the course of healthy pregnancy.

Materials and Methods: The present longitudinal cohort study was conducted from August 2019 to April 2021 in SKNMC & GH, Pune, Maharashtra, India. A total of 31 pregnant females who underwent repeated HRV assessment between 11th-13th, 18th to 20th, and 24th to 26th weeks of gestation and tracked for pregnancy outcome till delivery, were included. High sampled Electrocardiogram (ECG) (1Kz) for 15 minutes was recorded in supine left lateral position and HRV indices from last five minutes were measured. Multiple group comparisons and between-group comparisons were done using non parametric tests and $p<0.05$ was considered significant.

Results: The mean age of 31 pregnant females was 24.1±3.4 years. Significant increase in average HR (p=0.002)was observed from first to third trimester significant decrease in overall HRV (p=0.01), total power (ms^2) (p=0.008), High Frequency (HF) (ms^2) (p=0.03) and Low Frequency (LH) (ms^2) (p=0.001) was also observed. A trend in HFnu decrement was observed.

Conclusion: As pregnancy advances, (till 26 weeks) a pattern of parasympathetic withdrawal (decreased overall variability and HF (ms^2) along with increase in average HR and reduced baroreflex sensitivity (decrease in LF power) was observed with healthy pregnancy.

Keywords: Autonomic activity, Healthy pregnancy, Maternal haemodynamics, Parasympathetic withdrawal

INTRODUCTION

Pregnancy is associated with various physiological changes in maternal haemodynamics to sustain the growing foetus. These changes are predominantly regulated by alterations in hormones that are well documented in literature, and clinically not so-understood alterations in the cardiac autonomic modulation [1,2]. Literature suggests that a combination of parasympathetic withdrawal and increased sympathetic activity could be an adaptive mechanism with advancing gestation that alters maternal haemodynamics [3,4].

Moreover, there are pointers suggesting a link between pregnancy-related complications, such as preeclampsia and preterm birth, and autonomic dysfunction that sets in early pregnancy [4]. Direct evaluation methods like sympathetic nerve electrical activity, plasma catecholamine levels, were used to test the autonomic modulation during pregnancy [5-7]. However, due to their invasiveness and requirement of controlled set-up, and contradictory results of these studies make it difficult to reach a common consensus on autonomic modulation during normal and abnormal pregnancies limiting their utility during routine antenatal check-ups [3].

Recently HRV, a non-invasive marker of cardiac autonomic activity, has gained clinical importance especially when reduced, as a predictive and prognostic marker of various diseases, viz., diabetes, obesity, metabolic syndrome, hypertension and cardiovascular diseases [8]. Moreover, various studies also point the potential utility of HRV for risk stratification, especially in conditions like ischaemic heart diseases, Type 2 Diabetes Mellitus (T2DM), neonatal sepsis etc., [9-11]. On the other hand, robust HRV is a hallmark of health and longevity [12]. The literature related to cardiac autonomic modulation during pregnancy reported an increase in HR and reduction in HRV longitudinally during healthy pregnancy [13]. Pregnant women with gestational hypertension have higher LF/HF ratio (marker of sympathetic dominance) in earlier stage [14]. Preeclamptic females have been found with lower HF power (marker of parasympathetic modulation) as compared to normal pregnant females [15]. However, some studies offer contradictory results stating that maternal HRV and autonomic activity are unaffected by the gestational age [16,17]. Whereas, some of those reported increased activity of the parasympathetic branch in earlier stages which changes to sympathetic over activation in later stages of pregnancy [18,19]. Most of these studies were cross-sectional studies, which limits the understanding of change in cardiac autonomic modulation during pregnancy [19-22].

To address these contradictory findings and gaps in the knowledge, it was thought useful to deep dwell into this issue, and gaining insights into cardiac autonomic modulation during the course of pregnancy may be useful in predicting maternal health issues in later stages. The results of the study may shed light on mechanisms contributing to haemodynamic changes during normal pregnancy. Thus, the present study was designed as a longitudinal cohort study, to explore the patterns of cardiac autonomic modulation in three trimesters of pregnancy, the outcome of which is tracked till delivery to confirm normal pregnancy.

MATERIALS AND METHODS

The present longitudinal cohort study was conducted from August 2019 to April 2021 in SKNMC & GH, Pune, Maharashtra, India. The study was approved by the Institutional Ethics Committee (SKNMC/Ethics/App/2019/518). A written informed consent was taken from all the study participants.

Inclusion criteria: Healthy pregnant females below 13 weeks of gestational age with no known morbidities were included in the study. The gestational age was based on Ultrasonography (USG) findings. Females who were able to attend all three sessions of HRV recording, were included for final analysis.

Exclusion criteria: The females with known diabetes, hypertension, or drugs affecting cardiac rhythm, were excluded from the study.

Sample size calculation: It was purposive sampling and a total of 113 females were enrolled who met the inclusion criteria of the study. Out of 113 pregnant females, the HRV data of 82 females who were unable to complete the study protocol of three visits due to then ongoing pandemic of COVID-19 was not used for analysis. The data of the remaining 31 females, who completed the protocol was used for final analysis. As the study was a longitudinal cohort, the baseline HRV served as the control for subsequent measurements. The volunteers were enrolled from Outpatient Department (OPD) of Obstetrics and Gynaecology Department, SKNMC & GH, Pune, Maharashtra, India.

Study Procedure

The ECG was recorded as per the protocol designed in consultation with the Obstetrician. The protocol included measurements at three intervals during the pregnancy. The first visit was planned between the 11th to 13th weeks of gestation for the baseline recording. Subsequently, the 18th to 20th and 24th to 26th weeks were scheduled for second and third interval recordings, respectively. All the recordings were taken between 9:00 AM to 1:00 PM. On the first visit, a cardiac autonomic reflex test was additionally performed along with a resting HRV assessment that included 15 minutes of resting supine HRV, five minutes of orthostatic challenge, and one-minute deep breathing. On the second and third visits, 15 minutes of resting supine HRV in the left lateral position was recorded [23].

High sampled maternal ECG (1 kHz) was recorded by placing the surface electrodes, using Chronovisor DX Data Acquisition System (make Promorphosis Pvt., Ltd., Pune). Out of 15 minutes ECG recordings, first ten minutes were provided to rest in supine so that autonomic modulation could reach to baseline and last five minutes were used for HRV analysis by Chronovisor software version 1.1.544. The analysed HRV indices were the time domain HRV indices {mean RR interval, average HR, and Standard Deviation of Normal-to-Normal intervals (SDNN) (ms)}, and frequency domain indices that included total power (ms^2), absolute powers and normalised values of low frequency (LF ms^2, LF nu), and high frequency (HF ms^2, HF nu) and LF/HF ratio [23].

STATISTICAL ANALYSIS

The data was subjected to test the distribution of normalcy by Kolmogorov test. The non-parametric tests such as Kruskal Wallis test for multiple group comparison and Mann Whitney test for two-group comparison were employed as HRV inherently has large inter and intra-individual fluctuations. Additionally, Wilcoxon signed-rank test was applied to compare dependent samples (two sets of scores that came from the same participant). The p-value <0.05 was considered as significant.

RESULTS

The mean age of all pregnant females (n=31) was 24.1±3.4 years. There was a gradual significant decline observed in SDNN as the pregnancy progressed (p=0 .01) from first to third trimester. Similar pattern of decline was found in frequency domain parameters; Total Power (TP) (p-value=0.008), the LF power (p-value=0.001) and the HF power (p=0.03). On the other hand, the average resting HR showed a gradual and highly significant rise from first (82.7±7.7 bpm) to third trimester (91.4±9.9 bpm) (p=0.002) [Table/Fig-1].

S. No.	Parameters	Visits			p-value
		1st	2nd	3rd	
1	SDNN (ms)	42.81±17.18	34.77±14.8	31.4±12.1	0.01*
2	TP (ms^2)	1251.16±1144.4	846±817.6	665.7±523.2	0.008**
3	LF (ms^2)	387.4±442.9	245.8±282.5	147.9±135.8	0.001**
4	HF (ms^2)	414.5±572.7	242.9±355.7	199.1±279.7	0.03*
5	LFnu	53.6±18.2	56.7±16.5	56.5±21.6	0.66#
6	HFnu	46.3±18.2	43.2±16.5	43.4±21.6	0.66#
7	LF/HF	1.79±2.01	1.73±1.24	2.43± 3.21	0.66#
8	Average Heart Rate (HR) (bpm)	82.7±7.7	86.9±10.6	91.4±9.9	0.0026**

[Table/Fig-1]: Descriptive statistics of HRV Indices during three visits.
Statistical test: Kruskal Wallis test; # Not Significant, * Significant, ** Highly significant

There was a significant decrease in SDNN (p-value=0.01), TP (p-value=0.01), LF (p-value=0.02) and increase in average resting HR (p-value=0.04) between first and second trimester However, between second and third trimester, only the HF (ms^2) showed highly significant reduction (p-value=0.006) and average resting HR showed a significant rise (p-value=0.04). A significant reduction in SDNN (p-value=0.0018), TP (p-value=0.001), LF (p-value=0.0001) and HF (p-value=0.006) was observed between first and third trimester and average resting HR had shown a highly significant rise (p-value=0.0003) [Table/Fig-2].

Parameters	Between 1st and 2nd visit			Between 1st and 3rd visit			Between 2nd and 3rd visit		
	U	z	p	U	z	p	u	z	p
SDNN (ms)	331.5	2.09	0.01*	273.5	2.91	0.0018**	416	0.9	0.18#
TP (ms^2)	330	2.11	0.01*	267	3	0.001**	414	0.93	0.17#
LF (ms^2)	341	1.9	0.02*	213	3.76	0.0001**	365	1.62	0.05#
HF (ms^2)	366	1.6	0.05#	301.5	2.51	0.006**	656	-2.4	0.006**
Average Heart Rate (HR) (bpm)	600.5	-1.6	0.04*	727	-3.4	0.0003**	602	-1.7	0.04*

[Table/Fig-2]: Comparison of mean of HRV parameters between the two visits: (Mann Whitney Test values).
Out of total eight parameters, only five have shown the significant differences along three trimesters. That's why, further statistical tests were implied on those five parameters; Statistical test: Mann-Whitney Test # Not Significant, *Significant, **Highly significant

The HRV values of first trimester serve as a baseline for comparison between subsequent trimesters. Between first and second visit, all HRV parameters i.e., SDNN, TP, LF and HF were significantly decreased (p-value <0.01). Between second and third visit, LF was reduced and HR increased significantly. Between the first and third visit, all the parameters showed a highly significant difference (p-value <0.01) [Table/Fig-3].

DISCUSSION

In the present study, HRV was tracked once in every trimester in 31 pregnant females. The methodology is consistent with minor modifications from the studies of Bester M et al., where HRV was recorded on 14th, 18th, 22nd, 24th, 26th, 30th, 34th, 36th, 38th and 40th week of gestation for 45-minute duration, and Garg P et al., recorded HRV between 11th-13th, 20th-22nd and 30th-32nd weeks of gestation [3,18]. The minor modification in recording protocol was due to the fact that clinical symptoms of preeclampsia usually appear after 20th week of gestation [24] and autonomic dysfunction sets early i.e., prior to 20th week in pregnancy may lead to pregnancy related complication later [25]. Therefore, it is logical to track HRV for its clinical relevance (especially for screening purpose) up to 26 weeks of gestation. As this is longitudinal study and the ECG was recorded in appropriate environment required for HRV analysis as per the task force guidelines, and with fall out of sample due to pandemic, the authors were able to gather longitudinal data of thirty-one females. Other studies with higher sample size than this study were either cross-sectional [22,26,27] or longitudinal but HRV was measured by wearable devices [28] where the recording conditions were not rigid as per the HRV guidelines.

Parameters	Between 1st and 2nd visit			Between 1st and 3rd visit			Between 2nd and 3rd visit		
	w	z	p	W	z	p	w	z	p
SDNN (ms)	280	2.74	0.0031**	310	3.03	0.001**	70	0.68	0.24#
TP (ms²)	276	2.7	0.003**	298	2.9	0.001**	84	0.82	0.2#
LF (ms²)	320	3.13	0.0009**	412	4.03	0.0001**	180	1.76	0.03*
HF (ms²)	278	2.72	0.003**	242	2.37	0.008**	96	0.94	0.176#
Average Heart Rate (HR) (bpm)	-156	-1.52	0.06#	-328	-3.21	0.0007**	-224	-2.19	0.01*

[Table/Fig-3]: Intra-individual comparison of HRV parameters.
Statistical test: Wilcoxon signed rank test # Not Significant, *Significant, **Highly significant

The resting HR increased progressively and significantly as the pregnancy advanced. In group comparison there was significant rise between first and second and second and third trimester while signed rank test revealed significant increase from the second to third trimester. This finding of the present study is in line with other longitudinal study [29]. The observed increase in HR could be a result of either parasympathetic withdrawal or sympathetic overdrive, the plausible explanation of which are as follows:

A significant reduction in SDNN and total power from first to third trimester reflects reduced overall HRV. These findings are in line with previous longitudinal studies [4,18,30]. Moreover, reduction in absolute HF (ms^2) (indicator of vagal activity) from first to third trimester, reflects decreased cardiac parasympathetic modulation. This finding is in agreement with results of other investigators [19,19].

Some studies [18,30] demonstrated the progressive sympathetic dominance during the course of normal pregnancy, based on increased LF power (ms^2/ nu) or LF /HF ratio. On the other hand, various studies reported progressive reduction in LF power of HRV during the course of normal pregnancy [4]. In the present study, we have observed significant decline in LF (ms^2) absolute power was observed. Advances in HRV research, based on empirical data have highlighted the fallacy in considering LF as a marker of sympathetic modulation, rather it is emphasised that LF power may be an index of baroreflex modulation of cardiac autonomic flow rather than cardiac sympathetic tone [31-33]. From this perspective, The present study results can be interpreted as progressive reduction in baroreflex modulation during the course of pregnancy. Moreover, the paradox associated with the normalised spectral HRV values, affects the physiological interpretations related to the ANS function and therefore debatable to interpret both LF nu and HF nu as physiologically separate entity (the indices LF (nu), HF (nu) are algebraically dependent and linearly associated, as the mathematical relationship can be exposed by their sum: {LF (nu)+HF (nu)}={LF/(LF+HF)}+{HF/(LF+HF)}=(LF+HF)/(LF+HF)=1. Therefore, each of the indices is predictable from the other: LF (nu)=1-HF (nu), and HF (nu)=1-LF (nu). According to this linear relationship, it becomes clear that reporting both values is considered redundant [34,35]. In the present study, it s therefore reported that only the HF nu values whose physiological interpretation as a marker of parasympathetic modulation is widely accepted. This study did not find significant change in HFnu, LFnu and LF/HF ratio however, HF nu showed a consistent decline during the course of pregnancy.

A drop in mean blood pressure has been reported during the first two trimesters of pregnancy which can be explained by change in baroreflex sensitivity [36]. Physiologically reduction in baroreflex sensitivity can help accommodate an increase in blood volume without significant increase in blood pressure. As mentioned in the previous paragraph, recently the accepted physiological explanation for LF power is baroreflex activity rather than sympathetic tone, with the decreased LF absolute power, the interpretation could be in favour of a reduction in BRS as a part of autonomic modulation up to 26th week of gestation. Similarly, studies that have assessed BRS by direct measurements (beat-to-beat blood pressure variability) among healthy pregnant females, also demonstrated a reduction in BRS [18,36].

In the present study, based on longitudinal tracking, the decline in group means of HRV indices and increase in HR was significant between the first (11th-13th week) and second visit (18th-20th week) as compared to second and third visit (24th-26th week). Similar findings were observed of Wilcoxon signed rank test which compared the HRV differences between first second and third trimester of same individual. These observations suggest that cardiac autonomic modulation sets in early weeks of pregnancy as a part of physiological adaptation. As reported in a systematic review, only few studies have mentioned these early changes in HRV [18,37,38]. Some of the investigators found no or partially significant decline in HRV from first to second trimester [28,38]. These findings could be attributed to differences in methodology and study design.

There are pointers indicating that autonomic dysfunction such as excessive reduction or increase in baroreflex sensitivity, excessive vagal withdrawal and sympathetic over activation in early stages of pregnancy may lead to pregnancy-induced complications in later phase of pregnancy [39-41].

Limitation(s)

In present study, sample size was small. Hence, results cannot be generalised to whole population.

CONCLUSION(S)

A pattern of parasympathetic withdrawal and reduced baroreflex sensitivity was observed during the course of a normal healthy pregnancy rather than sympathetic over activation. This pattern was especially observed between the first and second trimesters. Failing of this adaptation or maladaptation may have clinical consequences. This study strengthens the view of utility of assessing autonomic functions during routine antenatal check-ups preferably in early phase of pregnancy (before 24 weeks) for predicting complications at later stages. These findings may pave the way for setting studies to explore the potential utility of HRV tracking as a novel, non-invasive method for screening pregnancy-induced complications along with traditional screening and diagnostic tests mentioned in the discussion.

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