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VALIDITY OF HEART RATE VARIABILITY IN PREDICTING PREECLAMPSIA

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ABSTRACT

Introduction- Hypertensive disorders during pregnancy remain the most common medical complications, leading to a majority of adverse perinatal and maternal outcome, despite numerous efforts have been made at early diagnosis, prevention and treatment. Many pathophysiological changes occur that gain momentum across gestation and gradually become clinically apparent and ultimately result in multi – organ involvement with a clinical spectrum ranging from barely noticeable to one of cataclysmic deterioration. Heart rate variability (HRV) is a non-invasive marker for the autonomic nervous system. The generality of time-domain indices of HRV are usually calculated from 24-h recording of heart rate, but the frequency-domain indices could be derived from either 24-h or as short as 2-min electrocardiographic (ECG) recordings. Autonomic efferent neurons and circulating hormones modulate SA node initiation of heartbeats. The complex dynamic relationship between the sympathetic and parasympathetic branches, and homeostatic regulation of HR via respiration and the baroreceptor reflex are responsible for short-term and ultra-short-term HRV measurements. Heart rate variability (HRV) analysis is gaining acceptance in the evaluation of cardiovascular disease, particularly for assessing the state of the autonomic nervous system. **Aims and Objectives-** 1) To assess maternal HRV indices cut-off and/or classifier for prediction of preeclampsia followed to full-term. 2)Validity of Heart Rate variability in predicting Preeclampsia. **Material and Methods-** This study was conducted on 100 patients to determine validity of Heart Rate Variability (HRV) in predicting preeclampsia in Obstetrics and Gynecology OPD of Smt. Kashibai Navale Medical College and General Hospital over period of 2 years from February 2020 to January 2022. 100 patients were selected after considering inclusion and exclusion criteria. **Results-**This study was performed in 100 pregnant women out of which 9 patients were pre-eclamptic in our study. Measurement of resting autonomic tone by HRV may be relevant for early screening for preeclampsia as well as for clinical follow-up of patients who are known to have preeclampsia. **Conclusions-** Pregnancy indicates a significant independent risk factor with reference to altered cardiac balance, and potential of use of HRV as a good tool to assess preeclamptic women.

KEYWORDS : Heart rate variability (HRV), Preeclampsia, Autonomic nervous system, Pregnancy.

INTRODUCTION:

Hypertensive disorders during pregnancy remain the most common medical complications, leading to a majority of adverse perinatal and maternal outcome, despite numerous efforts have been made at early diagnosis, prevention and treatment. Preeclampsia prevalence is variable, the estimated incidence is 5–10 % of all pregnancies, with a higher incidence in the first pregnancy especially in women aged less than 20 years[1].Pregnancy induced Hypertension (PIH) is a pregnancy specific syndrome that can virtually affect every organ system. It is defined as rise of blood pressure ≥ 140/90 mmHg after 20 weeks gestation with proteinuria ≥ 300 mg/24 hours or ≥ +1 on dipstick. Although the cause of PIH still remains unknown, its manifestation begins early in pregnancy. Many pathophysiological changes occur that gain momentum across gestation and gradually become clinically apparent and ultimately result in multi-organ involvement with a clinical spectrum ranging from barely noticeable to one of cataclysmic deterioration. Maternal complications like antepartum haemorrhage, eclampsia, HELLP syndrome, disseminated intravascular coagulopathy, acute renal failure, intracerebral haemorrhage and even maternal death can occur. Long term complications like persistent hypertension and cardiovascular morbidity are also not rare. Fetal complications like intra - uterine growth restriction, preterm delivery, sudden intra - uterine fetal death, still births, preterm and low birth weight babies, increased need for NICU care, increased neonatal morbidity and mortality are prevalent[2-4].

PIH is the most common medical disorder of pregnancy, that leads to a complicated multi-organ failure in the mother. It is one of the most common causes of both maternal and neonatal morbidity[5]. It is a global problem and complicates approximately 10-17% of pregnancies. The incidence of PIH in India ranges from 5% to 15%[6]. Hemorrhage occupies is an important factor in the etiology of maternal mortality and therefore, remains a major problem[7].Hypertensive disorders complicating pregnancy (HDP) is the most common complication in pregnancy. The incidence varies in different populations and is affected by the definition used. HDP is influenced by nulliparity, age, and race. In India in 2006, the incidence of HDP was 5.38%, while preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome accounted for 44%, 40%, and 7% of complications, respectively[11]. Maternal and perinatal deaths have been reported in 5.5% and 37.5% of deliveries, respectively. HDP comprises preeclampsia and eclampsia.

Heart rate variability (HRV) is a non-invasive marker for the autonomic nervous system[8,9].The generality of time-domain indices of HRV are usually calculated from 24-h recording of heart rate, but the frequency-domain indices could be derived from either 24-h or as short as 2-min electrocardiographic (ECG) recordings. Autonomic efferent neurons and circulating hormones modulate SA node initiation of heartbeats. The interdependent regulatory systems that generate the complex variability of a healthy heart operate over different time scales to achieve homeostasis and optimal. Heart rate variability (HRV) analysis is gaining acceptance in the evaluation of cardiovascular disease, particularly for assessing the state of the autonomic nervous system[10].Its use in preeclampsia has been limited and coupled with the more difficult-to- obtain blood pressure variability[11]. High-frequency changes correspond to vagal modulatory effects, and low-frequency changes are considered as a marker of either sympathetic or parasympathetic modulation[12].Vascular parameters, as assessed non-invasively by photoplethysmography and heart rate variability, may have a role in screening women suspected of having preeclampsia, particularly in areas with limited resources. Most studies based on these new techniques, namely HRV and blood pressure variability (BPV), suggest that pregnancy per se shifts cardiac autonomic balance towards sympathetic dominance and this shift is even more prominent if pregnancy is complicated with preeclampsia[13].Hence the present study was done at our tertiary care centre to evaluate the validity of Heart Rate variability in predicting Preeclampsia and assess maternal HRV indices cut-off and/or classifier for prediction of preeclampsia followed to full- term.

MATERIALS AND METHODS:

A hospital based prospective study was conducted with 100 patients to determine validity of Heart Rate Variability (HRV) in predicting preeclampsia. A hospital based prospective study for 2 years was done at our tertiary care centre in the department of Obstretics and Gynaecology on attending OPD/IPD. All pregnant female patients attending OPD/IPD of Tertiary care Hospital who fulfilled the inclusion criteria and exclusion criteria.

Inclusion criteria:

Consenting pregnant subjects, recruited from Obstetrics and Gynecology OPD of SKNMC & GH. After through clinical examination and taking informed consent pregnant women will be enrolled at their first visit.

Exclusion criteria:

No specific criteria except investigator's judgment about issues that may impede successful follow-up till term. Study was carried out in first trimester patients with the help of HRV helping in predicting preeclampsia patients (after 20 weeks). HRV studies-Beat-to-beat variation in SA nodal discharge as recorded by ECG was computed and analyzed by the software Variowin HR to determine the spectral indices of HRV. Assessment of heart rate variability was carried out between 8.30 am and 12.00 noon in an isolated examination room. Patients were requested to avoid coffee, tea, cola drinks, and smoking for 12 h and alcoholic beverages for 24 h before procedure. We recorded ECG for the analysis of beat-to-beat heart rate variability after supine rest for at least 5 min, while the subject was in supine position and breathing freely. The ECG was recorded from the precordial leads and transferred on-line to a microcomputer for the analysis of heart rate variability. Only stationary time series of approximately 5-min duration free of arrhythmia and artifacts were used. Frequency-domain analysis of HRV included the power of high-frequency (HF), (0.15–0.40 Hz); low-frequency (LF), (0.04–0.15 Hz); and very low-frequency (VLF), (below 0.04 Hz) power ranges. Patients were followed up by observing mode of delivery, indication for termination of pregnancy and maternal and fetal outcome.

Heart Rate Variability Metrics

Heart Rate Variability Metrics describes 24 hours, short-term (ST, ~5min) or brief, and ultra-short-term (UST, <5 min) HRV using time-domain, frequency-domain, and non- linear measurements. Since longer recording epochs better represent processes with slower fluctuations (e.g., circadian rhythms) and the cardiovascular system's response to a wider range of environment stimuli and workloads, short-term and ultra-short-term values are not interchangeable with 24h values.

Time-domain indices of HRV quantify the amount of variability in measurements of the interbeat interval (IBI), which is the time period between successive heartbeats. These values may be expressed in original units or as the natural logarithm (Ln) of original units to achieve a more normal distribution.

HRV time-domain measures

Parameter	Unit	Description
SDNN	ms	Standard deviation of NN intervals
SDRR	ms	Standard deviation of RR intervals
SDANN	ms	Standard deviation of the average NN intervals for each 5min segment of a 24h HRV recording
SDNN index (SDNNI)	ms	Mean of the standard deviations of all the NN intervals for each 5min segment of a 24h HRV recording
pNN50	%	Percentage of successive RR intervals that differ by more than 50ms
HR Max−HRMin	bpm	Average difference between the highest and lowest heart rates during each respiratory cycle
RMSSD	ms	Root mean square of successive RR interval differences
HRV triangular index		Integral of the density of the RR interval histogram divided by its height
TINN	ms	Baseline width of the RR interval histogram

Interbeat interval, time interval between successive heartbeats; NN intervals, interbeat intervals from which artifacts have been removed; RR intervals, interbeat intervals between all successive heartbeats.

Frequency-domain measurements estimate the distribution of absolute or relative power into four frequency bands. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) divided heart rate (HR) oscillations into ultra-low-frequency (ULF), very-low- frequency (VLF), low-frequency (LF), and high-frequency (HF) bands.

HRV frequency-domain measures:

Parameter	Unit	Description
ULF power	ms2	Absolute power of the ultra-low-frequency band (≤0.003Hz)
VLF power	ms2	Absolute power of the very-low-frequency band (0.0033– 0.04Hz)
LF peak	Hz	Peak frequency of the low-frequency band (0.04–0.15Hz)
LF power	ms2	Absolute power of the low-frequency band (0.04–0.15Hz)
LF power	Nu	Relative power of the low-frequency band (0.04–0.15Hz) in normal units
LF power	%	Relative power of the low-frequency band (0.04–0.15Hz)
HF peak	Hz	Peak frequency of the high-frequency band (0.15–0.4Hz)
HF power	ms2	Absolute power of the high-frequency band (0.15–0.4Hz)
HF power	Nu	Relative power of the high-frequency band (0.15–0.4Hz) in normal units
HF power	%	Relative power of the high-frequency band (0.15–0.4Hz)
LF/HF	%	Ratio of LF-to-HF power

OBSERVATIONS AND RESULTS:

A hospital based prospective study was conducted with 100 patients to determine validity of Heart Rate Variability (HRV) in predicting preeclampsia.

Distribution of patients according to Frequency Domain parameters:

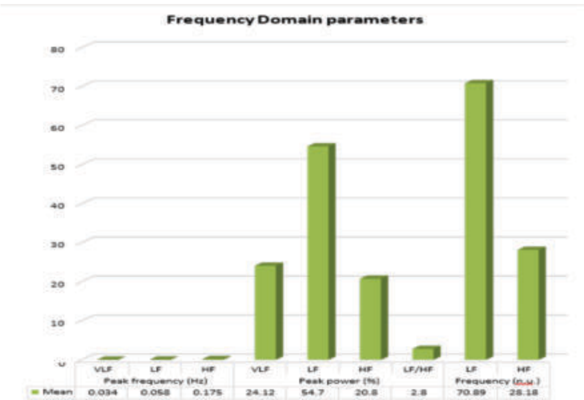
Frequency domain analysis of heart rate variability noted that three components were recorded in spectral analysis i.e. peak frequency (Hz), peak power (%) and frequency (normalized units). The peak frequency components were noted as follows: Very Low Frequency (VLF) (0.034 ± 0.005Hz), Low Frequency (LF) (0.058 ± 0.027Hz) and High Frequency (HF) (0.175 ±

0.018Hz). The peak power components were noted as follows: VLF (24.12 ± 8.08Hz), LF (54.70 ± 35.37Hz), HF (20.80 ± 6.28Hz) and LF/HF ratio (2.80 ± 1.94). The frequency (normalized unit) components were noted as follows: LF (70.89 ± 3.28Hz) and HF (28.18 ± 6.22Hz).

Table 1: Distribution of patients according to Frequency Domain parameters

Spectral analysis		Mean ± SD
Peak frequency (Hz)	VLF	0.034 ± 0.005
	LF	0.058 ± 0.027
	HF	0.175 ± 0.018
Peak power (%)	VLF	24.12 ± 8.08
	LF	54.70 ± 35.37
	HF	20.80 ± 6.28
	LF/HF	2.80 ± 1.94
Frequency (n.u.)	LF	70.89 ± 3.28
	HF	28.18 ± 6.22

VLF – Very Low Frequency; LF – Low Frequency; HF – High Frequency



Graph 1: Distribution of patients according to Frequency Domain parameters

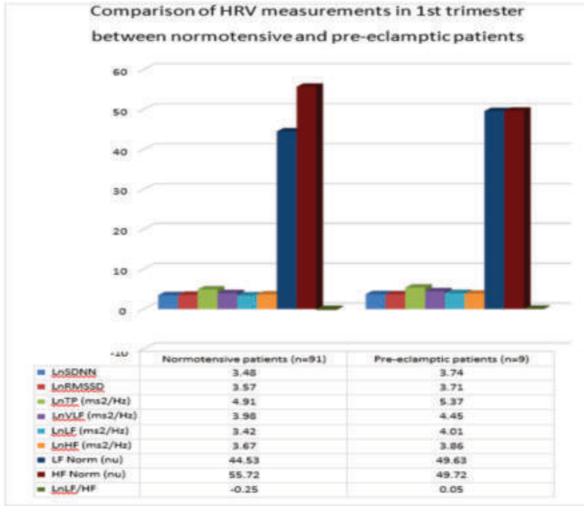
Comparison of HRV measurements in 1st trimester between normotensive and pre-eclamptic patients

There was no significant difference in LnSDNN, LnRMSSD, LnTP, and LnHF between patients with normotensive and pre-eclamptic patients. In comparison to normotensive patients, pre-eclamptic patients had significantly higher LnVLF (3.98 ± 1.12 ms^2/Hz vs. 4.45 ± 1.03 ms^2/Hz; **p<0.05**), LnLF (3.42 ± 1.35 ms^2/Hz vs. 4.01 ± 1.33 ms^2/Hz; **p<0.05**), LF Norm (44.53 ± 19.26 nu vs. 49.63 ± 16.32 nu; **p<0.05**) and

LnLF/HF (-0.25 ± 0.83 vs. 0.05 ± 0.56; **p<0.05**). In contrast, HF Norm was significantly lower in pre-eclamptic patients compared with normotensive patients as per Student t-test (55.72 ± 19.47 vs. 49.72 ± 15.14; **p<0.05**).

Table 2: Comparison of HRV measurements in 1st trimester between normotensive and pre-eclamptic patients

Parameters	Normotensive patients (n=91)	Pre-eclamptic patients (n=9)	p Value
	Mean ± SD	Mean ± SD	
LnSDNN	3.48 ± 0.42	3.74 ± 0.67	>0.05
LnRMSSD	3.57 ± 0.47	3.71 ± 0.64	>0.05
LnTP (ms2/Hz)	4.91 ± 1.04	5.37 ± 1.32	>0.05
LnVLF (ms2/Hz)	3.98 ± 1.12	4.45 ± 1.03	<0.05
LnLF (ms2/Hz)	3.42 ± 1.35	4.01 ± 1.33	<0.05
LnHF (ms2/Hz)	3.67 ± 1.41	3.86 ± 1.76	>0.05
LF Norm (nu)	44.53 ± 19.26	49.63 ± 16.32	<0.05
HF Norm (nu)	55.72 ± 19.47	49.72 ± 15.14	<0.05
LnLF/HF	-0.25 ± 0.83	0.05 ± 0.56	<0.05



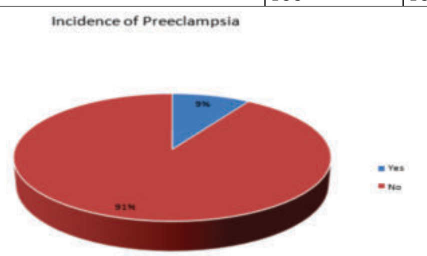
Graph 2: Comparison of HRV measurements in 1st trimester between normotensive and pre-eclamptic patients

Distribution of patients according to Incidence of Preeclampsia

9 (9%) patients were pre-eclamptic in our study.

Table 3: Distribution of patients according to Incidence of Preeclampsia

Incidence of Preeclampsia	N	%
Yes	9	9%
No	91	91%
Total	100	100%



Graph 3: Distribution of patients according to Incidence of Preeclampsia

DISCUSSION:

Heart rate is the number of heartbeats per minute. Heart rate variability (HRV) is the fluctuation in the time intervals between adjacent heartbeats[14]. HRV indexes neurocardiac function and is generated by heart-brain interactions and dynamic non- linear autonomic nervous system (ANS) processes. HRV is an emergent property of interdependent regulatory systems which operate on different time scales to help us adapt to environmental and psychological challenges. HRV reflects regulation of autonomic balance, blood pressure (BP), gas exchange, gut, heart, and vascular tone, which refers to the diameter of the blood vessels that regulate BP, and possibly facial muscles[15].

The heart rate variability is a considerably powerful and reliable tool of assessing the fluctuations in the autonomic nervous system that can be observed in healthy individuals or in many diseases. Depending on physical and mental stress, exercise, respiration and metabolic values, alterations (fluctuations) are experienced in the heart rate variability. HRV that provides information about the sympathetic-parasympathetic balance is used as a measure of the cardiac autonomic tone and as an indicator of the cardiorespiratory system. Preeclampsia: BP ≥ 140/90 mm Hg after 20 weeks gestation Proteinuria ≥ 300 mg/24 hours or ≥ 1+ dipstick. Preeclampsia has remained a significant public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally.

Navi Khan GN et al[16] in 2014 compared the maternal HRV changes between normal pregnancy and pre-eclamptic pregnancy. The authors found no significant difference of body mass index was present between them but BMI of pre-eclamptic pregnant women was higher than normotensive pregnant women and it come under obese category (>25). All the component of spectral analysis i.e., peak frequency (in Hz) and peak frequency (in normalized unit) of pre-eclamptic pregnant women was significantly higher than normotensive pregnant women while in peak power (%) Low Frequency (LF) & ratio between LF/HF of peak power was significantly higher than normotensive pregnant women.

Musa SM et al[17] in 2016 in a case-control study investigated heart rate variability (HRV) and autonomic modulations in pregnant women with preeclampsia. The authors found patients with preeclampsia achieved significantly higher LF Norm [49.80 (16.25) vs. 44.55 (19.15) and LnLF/HF [0.04 (0.68) vs. -0.28 (0.91) readings, but lower HF Norm [49.08 (15.29) vs. 55.87 (19.56), compared with healthy pregnant women. Euliano TY et al[18] in 2018 determined a set of timing, shape, and statistical features available through non-invasive monitoring of maternal electrocardiogram and photo plethysmography that identifies preeclamptic patients. This indicates pregnancy as a significant risk with reference to altered cardiac balance and use of HRV as a good tool to assess the same.

Chaswal M et al[19] study determining autonomic tests to distinguish between normal and hypertensive pregnancy found preeclamptic group did not differ significantly from the normotensive pregnant women with respect to period of gestation and body mass index and women with preeclampsia had significantly higher BMI compared to nonpregnant females.9 (9%) patients were pre-eclamptic in our study. This finding was like the study of Solanki JD et al[20]. Solanki JD et al[20] study showed Primiparous women had significantly reduced LF power, HF power, and LF: HF ratio while multiparous women had significantly reduced total power, heart rate. Most time-domain parameters were lower in primiparous than multiparous women but statistical significance was evident only for SDNN. SD1, SD2, but not scatter index, were lower in primiparous than multiparous women, with statistical significance. In the present study, in all the components, the Low Frequency (LF) was significantly higher in pre-eclamptic patients than normotensive patients while High Frequency (HF) was significantly low in pre-eclamptic patients than normotensive patients. The ratio between the LF/HF and VLF component in peak frequency was significantly higher in pre-eclamptic patients compared to normotensive pregnant women while VLF component in peak power was comparable between the groups as per Student t-test ($p>0.05$). Similar observations were noted in the studies of Navi Khan GN et al[16], Musa SM et al[17] and Yang CC et al[23].Yang CC et al[23]observed higher LF/HF and LF, but lower HF, in pregnant compared with the non-pregnant women and preeclamptic group demonstrated lower HF, but higher LF/HF, compared with the non-pregnant as well as normal pregnant women. The normal pregnancy readjusted to autonomic modulation towards predominance of sympathetic over parasympathetic tone and this readjustment is further augmented if the pregnant women developed preeclampsia.

SUMMARY:

A hospital based prospective study was conducted with 100 patients to determine validity of Heart Rate Variability (HRV) in predicting preeclampsia. The following observations were noted:

1) Frequency domain analysis of heart rate variability noted that three components were recorded in spectral analysis i.e. peak frequency (Hz), peak power (%) and frequency (normalized units). The peak frequency components were noted as follows: Very Low Frequency (VLF) (0.034 ± 0.005Hz), Low Frequency (LF) (0.058 ± 0.027Hz) and High components were noted as follows: LF (70.89 ± 3.28Hz) and HF (28.18 ± 6.22Hz).

2) 9 (9%) patients were pre-eclamptic in our study.

3) In all the components, the Low Frequency (LF) was significantly higher in pre- eclamptic patients than normotensive patients while High Frequency (HF) was significantly low in pre-eclamptic patients than normotensive patients.The ratio between the LF/HF and VLF component in peak frequency was significantly higher in pre-eclamptic patients compared to normotensive pregnant women while VLF component in peak power was comparable between the groups as per Student t-test ($p>0.05$).

4) There was no significant difference in LnSDNN, LnRMSSD, LnTP, and LnHF between patients with normotensive and pre-eclamptic patients. In comparison to normotensive patients, pre-eclamptic patients had significantly higher LnVLF (3.98 ± 1.12 ms2/Hz vs. 4.45 ± 1.03 ms2/Hz; $p<0.05$), LnLF (3.42 ± 1.35 ms2/Hz vs. 4.01 ± 1.33 ms2/Hz; $p<0.05$), LF Norm (44.53 ± 19.26 nu vs. 49.63 ± 16.32 nu; $p<0.05$) and LnLF/HF (-0.25 ± 0.83 vs. 0.05 ± 0.56; $p<0.05$). In contrast, HF Norm was significantly lower in pre-eclamptic patients compared with normotensive patients as per Student t-test (55.72 ± 19.47 vs. 49.72 ± 15.14; $p<0.05$).

CONCLUSION:

Pregnancy indicates a significant independent risk factor with reference to altered cardiac balance, and potential of use of HRV as a good tool to assess preeclamptic women.

Measurement of resting autonomic tone by HRV may be relevant for early screening for preeclampsia as well as for clinical follow-up of patients who are known to have preeclampsia.

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