Original Article

A study on cardiac autonomic modulation during pregnancy by non-invasive heart rate variability measurement

Abstract

Purpose: Remarkable and uncontrollable changes with modification during pregnancy are connected with the autonomic control and consequently with the heart rate variability (HRV). Heart rate variability is a sum of different mechanisms and if pregnancy is a state of change, these modifications could be extracted from HRV analysis. **Objective:** To assess the effect of pregnancy on heart rate variability among pregnant mothers during first trimester of pregnancy and third trimester of pregnancy. **Materials and Methods:** HRV was measured for 5 minutes of continuous recording of electrocardiogram (ECG) lead II, using windows based HRV analysis system variowin-HR after obtaining permission from the Institutional Review Board of Government Medical College, Bhavnagar and written consent from 30 pregnant subjects and 30 non-pregnant control subjects at autonomic function lab, Dept of Physiology, Bhavnagar. **Result:** Frequency domain parameters, very low frequency (VLF), low frequency (LF), high frequency (HF) and HF normalized unit (nu) were significantly decreased and LF (nu) and LF/HF significantly increased in pregnant subject in 3rd trimester as compared to their 1st trimester of pregnancy. Time Domain parameters like SDNN, RMSSD, SDSD, NN50 count, pNN50, SD1/SD2, triangular HRV index and average R-R interval were significantly decreased during 3rd trimester of pregnancy. **Conclusion:** The inhibition of resting parasympathetic activity or vagal blockage and an increment of the sympathetic modulation during the 3rd third trimester of gestation in pregnancy as compared to their 1st trimester and healthy non-pregnant subjects. Sympathovagal imbalance and abnormally low HRV may more pronounce during later stage of normal pregnancy.

Key words: Autonomic function test, gestation, heart rate variability, pregnancy

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INTRODUCTION

The last three decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death.[1] Heart rate variability (HRV) is a non-invasive, easy and economical technique to assess the status of autonomic nervous regulation of cardio vascular system. Heart with a stable and regular heart beat periodically is now considered as the marker for a poor prognostic for longevity.[2] HRV studies enhance understanding of physiological phenomenon of heart activity especially during pregnancy. The changes in the function of every regulatory system during pregnancy are initiated by ovarian and placental hormones in the first trimester, but may also be modified by placental and fetal endocrine factors as gestational age advances. Pregnancy-induced effects on cardiovascular function are increases in heart rate (HR), stroke volume (SV), and cardiac output.[3,4] These changes result from the interactive effects of a primary reduction in peripheral vascular resistance,[5] cardiac autonomic modulation and baroreflex function that lead to a higher resting heart rate.

It is well established that high-frequency (HF) power (0.15-0.40 Hz) of HRV is mediated by parasympathetic nervous system (PNS) modulation and respiratory sinus arrhythmia,[6-8] whereas low-frequency (LF) power (0.03-0.15 Hz) reflects both sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) autonomic influences.[8,9] The ratio of low-frequency power to high-frequency power (LF/HF) has been used to reflect cardiac sympathetic modulation (SNS

indicator).[3,9] Ekholm *et al.* studies on cardiac autonomic function in human pregnancy have produced conflicting results. Their findings of reduced total power[10,11] and attenuated HR responses to orthostatic tests and the Valsalva maneuver[11] suggest that cardiac parasympathetic modulation is reduced in the resting state during mid pregnancy (22-29 wk of gestation). Studies conducted in early to mid gestation (11-27 wk)[12] were reported reduction in low-frequency HRV during the day and reduction in high-frequency HRV at night.

OBJECTIVE

- To assess the heart rate variability during first trimester of gestation in pregnancy and third trimester of gestation in pregnancy.
- To study the effect of various stages of normal pregnancy on heart rate variability.

MATERIALS AND METHODS

Pregnant subjects were enrolled into the study from Obstetric department after permission was taken from Institutional Review Board (IRB) and Human Ethics Committee of Government Medical College, Bhavnagar. This study was carried out at autonomic nerve function lab, Dept. of Physiology, Govt. Medical College and Sir T Hospital, Bhavnagar. Short HRV was measured for 5 minutes from continuous recording of ECG (heart rate) using windows based HRV analysis system variowin-HR.

Sample size

Due to pregnancy termination or development of pregnancy-induced complication, out of 42 in 1st visit, 30 pregnant subjects were selected for 2nd visit. 30 normal pregnant subjects and 30 ages matched healthy non-pregnant control subjects were enrolled.

Criteria for selection

Inclusion criteria of pregnant subjects

Age of 18 yrs-45 yrs and Hb is of >9.0 gm% pregnant subject and giving written consent for HRV recording.

Exclusion criteria of pregnant subjects

Any illness and pregnancy-induced complication develop at any stage of pregnancy during this study.

Inclusion criteria of non-pregnant subjects

Age of 18 yrs-45 yrs non-pregnant subject having Hb >9.0% and ready for giving written consent for HRV recording.

Exclusion criteria of controls

Any illness.

Procedure

In the presence of relatives and one female staff, all participants were allowed to relax for ten minutes. Case record form containing personal information of subjects, anthropological measurements, last menstrual period, total month of amenorrhea, obstetric history, clinical history and vitals were filled up. Subjects were asked to lie down in a supine position and remain quiet, without speaking or making any movements for 5 minutes.

Four electrodes were placed at both infraclavicular and both hypochondrial regions of the subjects. HRV were measured by continuous lead II ECG recording for 5 minutes (short-term HRV) based on R-R interval. The pregnant women were called for two times for HRV measurement, during 1st trimester of gestation (6-12 weeks of pregnancy) and during 3rd trimester of gestation (25-36 weeks of pregnancy). Both time domain (SDNN, RMSSD, SDSD, NN50 Count, pNN50%) and frequency domain (VLF, LF, HF, LF/HF ratio) parameters of HRV analyses were measured.

Statistical analysis

We were using graph Pad InStat statistical software for data analysis.

RESULTS

There is no any significant difference in age and height between cases and controls. This infers that the case subjects and healthy controls were ideally matched for age and height to relatively nullify the effect of confounding variable factor on HRV. The weight and body mass index (BMI) values were statistically significant in both groups. {1st trimester of gestation and Controls; 3rd trimester of gestation and Controls} [Table 1a and b].

There were no significant difference in values of HRV parameters among 1st trimester subject group and control group. This infers that in early normal pregnancy, there may not be any change in the cardiac autonomic regulatory mechanism in spite of hormonal changes. This may be due to other compensatory mechanism [Table 2].

There was significant decrease in both frequency domain parameters and time domain parameters during 3rd trimester of gestation in pregnancy as compared to healthy control [Table 3].

Table 1: (a) Mean ± SD values of anthropological measurement among 1st trimester of gestation in pregnant subject and 3rd trimester of pregnancy and healthy non pregnant control subjects

Parameters	1st trimester of gestation (*n* = 30)	Control non pregnant (*n* = 30)	*P*-value
Age (yrs)	24.63±3.05	23.43±2.91	0.1240, NS
Ht (cm)	151.03±2.92	151.63±4.39	0.5355, NS
Wt (kg)	48.5±5.81	51.7±5.33	0.030, S
BMI	21.24±2.28	22.49±2.3	0.0382, S
Parameters	3rd trimester of gestation	Control non pregnant	*P*-value
Wt (kg)	53.67±6.31	51.7±5.33	0.1969, NS
BMI	23.5±2.43	22.49±2.3	0.1038, NS

SD = Standard deviation, *n* = Number of participants, NS = No significance, S = Significance, *P*-value <0.05 indicates significance

Table 1: (b) Mean ± SD values of weight, BMI, Parity, Hb%, systolic and diastolic pressure, weeks of gestation of same cases during 1st trimester of gestation and 3rd trimester of gestation in pregnancy (*n* = 30)

Parameters	1st trimester of gestation in pregnant subject	3rd trimester of gestation in pregnant subject	*P*-value
Wt (kg)	48.5±5.81	53.67±6.31	0.0016, S
BMI	21.24±2.28	23.5±2.43	0.0004, S
Parity	1.333±0.6814	1.333±0.6814	0.99, NS
Hb%	9.95±0.36	9.82±0.43	0.2091, NS
SBP	115.87±8.37	124.5±7.33	0.0001, S
DBP	72.6±5.31	77.53±5.03	0.0005, S
No Weeks of gestation	9.27±1.72	28.3±1.51	—

Frequency domain parameters like VLF, LF, HF and HF (nu) were significantly decreased and LF (nu) and LF/HF were significantly increased during 3rd trimester of gestation as compared with their 1st trimester of pregnancy. In time domain (power spectral) parameters, there are decreased mean values of SDNN, RMSSD, SDSD, NN50 count, pNN50, SD1/SD2. Triangular HRV index and average R-R interval are more decreased during 3rd trimester of pregnancy. Heart Rate and Mode values are increased in 3rd trimester as compare with 1st trimester [Table 4].

DISCUSSION

As per Table 2, there were no statistical significant difference in the mean values of frequency domain parameters and time domain parameters among the 1st trimester of gestation in pregnancy subjects

Table 2: Comparative values of frequency domain parameters and time domain parameters between 1st trimester of gestation in pregnant subjects and controls. (*n* = 30)

Parameters	1st trimester of gestation in pregnant subject (Mean ± SD)	Controls non pregnant Mean ± SD	*P*-value
Frequency domain parameters			
VLF (ms^2)	1107.7±720.42	1059.9±503.57	0.4926, NS
LF (ms^2)	↓899.19±527.80	979.49±696.1	0.6166, NS
HF (ms^2)	↓801.06±898.32	906.72±674.94	0.6085, NS
LF (nu)	↓0.4903±0.18	0.52±0.10	0.4154, NS
HF (nu)	↓0.4417±0.1994	0.48±0.1	0.3673, NS
LF:HF	↓0.9480±0.7754	1.194±0.526	0.1551, NS
Time domain parameters			
SDNN (ms)	43.899±13.65	42.92±10.36	0.7632, NS
RMSSD (ms)	36.43±16.27	35.17±11.34	0.7289, NS
SDSD (ms)	35.35±16.91	34.37±11.59	0.7935, NS
NN50 Count	48.50±52.0	50.57±33.22	0.8551, NS
pNN50%	14.38±14.87	12.83±9.29	0.6294, NS
SD1/SD2	↑0.51±0.15	0.46±0.1	0.1648, NS

VLF = Very low frequency, LF = Low frequency, HF = High frequency, LF = HF- LF and HF ratio, LF(nu) = Normalized LF, HF(nu) = Normalized HF, SDNN = Standard deviation of all NN interval, RMSSD = The square root of the mean of the sum of the squares of differences between adjacent NN intervals, SDSD = Standard deviation of differences between adjacent NN intervals, NN_{50} = Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording, pNN_{50}% = NN_{50} count divided by the total number of all NN intervals, HR = Heart rate

Table 3: Comparative values of frequency domain parameters and time domain parameters between 3rd trimester pregnant subjects and healthy non pregnant controls

Parameters	3rd trimester of gestation Mean ± SD (*n* = 30)	Controls non pregnant Mean ± SD (*n* = 30)	*P*-value
Frequency domain parameters			
VLF (ms^2)	↓858.82±773.55	1059.9±503.57	0.2376, NS
LF (ms^2)	↓425.09±361.72	979.49±696.1	0.0003, S
HF (ms^2)	↓201.03±179.79	906.72±674.94	<0.0001, S
LF (nu)	↑0.7273±0.12	0.52±0.10	<0.0001, S
HF (nu)	↓0.2663±0.1030	0.48±0.1	<0.0001, S
LF: HF	↑2.930±1.785	1.194±0.526	0.0001, S
Time domain parameters			
SDNN (ms)	↓27.93±12.5	42.92±10.36	0.0001, S
RMSSD (ms)	↓22.25±19.29	35.17±11.34	0.0025, S
SDSD (ms)	↓21.35±18.68	34.37±11.59	0.0020, S
NN50 Count	↓20.67±56.62	50.57±33.22	0.0155, S
pNN50 %	↓5.96±15.15	12.83±9.29	0.0387, S
SD1/SD2	↑0.47±0.3	0.46±0.1	0.9452, NS

Table 4: Comparison of frequency domain parameters and time domain parameters among same subjects between their 1st trimester of gestation and 3rd trimester of gestation in pregnancy

Parameters	1st trimester of gestation (Mean ± SD) (*n* = 30)	3rd trimester of (Mean ± SD) (*n* = 30)	*P*-value
Frequency domain parameters			
VLF (ms²)	1107.7±720.42	↓858.82±773.55	0.1115,NS
LF (ms²)	899.19±527.80	↓425.09±361.72	0.0001, ES
HF (ms²)	801.06±898.32	↓201.03±179.79	0.0007, ES
LF (nu)	0.4903±0.18	↑0.7273±0.12	<0.0001, ES
HF (nu)	0.4417±0.1994	↓0.2663±0.1030	<0.0001, ES
LF: HF	0.9480±0.7754	↑2.930±1.785	<0.0001, ES
Time domain parameters			
SDNN (ms)	43.899±13.65	↓27.93±12.5	<0.0001, ES
RMSSD (ms)	36.43±16.27	↓22.25±19.29	0.0032, S
SDSD (ms)	35.35±16.91	↓21.35±18.68	0.0035, S
NN50 Count	48.50±52.0	↓20.67±56.62	0.0521, NS
pNN50%	14.38±14.87	↓5.96±15.15	0.0339, S
SD1/SD2	0.51±0.15	↓0.47±0.3	0.4940, NS
Tri. HRV Index	11.4±3.95	↓7.72±2.96	0.0001, S
Others			
Mode Value	602.23±125.29	↑643.06±85.62	0.1459, NS
HR	80.4±2.94	↑85.2±3.5	<0.0001, ES
Avg R-R	738.31±95.32	↓689.67±97.98	0.0561, NS

and healthy non-pregnant control subjects. However, LF, HF and normalized HF were reduced in 1st trimester of gestation subjects. This may be due to the effect of maternal or placental hormones during the early phase of pregnancy.

Stein *et al.*, reported that in early pregnancy, statistical differences in the spectral indexes tend to be smaller than in late pregnancy with major contradictions in the published data.[13] They were no reported significant differences in early pregnancy (with respect to non-pregnancy) except for LF region and RRsd and mainly, during the sleep-time but no differences were observed at all with respect to late pregnancy.[13] This study among 1st trimester of gestation shows similar type of result.

As per Table 3, there were statistical significant difference in the mean values of frequency domain parameters and time domain parameters among the 3rd trimester of gestation in pregnancy subjects and healthy non- pregnant control subjects. Frequency domain parameters like VLF (858.82 ± 773.55 ms²), LF (425.09 ± 361.72 ms²), HF (201.03 ± 179.79 ms²) and normalized HF (0.2663 ± 0.1030) were significantly reduced and normalized LF (0.7273 ± 0.12), LF: HF (2.930 ± 1.785) was significantly incremented in the 3rd trimester of gestation as compared to non-pregnant healthy control and of 1st trimester of gestation [Table 4]. These represent the sympathetic modulation or over activity become prominent and vagal or parasympathetic inhibition or blockage occurs during the 3rd trimester of gestation in normal pregnancy. During the 3rd trimester of gestation, time domain parameters, SDNN (27.93 ± 12.5 ms), RMSSD (22.25 ± 19.29 ms), SDSD (21.35 ± 18.68 ms), NN50 (20.67 ± 56.62) count, pNN50 (5.96 ± 15.15) were significantly reduced and SD1/SD2 (0.47 ± 0.3) was increased as compare with Control group. This may be interpreted as sympathetic modulation due to vagal inhibition during that stage.

Greenwood *et al.*[14] found that the vasomotor sympathetic activity increased in women with normal pregnancy and was even greater in hypertensive pregnant women during the 3rd trimester of gestation. They concluded that the marked sympathetic hyperactivity during the latter months of normal pregnancy helped to return the arterial pressure to non-pregnant levels, but when the increase in sympathetic nerve activity was excessive, hypertension ensued. Their preliminary data suggest that normal pregnancy may also be associated with an increase in resting vasomotor sympathetic outflow, and pregnancy *per se* can result in sympathetic activation despite a normal blood pressure. That is quite comparable to our study result as LF: HF and LF (nu) increment during the 3rd trimester of gestation that represents the sympathetic over activity.

As per Table 4, in frequency domain parameters, mean values of VLF, LF, HF, HF normalized were significantly reduced in 3rd trimester of gestation in pregnancy and mean values of LF: HF and LF normalized were significantly increased during the 3rd trimester of pregnancy as compared to the 1st trimester of gestation in pregnancy. This shows the sympathetic dominance is more during 3rd trimester of pregnancy as compared to 1st trimester of gestation. Reduction in HF and LF during 3rd trimester of gestation in pregnancy shows the decreased activity of parasympathetic system or its turn to developing vagal blockage as pregnancy advance.

In normalized units, an increased LF (0.7273 ± 0.12) and a diminished HF (0.2663 ± 0.1030) were observed during 3rd trimester of gestation in pregnancy. These indicate a shift of sympathovagal balance towards a sympathetic predominance and a reduced vagal tone during 3rd trimester of gestation. Similar conclusions were obtained by considering the changes in LF/HF ratio. Significant reduction in RMSSD, NN50 count, pNN50% and HF (ms²) during

the 3rd trimester of pregnancy suggest marked reduction in vagal modulation in HRV regulation and aggravate in sympathovagal imbalance.

SDNN is mathematically equal to total power of spectral analysis; SDNN reflects all the cyclic components responsible for variability in the period of recording. The mean values of SDNN were reduced in 3rd trimester (27.93 ± 12.5) of pregnancy as compared to 1st trimester (43.899 ± 13.65) of pregnancy. Reduction in SDNN represents abnormally low HRV with sympathovagal imbalance is more during 3rd trimester even in normal pregnancy.

Heiskanen *et al*'s.,[15] study showed that in normal pregnancy, the increment of the heart rate could be partially associated with the inhibition of resting parasympathetic activity connected with an increment of the sympathetic modulation but during the 3rd third trimester of pregnancy there could be a parasympathetic deactivation instead of an increment of the sympathetic activity (under unstimulated conditions) even when the head-up tilt test induce changes in the parasympathetic activity and the sympathovagal balance.

The presence of a high vagal tone seems to be a marker of physiological, biological and psychological flexibility. So, decreased vagal tone in 3rd trimester of gestation group in our study may cause loss of flexibility in physiological systems in general, and in the cardiovascular system in particular, which has been linked with a number of diseases and dysfunctions. So, abnormally low heart rate variability in our study indicates that even normal pregnancy without any complication can impact dramatically on dynamic autonomic control of heart. This is an issue that requires inter-disciplinary approaches across multiple levels of analysis, ranging from the psychological to the biochemical investigation.

CONCLUSION

As normal pregnancy advances in its stage, the inhibition of resting parasympathetic activity connected with an increment of the sympathetic modulation is noted. The effect of sympathetic dominance may be controlled by other mechanism of the body during the 3rd trimester of gestation in pregnancy such as regulation of blood pressure, heart rate and cardiac output in normal pregnancy. HRV can be applied as early diagnosis of pregnancy induced cardiac abnormalities with correlate it with other investigation.

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