Original Article

Heart rate variability is reduced in normal pregnancy irrespective of trimester: A cross-sectional study from Gujarat, India

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Abstract

Background: Pregnancy is associated with profound cardiovascular adaptation with altered cardiac autonomic balance. It can be studied by heart rate variability (HRV) which indicates beat to beat RR interval variation on ECG. **Objective:** We studied 5 min HRV in normal pregnant females divided by trimesters, compared to matched control. **Methodology:** We recruited 89 normal pregnant females and 30 age matched controls. Five minutes resting HRV was measured by Variowin HR, software-based instrument, by standard protocols to yield time-domain, frequency domain, and Poincare plot parameters. They were further compared between groups for difference. **Results:** Case groups (three based on trimesters) and control group were comparable. There was reduced HRV in case than control group, with statistical significance for all, more for frequency domain than time-domain or Poincare plot parameters. There was no pattern of HRV trend across three trimesters, but mostly second trimester was associated with major decline. Primipara revealed significantly reduced HRV than multipara, but anemia or working status was not significantly associated with HRV in case group. **Conclusion:** There is global HRV reduction in normal pregnancy across all trimesters, associated with primiparity. 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.

Keywords: Heart rate variability, normal, pregnancy, primipara, trimester

Introduction

Pregnancy is a period with profound adaptive changes in body with remarkable burden on cardiovascular system.[1] It is, in part, achieved by varying the cardiac autonomic control, which if altered, can produce aftermaths like hypertension.[2] Symapatho vagal imbalance is known in pregnancy[3] that can be studied in terms of heart rate – as a parasympathetic function test; and blood pressure - as a sympathetic function test. Heart rate variability (HRV), a better and detailed autonomic function test, is beat to beat variation in RR interval of electrocardiogram.[4] Healthy heart exhibits good HRV, and reduced HRV indicates a risk for cardiovascular morbidity.[4] We aimed to study HRV parameters in normal pregnant females with respect to trimesters and various correlates of it.

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Materials and Methods

Study type and subjects

Ethics committee approval was given by IRB committee number: IRB(HEC)593/2016 dated 29/04/2016. We conducted a cross-sectional case control study in outdoor obstetric patients from a tertiary center. Prior permission was taken from the Physiology and Obstetric department of our college followed by the approval of institutional review board of our college.

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Written informed consent from subjects undergoing study was taken, and they were informed about benefit, objectivity, and aim of this study. There were 89 gravid females with detected uncomplicated pregnancy as case group and 30 females without detected pregnancy matched by age as control group.

Inclusion and exclusion criteria

We enrolled apparently healthy females, aged between 18 and 40 years of any parity, ready for written informed consent, with no history of cardiovascular disease, not taking any drugs affecting autonomic nervous system, taking regular ante-natal check-up. Control group was matched by age to case group. Apart from the lack of compliance to these criteria, we excluded 2 subjects with abnormal ECG recording for HRV. Anemia was defined,[5] depending on trimester (<11 g/dl in the first trimester, <10.5 g/dl in the second trimester, <11 g/dl in the third trimester) of pregnancy.

HRV measurement

We used HRV measurement protocol as used in our previous[6,7] 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.

HRV parameters

HRV was studied in detail with respect to frequency domain, time-domain and poincare plot parameters as we published previously[6,7] and are mentioned here.

Time-domain analysis of HRV parameters encompassed RR interval, standard deviation of all RR intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD), standard deviation of successive differences (SDSD) and pNN50, which is the percentage of consecutive RR intervals that differ by >50 ms.

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. LF and HF were presented also in normalized units and as a ratio.

Poincare plot analysis consisted of SD1 and SD2 which are standard deviation of RR interval along major and minor axis, respectively. Scatter index is expressed as ratio of SD1 to SD2 reflecting the non-linear HRV.

Statistical Analysis

The HRV data were transferred on Excel spreadsheet and descriptive variables were expressed as mean ± standard deviation while categorical variables were expressed as numbers. All calculations were done using Graph Pad in Stat 3 software (demo version free statistical software of GraphPad Software, Inc. California, USA). Normality test was run prior to selection of test to check for parametric or non-parametric distribution of data. Groups based on trimesters, parity, anemia, and working status were compared further. We calculated the difference in distribution of various parameters by Mann–Whitney test, unpaired Student's *t*-test or ANNOVA test followed by *post hoc* test for quantitative data and by Chi square test for qualitative data. Difference was taken as statistically significant with $P < 0.05$.

Results

There were 89 cases and 30 controls with mean age in mid-twenties and having comparable height, weight, BMI, while prevalence of non-working state was significantly higher in cases than control. In case group, 58 participants were multipara and 31 participants were primipara. Hemoglobin levels were comparable between groups, mean being lower in both [Table 1].

Cases had, in general, decreased frequency spectrum HRV parameters than control, with most results being significantly reduced in cases than control except heart rate. The intergroup difference was significant between control and either of case group. Most parameters showed a trend of decrease from

Table 1: Baseline data of stud1y groups

Parameter, Unit	A) T1 (*n*=24)	B) T2 (*n*=37)	C) T3 (*n*=28)	D) Control (*n*=30)	*P*	Pair with significant difference
Age, years (mean±SD)	26.83±3.96	27.42±4.60	28.07±4.35	26.57±6.66	0.28	-
Height, cm (mean±SD)	156.92±4.55	157.38±3.02	157.36±4.51	153.93±9.29	0.0001*	A-D, B-D, C-D
Weight, kg (mean±SD)	60.54±11.2	67.46±14.64	66.29±12.48	57±11.05	0.0038*	B-D, C-D
BMI, kg/m^2 (mean±SD)	24.57±4.28	27.16±5.40	26.68±4.21	24.29±5.35	0.0494*	None
Hb, gm/dL (mean±SD)	11.06±1.13	11.39±1.01	11.19±1.42	10.68±1.35	0.20	-
P/M (number)	15/9	26/11	17/11	-	0.86	-
W/NW (number)	7/17	5/32	8/20	24/6	<0.0001*	-

T1=first trimester, T2=second trimester, T3=third trimester, BMI=body mass index, Hb=haemoglobin, P=primipara, M=multipara, W=working women, NW=non-working women. *indicates statistical significance

T1 to T3 group except LF: HF ratio that showed reverse trend. Comparison of time-domain HRV parameters between 3 subgroups of case group and control group showed, though statistically insignificant, reduced values of all parameters in time domain as compared to controls except NN50% and HRV triangular index. There was no single trend of change across T1, T2, and T3 for time-domain parameters. Geometric HRV analysis done by Poincare plotting showed insignificantly reduced SD1, scatter index, and significantly reduced SD2 values in cases as compared to control [Table 2].

Primipara and multipara subgroups of cases were comparable with respect to age, BMI, hamoglobin, trimester distribution, prevalence of working women. 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 [Table 3].

Anemic and non-anemic subgroups of cases were comparable with reference to age BMI, haemoglobin, trimester distribution, prevalence of working women. Non-anemic group had lesser power of HRV values for most parameters but statistical significance was lacking. HR was higher in anemic than non-anemic group. Time-domain and poincare plot HRV parameters were smaller in anemics than non-anemics without statistical significance [Table 4].

Working women and non-working subgroups of cases were exactly matched by number, parity, and trimester and had comparable age, BMI, and haemoglobin. Non-working women group had lesser HRV values for most parameters than working women group but statistical significance was lacking. LF: HF ratio was significantly lower in working than non-working women. Time-domain and poincare plot HRV parameters were smaller in non-working women than working women without statistical significance [Table 5].

Discussion

Pregnancy is a state where multiple physiological readjustments are required for the growth of embryo, perhaps affecting cardiovascular system the most.[1] The profile of cardiovascular parameter changes, and it is varied compared to non-pregnant state it advances.[8] Cardiac dysautonomia can be seen when females fail to adapt increased demand and cardiovascular readjustment.[9] This can be seen in the form of reduced vagal tone and/or increased sympathetic tone that manifest as reduced heart rate variability.[10] We explored whether it is reduced significantly in normal pregnancy too. We found, in general, reduced heart rate variability in pregnant females than controls. Though frequency domain revealed stronger differences than time-domain HRV parameters, our results are in line with previous HRV studies done with reference to normal pregnancy which have reported the same finding.[8,10-13] This can be due the fact that time-domain analysis needs 24 h HRV,[14] and we used only 5 min HRV. Apart from pregnancy itself, other factors contributing to reduced HRV in this study can be: 1) higher BMI (27 kg/m^2), 2) middle to upper socio economic class rather than lower, 3) presence of primipara (two-third), 4) low mean haemoglobin level (mean 11 gm%), 5) urban life style, 6) dietary salt intake, and 7) subjective apprehension of procedure.

Two recent studies are noteworthy here. One study[13] compared HRV in pregnancy indicating reduced HRV in first as compared

Table 2: Heart rate variability parameters (mean±SD) of study groups

Parameter, Unit	A) T1 (*n*=24)	B) T2 (*n*=37)	C) T3 (*n*=28)	D) Control (*n*=30)	*P*	Pair with significant difference
Frequency domain HRV parameters						
VLF	1125.94±937.2	1125.60±1255.5	1078.59±1027.2	1933.33±1966.0	0.049*	None
LF (nu)	0.301±0.10	0.32±0.10	0.29±0.11	0.529±0.23	<0.0001*	A-D, B-D, C-D
HF (nu)	0.69±0.09	0.67±0.10	0.66±0.14	0.48±0.23	<0.0001*	A-D, B-D, C-D
LF: HF Ratio	0.61±0.48	0.81±0.95	0.69±0.90	2.18±4.14	0.0007*	A-D, B-D, C-D
Heart rate	89.75±41.49	98.38±30.83	112.03±41.15	98.73±60.92	0.08	-
Mode Value	784.59±457.45	618.06±249.85	618.71±330.46	2248.86±2903.3	0.0241*	C-D
Time-domain HRV parameters						
SDNN	101.92±62.23	75.70±37.89	78.88±51.70	323.65±547.71	0.09	-
RMSSD	137.66±96.15	101.19±59.41	103.6±83.85	554.98±922.49	0.11	-
SDSD	418.16±812.68	201.42±316.02	100.26±60.13	350.83±1308.8	0.29	-
NN 50%	58.33±37.71	83.73±56.60	75.21±53.79	51.63±56.06	0.0445*	B-D
PNN50%	49.59±34.59	48.76±27.71	57.98±45.82	45.46±34.96	0.87	-
HTI	12.97±4.64	13.82±4.22	13.00±4.05	10.03±4.32	0.0082*	B-D
Poincare plot HRV parameters						
SD1	81.67±53.23	61.28±35.69	57.65±39.56	197.72±271.93	0.22	
SD2	83.25±44.70	65.93±28.66	62.91±37.23	185.17±241.60	0.0002*	A-D, B-D, C-D
Scattered index	0.91±0.30	0.81±0.31	0.81±0.34	0.93±0.43	0.48	

T1=first trimester, T2=second trimester, T3=third trimester, HRV=heart rate variability, VLF=very low frequency, LF (nu) = low frequency in normalized unit, HF (nu) = high frequency in normalized unit, SDNN=standard deviation of NN intervals, RMSSD=root mean square of standard deviation, SDSD=standard deviation of standard deviations, pNN50% = percentage of NN50%, HTI=HRV triangular index, SD=standard deviation, * indicates statistical significance

Table 3: Comparison of HRV parameters between primipara and multipara of case group

Parameters	Primipara (*n*=58)	Multipara (*n*=31)	*P*
Age, years (mean±SD)	27.16±4.08	28.2±4.94	0.89
BMI, kg/m^2 (mean±SD)	26.15±5.01	26.72±4.63	0.6000
Hb, gm/dL (mean±SD)	11.39±1.23	10.93±1.03	0.08
Trimester -1/2/3 (number)	16/27/17	8/11/13	0.46
Working/Nonworking (number)	12/47	8/22	0.50
LF (nu) (mean±SD)	0.31±0.09	0.69±0.36	<0.0001*
HF (nu) (mean±SD)	0.66±0.11	0.86±0.16	<0.0001*
LF/HF (mean±SD)	0.67±0.56	0.91±0.78	0.0003*
Mode (mean±SD)	522.38±375.77	380.85±449.64	0.0120*
Heart rate (mean±SD)	109.03±38.51	84.77±30.01	0.0013*
SDNN (mean±SD)	74.51±49.77	260.35±255.01	0.0001*
RMSSD (mean±SD)	103.51±69.18	84.40±79.75	0.0544
pNN50% (mean±SD)	46.76±28.00	53.46±31.87	0.0711
SD1 (mean±SD)	57.65±40.79	80.09±44.91	0.0200*
SD2 (mean±SD)	62.78±35.54	81.25±37.92	0.0241*
Scatter index (mean±SD)	0.84±0.32	0.82±0.33	0.7514

Abbreviations are same as Tables 1 and 2, *indicates statistical significance

Table 4: Comparison of HRV parameters between anemic and non-anemic pregnant females

Parameters	Anemic women (*n*=41)	Non-anemic women (*n*=49)	*P*
Age, years (mean±SD)	26.95±4.17	28.02±4.52	0.18
BMI, kg/m^2 (mean±SD)	26.00±5.44	26.72±4.36	0.49
Working/non-working (number)	9/32	11/38	>0.99
Trimester - 1/2/3 (number)	9/16/16	15/21/12	0.33
Primipara/multipara (number)	27/14	34/15	0.82
LF (nu) (mean±SD)	0.30±0.10	0.32±0.11	0.27
HF (nu) (mean±SD)	0.68±0.12	0.68±0.11	0.94
LF/HF (mean±SD)	0.72±1.03	0.72±0.62	0.99
Mode (mean±SD)	606.47±348.86	702.59±345.11	0.13
HR (mean±SD)	103.80±36.76	97.61±38.90	0.35
SDNN (mean±SD)	79.85±52.85	84.25±50.31	0.58
RMSSD (mean±SD)	104.17±79.15	116.04±80.71	0.49
pNN50% (mean±SD)	48.76±30.18	46.59±30.61	0.87
SD1 (mean±SD)	61.54±42.14	67.67±44.60	0.51
SD2 (mean±SD)	67.18±39.03	70.67±35.97	0.61
Scatter index (mean±SD)	0.79±0.37	0.86±0.29	0.21

Abbreviations are same as Tables 1 and 2

to third trimester indicating that sympathovagal imbalance and abnormally low HRV are more pronounced using the later stage of normal pregnancy. However, here we have taken all subjects with previous good obstetric and reproductive history and matched controls to compare with. So even first trimester HRVs showed significant lowering as compared to non-pregnant controls. In another study,[15] the same sympathovagal imbalance was found altered but with the use of other autonomic function testing than HRV in the third trimester of pregnancy. We included all three trimesters and despite overall reduced HRV, could not find any trimester of three as dominant for major change. In general, second and third trimester showed decline as compared to first trimester. But in *post hoc* test analysis there was no significant inter-trimester difference of HRV, indicating that cardiac autonomic change ensues in pregnant female from first trimester and it can accumulate to culminate in some aftermaths like arrhythmia and hypertension with months of amenorrhoea to come. However, it needs follow up study on the same gravid subjects from first trimester to ascertain it further.

A similar study done similarly has shown that reduced HRV indicates either increased sympathetic activity or reduce vagal activity or both.[16] Altered LF/HF ratio indicates the same cardiac dysautonomia. Normal value of this ratio is 1.5-2,[16] but cases had low ratio indicating alteration in cardio vagal balance. Even in controls we found this ratio low than this range and that indicates sympathetic over activity in young non-gravid females. Similarly, SD1:SD2 ratio based on HRV geometric analysis was reduced that shows sympathetic over activity in gravid subjects.[17] Raised heart rate with significance difference also indicated sympathetic overdrive. Pregnancy requires cardiac adjustments which are mediated by change in cardiac autonomic balance towards sympathetic than normal vagal influence. However, excess of sympathetic activity and reduced HRV indicates that heart is under physiological stress. This stress can lead to pre-eclampsisa and pregnancy-induced hypertension which adversely affects the overall outcome and proceedings of pregnancy which is otherwise a physiological adaptation.[18]

Parity is one of the factor affecting cardiac autonomic balance and alteration in pregnancy. Primipara with the first exposure to need of cardiorespiariotory adjustment is more at risk for the cardiac dysautonomia than multigravida, where body has been through similar changes before.[19] We found the same as HRV was reduced in primiparous than multiparous participants. Results of Puente ET[20] *et al.* demonstrated that general autonomic balance is modified by parity effect. Results of study by van der Zwan JE *et al.* indicated a statistically significant beneficial effect of HRV-biofeedback on psychological well-being for all women, and an additional statistically significant beneficial effect on anxiety complaints for pregnant women.[21] They also suggested the use of HRV-biofeedback as a stress-reducing technique among women reporting stress and related complaints in clinical practice to improve well-being,[21] needed more so for anxious–primigravid women.

Indeed, it has long been established that prolonged exposure to stressors incurred at work is linked to a vast array of negative attitudinal, health and, in particular, cardiovascular outcomes for employees.[22] Working women have documented to have lesser HRV than non-working woman. But we found inverse in case group as non-working women had lesser HRV than working women. This difference was small and insignificant but it indicates mental stress of physiological changes of pregnancy to be more significant than physical stress of working environment. Anemia is related to enhanced haemodynamic with sympathetic over activity,[23] but we do not find the same effect of anemia on HRV during pregnancy. It can be due to the fact that anemia was mild in all subjects and it also underscores pregnancy as overriding factor affecting HRV irrespective of mild anemic

Table 5: Comparison of HRV parameters between working and non-working pregnant females (*n*=20 each, matched by trimester and parity)

Parameters	Working women (*n*=20)	Non-working women (*n*=20)	*P*
Age, years (mean±SD)	29.25±3.71	28.70±3.57	0.64
BMI, kg/m^2 (mean±SD)	27.41±5.27	25.74±4.29	0.27
Hb, gm/dL (mean±SD)	11.21±0.94	11.22±1.44	0.97
Trimester -1/2/3 (number)	7/5/8	7/5/8	-
Primipara/multipara (number)	13/7	13/7	-
LF (nu) (mean±SD)	0.29±0.09	0.30±0.12	0.88
HF (nu) (mean±SD)	0.71±0.09	0.68±0.11	0.44
LF/HF (mean±SD)	0.58±0.67	1.41±1.68	0.0484*
Mode (mean±SD)	735.83±422.31	634.08±307.82	0.24
Heart rate (mean±SD)	93.85±41.21	100.55±28.08	0.09
SDNN (mean±SD)	97.65±59.46	74.45±47.49	0.09
RMSSD (mean±SD)	136.82±93.12	97.9±76.79	0.17
pNN50% (mean±SD)	51.69±29.99	42.78±36.20	0.45
SD1 (mean±SD)	75.40±44.02	56.88±42.60	0.18
SD2 (mean±SD)	78.59±42.25	56.88±42.60	0.11
Scatter index (mean±SD)	0.86±0.31	0.78±0.35	0.57

Abbreviations are same as Tables 1 and 2, * indicates statistical significance

status that is very common. Yet, moderate and severe anaemia in pregnancy demands further clarification.

A healthy heart is not a metronome and entropy of heart rate is a sign of healthy heart. HRV is indicative of health and well being[24] yet under-rated and under-used in countries like India. Pregnancy leads to reduced interplay between higher autonomic nervous system and heart, and the same we saw as reduced power of HRV to one-third. This indicates cardiac compromise even if the pregnancy was normal. Modern era is the era of going beyond conventional subjective instruments like sphygmomanometer more so when one need to screen for discrete cardiovascular parameters like cardiac autonomic status. HRV is a surrogate of cardiac dysautonomia and a validated, objective tool. Providing ante-natal health service is one of the areas of maternal health. Especially pregnancy-induced cardiovascular changes that can lead to aftermaths like hypertensive disorders of pregnancy need a good screening. HRV can be used at a primary care level by family physician to screen those at risk and to monitor progress of the same. This baseline study can be explored further with vertical follow up and with reference to some cardiovascular conditions.

There were few limitations to be mentioned here such as small sample, use of 5 min rather than 24 h HRV, complex nature of HRV itself, three subgroups of cases were different not the same individuals, subjective apprehension, lack of baseline HRV data of subjects, and no vertical follow up.

Conclusion

There is global HRV reduction in normal pregnancy across all trimesters, associated with primiparity, but not, anaemia or working status. This indicates pregnancy as a significant independent risk factor with reference to altered cardiac balance, and potential of use of HRV as a good tool to assess the same using this study as a reference for further work.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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