Original Research Article

Cardiovascular autonomic changes in third trimester of pregnancy studied by Heart Rate Variability

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Abstract

Background: Pregnancy is the greatest physiological challenge in a woman's life that needs wide cardiovascular adjustment to overcome metabolic demands from the growing fetus. Cardiovascular Autonomic nervous control plays a key factor in pregnancy, Derangement of this may end in certain complications such as pregnancy induced hypertension, foetal growth retardation etc. **Aim:** This study is aimed to find out the changes and adaptations in cardiovascular autonomic control during normal pregnancy especially in third trimester primi based on Heart rate variability(HRV) and compared with age matched non-pregnant women. **Materials and methods:** Following Institutional Ethical clearance, Lead II Electrocardiogram (ECG) was acquired from 30primi women in third trimester using RMS polyrite 2.2 at supine rest for 10 minutes with normal respiration. HRV parameters such as Time and Frequency Domain measures were analyzed using Finland Software 2.1. Statistical Results were taken as significant for $p<0.05$. **Results:** This study showed reduced HRV with significant parasympathetic withdrawal and sympathetic overdrive in advanced trimester pregnant primi.

Key word: autonomic nervous system, heart rate variability, pregnancy, third trimester

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Introduction

Physiological changes occurring in pregnancy are mainly due to hormonal and metabolic demands in early part, while anatomical in later part. [1,2] These physiological challenges have influence on various systems to meet the needs of growing foetus. Changes in autonomic cardiovascular control have an important role in certain conditions like PIH and insufficient uteroplacental blood flow.

It is necessary to develop a methodology by which these variables can be monitored & studied. These Cardiovascular adjustments play a pivotal role in the nourishment of foetus and mother herself, so that it helps in maintaining integrity. Although many factors accounts to these hemodynamic changes such as social status, age , nutrition, gravidity, etc, Autonomic Nervous System (ANS) plays a vital role in the adaptation of the heart and circulation to this wide shift in blood volume and increased peripheral demands.

ANS, an involuntary system, functions with two limbs namely, Sympathetic and Parasympathetic system innervating the heart predominantly in the ventricles and sinoatrial (SA) node respectively. The SA node is mainly innervated by efferent branches of the right vagus nerves.

The SA node being pacemaker of heart, displays intrinsic automaticity at a rate of 100-110 beats per minute. This intrinsic rhythm is primarily influenced by autonomic nerves, with vagal

influences being dominant over sympathetic influences at rest and that is the reason HRV is better studied at rest.[3]

This vagal innervation reduces the resting heart rate down to 60-80 beats/min. But all blood vessels out branching from the heart supplying and draining the whole body is under sympathetic tone alone, which aids in regulating blood pressure.[3]

Changes in this autonomic cardiovascular control have an important role in certain conditions like PIH and insufficient uteroplacental flow. [4,5] Hypertensive disorders complicate nearly5% of pregnancies of which 3% are affected by Preeclampsia, which remains a major cause of fetal complications.[4]

This knowledge about relationship between autonomic nervous system and PIH triggered us to measure autonomic status in normal pregnancy.

The Autonomic nervous regulatory system is difficult to study because of its wide interconnection, complexity and integration. It is also necessary to describe variables which are known to be related to closed loop.

It is necessary to develop a methodology by which these variables can be monitored. Heart Rate Variability is one such reliable, non-invasive measure to assess this autonomic modulation. [5]

HRV basically a beat to beat variation in instantaneous heart rate or variation in beat to beat interval (RR interval). This instantaneous heart rate in every beat originate from SA node which is under the influence of various inputs.

The main inputs are parasympathetic and sympathetic nervous system. Others inputs are baroreflex, thermoregulatory, hormones, stress and sleep wake cycle. [6]

We are aware of fact that the third trimester period of pregnancy has more cardiovascular changes and so it is the proper period to study Cardiovascular Autonomic function using HRV.

Aim & objectives

- To study the cardiovascular autonomic functions in primigravida during third trimester of pregnancy.
- To study Cardiovascular Autonomic status using Heart rate variability (HRV) and compare with age matched nulliparous women.

Methods

After the approval from the Institutional Ethical Committee of Kilpauk Medical College, Chennai-10, for this case control study, we recruited thirty eight third trimester primi antenatal women of age 18 -30 years from the Department of Obstetrics and Gynecology while age matched nulliparous females came from Master Health Check-up Department, Kilpauk Medical College.

Antenatal women suffering from anemia, diabetes, PIH, cardiac disease and on drugs that disturb ANS were excluded. The study protocol was explained, informed and written consent were obtained.

A detail clinical examination was done for all subjects. Each subject is made to accustom to the ambient lab environment, ECG Lead II was acquired at 200 Hz(6) in supine rest with eyes closed with normal respiratory rate(12-16/Min) for 10 minutes using RMS Polyrite D 2.2 (INDIA) in the Neurophysiology lab, Kilpauk Medical College between 10AM – 12PM.

RR series was extracted using a rate-detector algorithm after exclusion of artifacts and ectopics. Power Spectral analysis was performed using the Fast Fourier transform algorithm.

The recommendations of the Task Force on HRV were followed. Short term HRV analysis was done using Linear methods – Time Domain (SDNN, RMSSD, NN50, pNN50) and Frequency Domain (LF in %,LF in ms^2, HF in %, HF in ms^2, LF/HF, LFn.u., HFn.u.).

Table I. Baseline characteristics of subjects

	Control (n=30)	Study (n=30)	t value	*p* value
Age	22.97±2.98	22.10 ± 2.52	0.187	0.85
Height	1.461± 0.030	1.455 ± 0.029	- 0.821	0.415
Weight	65.63± 4.694	66.27 ± 7.705	1.599	0.115
BMI	29.02±1.96	29.31 ± 3.38	1.805	0.076
Blood sugar	98± 5.336	99.06±6.443	3.972	0.000**
Hb	11.1±0.527	11.07 ± 0.728	-14.11	0.000**

Parameters expressed as mean ± SD. * p< 0.05 significant.
Age (in years) , Height (in metres, M), Weight (in Kilograms, Kg),BMI, Body Mass Index(Kg/ M^2), Blood sugar (in milligrams/ decilitre), Haemoglobin (Hb) in grams/ decilitre

Table II. Resting Mean blood pressure and heart rate in supine position

Parameters	Control (n=30)	Study (n=30)	t value	*p* value
Mean HR	78.00 ±7.37	80.20±6.29	4.635	0.000**
SBP	108± 7.022	101± 7.46	-2.85	0.006**
DBP	74.67± 5.71	68.00±5.35	-4.663	0.000**
PP	32.33±6.78	33.67±7.81	0.706	0.483
MAP	85.44±5.28	79.22±4.91	-4.721	0.000**

Data are expressed as mean ± SD, 95% confidence interval of the mean.
** p< 0.01 – Highly significant. HR – Heart Rate(in bpm- beats per minute), SBP – Systolic Blood Pressure, DBP – Diastolic Blood Pressure , PP – Pulse Pressure, MAP –Mean Blood Pressure (mmHg)

Table III.Heart rate Variability Indices (Time Domain Measures) during supine rest

Parameters	Control (n=30)	Study (n=30)	t value	*p* value
Mean HR	78.00 ± 7.37	80.2±6.29	4.635	0.000**
Mean RR	814.15±79.80	722.26±78.04	-4.509	0.000**
SDNN	54.59 ± 14.90	41.76± 19.91	-4.588	0.000**
RMSSD	63.29± 19.86	38.96±15.65	-4.108	0.000**
NN50	149.63±52.42	69.70±12.14	-4.493	0.000**
pNN50	43.50± 15.92	16.62±5.76	-5.154	0.000**

Data are expressed as mean ± SD, 95% confidence interval of the mean.

** p< 0.01 – Highly significant. HR – Heart Rate (in bpm- beats per minute), SDNN – in milliseconds, RMSSD – in millisecond, NN50 , pNN50 (ratio)

Table IV. Heart rate variability indices (Frequency Domain) during supine rest

Parameters	Control (n=30)	Study (n=30)	t value	*p* value
Total Power ms^2	2297.62±398.98	742.15±97.19	-5.258	0.000**
LF ms^2	1040.44±119.62	312.28±69.94	-4.216	0.000**
HFms^2	1410.05±799.54	452.86±63.72	-5.318	0.000**
LF%	40.39±15.15	39.915±16.58	0.127	0.899
HF%	80.55±10.76	55.56±19.51	-1.179	0.243
LF/ HF	0.806±0.611	1.018±0.939	1.036	0.304
LF n.u	38.86±16.08	43.47±18.83	1.021	0.304
HF nu	62.01±15.60	59.07±18.89	-0.656	0.514

Data are expressed as mean ± SD, 95% confidence interval of the mean.
** p< 0.01 – Highly significant. LF – low frequency, HF- High frequency, ms- millisecond n.u.-normalised units

Results

All parametric and non parametric variables were tested by SPSS version 15. All the parameters were checked for normal distribution using Kolmogorov Smirnov and Shapiro Wilk test and normally distributed data were analysed by independent student 't' test.

In this study, Table I. shows no significant difference in age (in years), Height (meters), weight (Kg) and BMI (Kg/M^2) between control and study groups. It shows significant difference in both blood sugar level (mg/dl) and Hemoglobin level(gm %) between control and study group.
Table II shows significant increase in HR(bpm), decreased Systolic BP (mmHg), Diastolic BP(mmHg)and Mean Arterial Blood Pressure(mmHg) in study group compared to Control group.

Table III, shows significant increase in HR(bpm) and significant decrease in RR interval (milliseconds , ms) in study group compared to control. It shows decreased SDNN(Standard Deviation of RR intervals) in ms^2, RMSSD (Square root of the mean squared differences of successive NN intervals) in ms^2, NN50 (Number of pairs of successive NN intervals that differ by 50 ms), pNN50 (proportion of NN50 divided by total number of NNs) in study group.

In frequency domain, High frequency band between (0.15- 0.4 Hz) (HF power in $millisecond^2$, %, normalized units [n.u.]) express vagal activity, Low Frequency band, 0.04- 0.15 Hz (LF power in $millisecond^2$, %, normalized units [n.u.]) express combination of sympathetic and parasympathetic activity, LF/HF ratio which usually tells about sympatho-vagal balance were all analyzed. Table IV, shows significant decrease in both LF and HF power (in ms^2) in study group compared to control. But increase in LF %, LFn.u. and LF/HF, decrease in HF % andHF n.u. appreciated in study groupwas not significant.

Discussion

In our study there is a reduced HRV in third trimester pregnant women, with decreased parasympathetic modulation and increased Sympathetic activity which goes in hand with Ekholm et al 1992 for increased sympathetic tone at third pregnancy.[7,8] Avery et al and Ekholm & Piha et al 1993 described the reduced HRV due to

decreased parasympathetic activity at rest.[9,10]This reduced HRV could have been contributed by many factors. It is well known fact that an increase in BMI is associated with reduced HR (Schmid et al 2010 & Tonhajerovah et al).[11,12] Weight gain in pregnancy is usually 10 – 12 kg of which fat deposition accounts for 3.5kg.[1] Here, there is mild difference in BMI between study and control group but not significant. Hence, change in BMI is less likely to reduce HRV.

The significant decrease in Hemoglobin in study group compared to control group ($p<0.01$) with 12.10 gm/dl in control group and 10.07gm/dl in study group clearly indicates hemodilution in pregnancy. Though, WHO has accepted up to 11gm percent as the normal level in pregnancy, in India and most of the other developing countries the lower limit is often accepted as 10 gm.[13] In accord with this, study group are not anemic which has potential to reduce HRV. Although subjects were screened for gestational diabetes, there is a significant increase in random blood sugar level in study group but within the normal range. This significant blood sugar rise may be due to resistance to Insulin, a Glucose lowering hormone with advancing gestation. Literature reveals that Insulin resistance is associated with reduced HRV.[14,15] This shows that reduced HRV in pregnant women could also be due to insulin resistance in pregnancy with increasing gestational weeks especially last trimester.

There is a definite increase in Resting Heart Rate (RHR) in pregnant women at supine rest ($p<0.01$). This change in RHR may be due to changes in the Blood volume. This increased blood volume is about 40- 50 % in third trimester pregnancy lead to increased venous return which in turn causes mechano electrical feedback due to stretch of SA Node there by increasingRHR. As the RHR increases, the overall HRV is low.[16] This is also emphasized with low total power , as the total power is inversely proportional to RHR.[17] In our study we have significantly increased RHR denoting that the HRV is low shown by the further HRV data. It is normal physiological phenomenon to have increase in RHR at third trimester and these increases as gestation increases. This increase in heart rate could have been higher if it were not in supine position. In supine posture, aortic caval compression decreases the venous return thereby decreasing the mechano-electrical feedback resulting in less rise in RHR.[18] It is therefore necessary to check the RHR and HRV regularly during the routine antenatal care to predict the risk factor.

Blood pressure, an important determinant of risk factor during pregnancy, decreased significantly ($p < 0.01$), This decrease could be due to reduction in peripheral resistance in third trimester. Diastolic BP contributed by this reduced total peripheral resistance, carries high significance especially in pregnancy for maintaining uteroplacental flow. During pregnancy, uteroplacental flow is very much needed for the fetal growth and development. Mean Arterial pressure(MAP) which is average pressure acting throughout one cardiac cycle is found to be decreased ($p<0.01$)and indicates decreased perfusion pressure. Despite this MAP decrease, this uteroplacental flow is maintained by this decrease in vascular resistance and increased blood volume. It is clear that BP which fluctuates regulated by baroreflex, controls ANS output through Heart rate variation and ultimately in HRV. Hence we selected normotensive pregnant women for assessing cardiac autonomic activity with blood pressure measurement as one of the main screening parameter.[19]

Time Domain Measures

The significant reduction in SDNN ($p<0.01$), which is equal to the total power of spectral analysis in pregnant women indicates parasympathetic withdrawal. Also , RMSSD, NN50, pNN50 signifying the parasympathetic regulation decreased significantly. It is also known that heart rate is inversely related to RR interval. In pregnancy, this reduction in parasympathetic activity may be due to less responsiveness of vagal neurotransmitters like Acetyl choline (20). Multiple other hormones known to influence the cardiovascular system and baroreflex regulation are increased, including progesterone, pressor hormones such as ANG-II and aldosterone, ovarian hormones such as relaxin, placental hormones such as corticotrophin-releasing hormone, pituitary

hormones such as oxytocin, adipokines such as leptin, and inflammatory factors such as TNF- and IL-6.[20]

Frequency Domain Measures

It is very clear that LF $ms^2$and HF ms^2(absolute powers) found to be decreased significantly ($p < 0.01$), while Total power (TP, ms^2) is significantly decreased in Pregnant women ($p<0.01$) compared to control group. The distribution of the power and the central frequency of LF and HF are not fixed due to the changes in autonomic modulations of RR interval. This is the reason why LF and HF go in direction with TP.[6] This prevents the appreciation of the fractional distribution of the energy. Ultimately this total power is going to give the autonomic modulation in cardiovascular system.

LF(n.u.) is a marker of sympathetic activity and LF $ms^2$is a marker of combinedsympathetic and parasympathetic influences whereas HF ms^2 and HF n.u. is a marker of vagal activity. Hence, the representation of LF and HF in normalized units emphasizes the controlled and balanced behaviour of the two branches of the Autonomic Nervous System. There is a definite increase in sympathetic activity and decrease in parasympathetic modulation activity, shown by increase in LF n.u. and decrease in HF n.u., though not significant. Though LF % is almost the same for both study and control group, HF % is
decreased in study group compared to control group indicating definite parasympathetic withdrawal.[21]

LF / HF ratio is a sensitive measure of sympathovagal balance. Increase in LF-HFratio indicates increased sympathetic activity and decrease in this ratio indicates increased parasympathetic activity LF/HF ratio is increased in pregnant women indicating sympatho-vagal balance shifting towards the sympathetic activation.[22-24] Here, the mechanism which shifts balance towards sympathetic activation is due to parasympathetic withdrawal as both LF $ms^2$and HF ms^2decreased significantly in pregnant women.[25.26]

Limitations

The limitation met in our study is the lack of provision of recording 24 hour heart rate variability, which is the standard HRV measure. Lack of facility to assay Sympathetic noradrenaline and pregnancy hormones are taken into considerations.

Conclusion

More than bedside test of measurement of BP and biochemical test routine in antenatal care checkup, HRV analysis would also give an insight to the ANS function in pregnancy

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Conflict of Interest : Nil

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