**Original article:**

# Role of Autonomic Nervous System in Hemodynamic Adaptations in Mid-trimester pregnant women

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**ABSTRACT:**

Pregnancy is biggest physiological challenge in a woman's life that necessitates cardiovascular adjustment to meet metabolic demands from the growing fetus. Multiple factors contribute to this physiologic hemodynamic alterations, of which Autonomic nervous control plays a vital role, derangement of which ends up in PIH .We aimed to study the adaptation in autonomic control during normal pregnancy especially in midtrimesterprimi based on heart rate variability(HRV) and compared with age matched non- pregnant women. Following Institutional Ethical clearance, Electrocardiogram (ECG) lead II was acquired from 30 mid trimester primi women using RMS polyrite 2.2 in supine rest and one minute controlled deep breathing. HRV parameters such as Time and Frequency Domain measures were analysed using Finland Software 2.1. Statistical Results were taken as significant for p<0.05. Our study showed reduced HRV with significant parasympathetic withdrawal and sympathetic overdrive, an indispensable physiological adaptation.

Key word: Pregnancy, Midtrimester, Autonomic Nervous System, Heart Rate Variability

## INTRODUCTION:

The proactive rather than reactive physiological changes occurring in pregnancy(1) are mainly due to metabolic demands and hormonal in early part , while anatomical in later part (2) . These physiological challenges imposed on various systems to meet the demands of growing foetus. In Cardiovascular System, Blood volume, Heart rate, Cardiac output increase, while total peripheral resistance, resting blood pressure decrease (2).This cardiovascular adaptation plays a vital role in nourishment of foetus and mother itself, thereby maintaining integrity. Though multiple factors contribute to these hemodynamic changes like gravidity, age, nutrition, social class etc, Autonomic Nervous System (ANS) plays a fundamental role in the adaptation of the heart and circulation to this dramatic shift in blood volume and increased peripheral demands.

ANS, commonly called as involuntary system, works with two limbs, Sympathetic and Parasympathetic system innervating the heart predominantly in the ventricles and Sinoatrial (SA) node respectively. The SA node is predominantly 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(3). This vagal innervation reduces the resting heart rate down to 60-80 beats/min. Whereas blood vessels out branching from the heart supplying and draining the whole body are under sympathetic tone alone, which aids in regulating blood pressure(3).

Any alteration in this autonomic cardiovascular control has an important causal role in certain conditions like PIH and insufficient uteroplacental flow(4,5). Hypertensive disorders complicate about 5% of pregnancies of which 3% affected by Preeclampsia, whichremains leading cause of foetal complications(4). This insight 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 complexity and integration.

There is a need to describe variables which are known to be related and develop a methodology by which these variables can be monitored. Heart Rate Variability is a one such reliable, non-invasive measure to assess this autonomic modulation (6). 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, thermoregulator, hormones, meals stress and sleep wake cycle(6).

As we aware of that midtrimester period of pregnancy has significant cardiovascular changes and an apt period to diagnose early PIH(7), we intended to study the Cardiovascular Autonomic function in midtrimester period of pregnancy.

**AIM & OBJECTIVE:**

To study the cardiovascular autonomic function during pregnancy among midtrimesterprimi.

Heart rate variability (HRV) is the tool used hereto study Cardiovascular Autonomic status and compare age matched nulliparous women with midtrimester pregnant women.

**METHODS:**

After the approval from the Institutional Ethical Committee of Stanley Medical College, Chennai-1, for this case control study, we recruited thirty midtrimesterprimi antenatal women of age 18 -30 years from the Department of Obstetrics and Gynaecology(RSRM) while age matched nulliparous females came from Master Health Check-up Department, Stanley Medical College. Antenatal women with ailments like anaemia, diabetes, PIH, cardiac disease and on drugs that disturb ANS were excluded. The study procedure was explained and informed and written consent was obtained. Study subject details were taken and thorough clinical examination been done. After having made them accustomed 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 20 minutesand one minute controlled deep breathing(6 breaths/ minute) using RMS Polyrite D 2.2 (INDIA) in the Neurophysiology lab, Stanley Medical College between 10AM – 12PM. Theinstantaneous heart rate at RR intervals were plottedforshort termHRV analysis.An RR series was extracted using a rate-detector algorithm after exclusion of artefacts and ectopics.Power Spectral analysis was performed using the Fast Fourier transform algorithm (Welch's Periodogram) after passing it through the Henning window. Then analysis of HRV did after detrendingRR series, using smoothness prior method with interpolation frequency of 4Hz using Kubios 2.1software. 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.).



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Table I

Baseline characteristics of subjects

| | Control (n=30) | Study (n=30) | t value | p value |
|---|---|---|---|---|
| Age | 21.97±2.98 | 22.10 ± 2.52 | 0.187 | 0.85 |
| Height | 1.561± 0.030 | 1.555 ± 0.029 | - 0.821 | 0.415 |
| Weight | 53.63± 4.694 | 56.27 ± 7.705 | 1.599 | 0.115 |
| BMI | 22.02±1.96 | 23.31 ± 3.38 | 1.805 | 0.076 |
| Blood sugar | 94± 5.336 | 100.06±6.443 | 3.972 | 0.000** |
| Hb | 12.1±0.527 | 10.07 ± 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.

| | Control (n=30) | Study (n=30) | t value | p value |
|---|---|---|---|---|
| MeanHR | 74.00 ±7.37 | 82.20±6.29 | 4.635 | 0.000** |
| SBP | 107± 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 | 74.00 ± 7.37 | 82.2±6.29 | 4.635 | 0.000** |
| Mean RR | 814.15±79.80 | 722.26±78.04 | -4.509 | 0.000** |
| SDNN | 52.59 ± 14.90 | 31.76± 19.91 | -4.588 | 0.000** |
| RMSSD | 62.29± 19.86 | 37.96±15.65 | -4.108 | 0.000** |
| NN50 | 139.63±52.42 | 59.70±12.14 | -4.493 | 0.000** |
| pNN50 | 38.50± 15.92 | 14.62±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 $ms^2$ | 2397.62±398.98 | 762.15±97.19 | -5.258 | 0.000** |
| LF $ms^2$ | 1038.44±119.62 | 311.28±69.94 | -4.216 | 0.000** |
| HF$ms^2$ | 1406.05±799.54 | 450.86±63.72 | -5.318 | 0.000** |
| LF% | 38.39±15.15 | 38.915±16.58 | 0.127 | 0.899 |
| HF% | 77.55±10.76 | 53.56±19.51 | -1.179 | 0.243 |
| LF/ HF | 0.804±0.611 | 1.016±0.939 | 1.036 | 0.304 |
| LF n.u | 37.86±16.08 | 42.47±18.83 | 1.021 | 0.304 |
| HF nu | 60.01±15.60 | 57.07±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

Table V

Heart rate variability indices during one minute controlled Deep Breathing.

| Parameters | control (n=30) | Study (n=30) | t value | p value |
|---|---|---|---|---|
| Mean HR | 78.20±8.903 | 82.57±10.68 | 1.719 | 0.091 |
| Mean RR | 795.26±90.93 | 770.47±101.84 | -0.994 | 0.324 |
| SDNN | 99.02±32.93 | 94.47±77.26 | -0.297 | 0.768 |
| HF $ms^2$ | 1493.48±735.97 | 3074.187±1096.9 | 0.780 | 0.439 |
| HF % | 66.48±21.8 | 30.14 ± 13.28 | -0.906 | 0.369 |
| HF nu | 28.27±16.60 | 26.96 ± 12.97 | 0.520 | 0.605 |

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

$p<0.05$ - significant. HR – Heart Rate (in bpm- beats per minute), RR (in milliseconds),

SDNN – in milliseconds, 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. Also shows significant difference in both blood sugar level (mg/dl) and Hemoglobin level (gm %) between control and study group.

Table II 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. Also, 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 $millisecond^2$, %, normalised units [n.u.]) express vagal activity, Low Frequency band, 0.04- 0.15 Hz (LF power in $millisecond^2$, %, normalised units [n.u.] ) express combination of sympathetic and parasympathetic activity, LF/HF ratio which usually tells about sympathovagal balance were all analysed. Table IV, shows significant decrease in both LF and HF power (in $ms^2$) in study group compared to control. But increase in LF %, LFnu. and LF/HF, decrease in HF % and HFn.u. appreciated in study groupwas not significant.

Table V: depicts that during one minute controlled deep breathing, HR (bpm) is higher and RR interval(ms) is lower in study group but not significant. There shows insignificant decrease in SDNN, HF %, and HF n.u. in study group.

**DISCUSSION:**

Our study shows reduced HRV in mid trimester pregnant women, with increased Sympathetic and decreased parasympathetic modulation which goes in hand with Ekholm et al 1992(8), for increased sympathetic tone at mid pregnancy. Avery et al(9) and Ekholm & Piha et al 1993(10) which described the reduced HRV due to decreased parasympathetic activity at rest. This reduced HRV could have been contributed by many factors. It is well known fact that an increase in BMI is associated with reduced HRV(11, 12) (Schmid et al 2010 &Tonhajerovah et al).Weight gain in pregnancy usually 10 – 12 kg of which fat deposition accounts for 3.5kg(1). Here, there is mild difference in BMI between study and control groups (Study group -23.31 $Kg/M^{2,}$ control – 22.02$Kg/M^2$ ), but not significant. Hence, 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 gms percent (13). In accord with this, study group are not anaemic which has potential to reduce HRV.

Though subjects were screened for gestational diabetes, there is a significant increase in random blood sugar levelin study group (study group -100.06 mg/dl ; control – 94 mg/dl, ($p<0.01$).), but within the normal range. This significant blood sugar rise explains resistance to Insulin, a Glucose lowering hormone with advancing gestation. Literature work 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 come across in pregnancy with increasing gestational weeks.

There is a definite increase in Resting Heart Rate (RHR) in pregnant women at supine rest ($p<0.01$). This change in RHR may due to changes in the Blood volume. This increased blood volume about 40- 50 % in midtrimester pregnancy lead to increased venous return which in turn causes mechano electrical feedback due to stretch of SA Node there by increases RHR. 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 midtrimester 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 ($p < 0.01$), with Systolic BP: study group -101mmHg ; control -107mmHg and Diastolic BP :study group - 68mmHg ; control -74mmHg . BP which gives us the status of hemodynamic, varies throughout gestation period with maximum drop at midtrimester.

This decrease could be due to reduction in peripheral resistance in midtrimester . 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 essential for the foetal growth and development. Mean Arterial pressure (MAP) which is average pressure acting throughout one cardiac cycle is found to be decreased (control – 85.44 mmHg; study – 79.22; p <0.01)and indicates decreased perfusion pressure. Despite this MAP decrease, this uteroplacental flow is maintained by thisdecrease 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 PIH has an impact on the maternal ANS (19). Hence we selected normotensive pregnant women for assessing cardiac autonomic activity with blood pressure measurement as one of the main screening parameter.

Time Domain Measures:

The significant decrease in SDNN (31.76 ± 19.91, 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 well 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 obvious 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 heart period. 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 what going to give the autonomic modulation in the system.

LF(n.u.) is a marker of sympathetic activity and LF $ms^2$is a marker of combined sympathetic 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 balance 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 LFn.u. and decrease in HFn.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-HF ratio indicates increased sympathetic activity and decrease in this ratio indicates increased parasympathetic activity 22,23. LF/HF ratio is increased in pregnant women indicating sympathovagal balance shifting towards the sympathetic activation.(24). Here, the mechanism which shifts balance towards sympathetic activation is due to parasympathetic withdrawal as both LF $ms^2$and HF $ms^2$decreased significantly in pregnantwomen. HRV in Deep Breathing:

During one minute controlled deep Breathing, there is an increase in mean HR in pregnant women compared to control group but not significant. The

Deep breathing which is primarily mediated by vagal influence results in respiratory sinus (RSA) arrhythmia. This RSA is blunted in study group shown by decrease in HF power in study group. Similarly, in Ekholm et al (8), there was significant decrease in HF power. An increase in the time domain measures, HF in absolute power and HF in n.u in the controls seems to occur through a relative increase in vagal activity and a reduction in sympathetic activity observed during slow breathing. Slow breathing may reduce sympathetic activity by enhancing central inhibitory rhythms. The increase in tidal volume, which compensates for the reduced breathing rate in order to maintain minute ventilation (25) be responsible for these autonomic changes through a reduction in sympathetic activity(26) . It was cumbersome procedure that even after explaining the method of deep breathing of 6 breathes/min, subjects were unable to breathe as trained.

It is well known that respiratory drive in pregnancy is activated by the hormone progesterone, low expiratory reserve volume and compensated respiratory alkalosis. There is an increase in airway conductance by hormone induced bronchial dilation. Lung compliance is unaffected but chest compliance is affected to some extent, thereby total lung compliance is 5% less than non-pregnant women(7). The Tidal Volume is significantly increased in pregnancy about 40% at term. Due to the presence of foetus (or) enlarged gravid uterus , diaphragm is displaced upwards about 4 cm which compromises the functional residual capacity and residual volume about 20 % at term(7). Actually , for the increase in tidal volume in pregnancy there should be increase in HF power but there is blunted response which is in explainable as in Ekholm et al(8) . This reduced HRV in one minute controlled deep breathing in pregnant women indicates that cardiac vagal effects are diminished to a certain extent in pregnancy during midtrimester.

**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 Noradrenalin and pregnancy hormones are taken into considerations.

**CONCLUSION:**

HRV is reduced in pregnancy with sympathovagal balance shifting towards sympathetic excitation and parasympathetic withdrawal . Both the hemodynamic adaptation and neurohormonal system contribute to this sympathetic activation.

Thus, Autonomic function in pregnancy could throw some light on unveiled causes of hemodynamic adaptations that take place in pregnancy. Therefore, other than bedside tests of measurement of BP and biochemical tests done routinely in antenatal care check up, this highly non invasive technique HRV analysis would give ANS status in pregnancy

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