Evaluation of autonomic status during three trimesters of pregnancy

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Abstract

Background: During pregnancy many organ systems of women undergo several adaptations in order to accommodate physiological demands of the growing foetus. Role of autonomic nervous system has been proposed for adaptation of blood circulation to meet requirements of pregnancy. Response of autonomic nervous system may vary during different stages of pregnancy.

Objective: The aim of the study was to compare autonomic status of pregnant and non-pregnant females and observe changes in autonomic functions during the three trimesters of pregnancy.

Material and Method: The study was conducted on 120 subjects, 90 pregnant (30 from each trimester of pregnancy) and 30 non-pregnant healthy volunteers. Batteries of non-invasive cardiovascular reflex tests providing information about sympathetic and parasympathetic autonomic nervous system were used for the assessment of autonomic status.

Result: On comparing pregnant females with study group (30 from each trimester), evidence of increased sympathetic and decreased parasympathetic tone was obtained. Increase in resting heart rate and systolic blood pressure was noted to be maximum and statistically significant in 3rd trimester of pregnancy in comparison to controls, indicating increased sympathetic tone during pregnancy. The decreased parasympathetic tone in study group was indicated by lesser heart rate variability and decreased E:I ratio and 30:15 ratio. The cardiovascular response to sustained handgrip test and cold pressor test was found to be blunted in the study group indicating a decrease in total peripheral resistance.

Conclusion: We conclude that marked adaptive changes take place in cardiovascular and autonomic nervous system during different trimester of pregnancy in order to meet the physiological demands of the foetus and maintaining maternal cardiovascular integrity.

Keywords: Pregnancy, autonomic functions, cardiovascular reflex tests

Introduction

There are various anatomic, physiologic, and biochemical adaptations taking place during human pregnancy, that begin soon after fertilization and continue throughout gestation. An equally astounding fact is that the pregnant woman returns back almost completely to her pre-pregnant state following delivery and lactation. In order to accommodate to the physiological demands of the growing foetus, profound adaptive changes take place in almost every system of the body. Most of these changes are due to the activity of various sex steroids and other hormones secreted mainly by the placenta.[1]

Cardiac output in a typical 55 kg woman increases from about 4.8 l/min before fertilization to more than 7 l/min after first trimester and remains elevated until delivery. This change in blood volume, cardiac output, and stroke volume occurs during the first trimester of pregnancy to accommodate the

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growing foetus.[2,3] Between 10th and 20th week there is notable increase in plasma volume, which increases to about 50% of pre-pregnant level at the end of 3rd trimester resulting in an increase in the preload.

Vascular capacity increases due to increase in vascular compliance.[4] During first half of pregnancy there is reduced systemic vascular resistance and an increase in heart rate. Increase in systemic vascular resistance in response to isometric exercise may be existent during last trimester, consequent to a generalized reduction in sympathetic tone.[5]

Haemodynamic studies during pregnancy suggest that autonomic nervous activity in the early stages of pregnancy is in fact different from the pre-pregnant state. The role of autonomic nervous system has long been proposed for the adaptation of blood circulation to the requirements of normal pregnancy, as it plays a central role in maintaining homeostasis of the body. The response of the autonomic nervous system to haemodynamic changes and aortocaval compression which occurs during pregnancy may vary with the different stages of pregnancy.[6,7]

Beginning of pregnancy is associated with sympathetic reactivity and the latter half is characterized by increased hemodynamic stability.[8] A failure in haemodynamic adaptation has been shown to be associated with hypertensive disorders and foetal growth retardation during pregnancy.[9]

In the present study assessment of autonomic status was done using a battery of standard non-invasive cardiovascular reflex tests in 3 trimesters of pregnancy and non pregnant females. Autonomic nervous system can be non-invasively studied with the help of standardized cardiovascular reflex tests, such as heart rate variability, postural challenge test, sustained handgrip test, E/I ratio, 30:15 ratio, and cold pressor test.

Materials and Methods

The study was conducted in the autonomic function laboratory of Department of Physiology, UCMS and GTB Hospital, Delhi. The subjects were selected from the outpatient antenatal clinic of Department of Obstetrics and Gynaecology, GTB Hospital. Age matched employees and students of UCMS and GTBH were taken as controls for the study. Informed written consent of the procedure performed was taken from all the subjects and healthy volunteers. Ethical clearance from the Institute Ethical Committee was also obtained.

Inclusion and grouping criteria:

The study was conducted on 90 pregnant women, who were divided into the following 3 groups based on their period of gestation: group I: 8–12 weeks, group II: 24–32 weeks, group III: 34–40 weeks

Each group had 30 subjects. The subjects were selected randomly from the last 4–8 weeks of each trimester.

Thirty age matched non-pregnant healthy volunteers were included as control group.

Exclusion criteria:

Pregnant females having any of the following complications were excluded from the study: multiple pregnancies, pregnancy induced or essential hypertension, diabetes mellitus or gestational diabetes or any other medical or surgical illness.

All subjects and controls were tested under similar laboratory conditions. The subjects were allowed to get familiarized to the experimental and environmental conditions of the laboratory. The following tests were performed to evaluate the autonomic status:

Basal heart rate variability, E/I ratio, 30:15 ratio, Sustained handgrip test and Cold pressor test.

To assess the autonomic status, the ECG was recorded from standard leads using the student physiograph machine (INCO), while the blood pressure was measured with a mercury sphygmomanometer.

Test for autonomic activity (tone)

- Basal heart rate variability: After making the subject lie down supine for 5 min, lead II ECG was recorded for 5 min using student physiograph machine. Each R–R interval was determined. The minimum and maximum R–R intervals were identified and converted into heart rate and expressed as the heart rate variability in one minute.

Tests for sympathetic reactivity

- Postural challenge test: Two non-invasive blood pressure readings were taken by using standard mercury sphygmomanometer in supine position after 5 min of rest and the average of 2 readings was taken. Subject was then instructed to stand up without any support for 2 min at the end of which blood pressure was recorded again. Change in systolic and diastolic blood pressure was calculated.
- Sustained handgrip test: After recording basal BP in sitting position, the subject was asked to grip a hand dynamometer 3 times with her dominant hand using maximal effort, at an interval of 2 min each. All the 3 readings on the dynamometer (force generated by the subject in kg) were noted and 30% of mean maximal voluntary capacity was calculated. The subject was then asked to grip the dynamometer at 30% of her maximum voluntary capacity and to maintain it for 2–3 min. BP was recorded on the contralateral arm every minute during contraction. Maximum change in both systolic and diastolic BP was calculated as compared with the basal BP.
- Cold pressor test: After making the subject sit comfortably on a chair, basal BP record was taken. Then she was instructed to immerse her dominant hand till wrist in cold water (temperature 6–8ºC) for 2 min. BP was taken every 1 min. Change in BP was calculated by comparing the recordings during immersion with the basal BP record.

Tests for parasympathetic reactivity

- Heart rate variation during respiration (E/I ratio): After lying down supine for 2–5 min, lead II ECG was recorded. After explaining the procedure, the subject was instructed to take deep inspiration followed by deep expiration each lasting 5 s for 1 min (6 breaths/min)while continuous lead-II ECG was being recorded. The result was expressed in terms of ratio of average of 6 maximum RR intervals during expiration to average of 6 minimum RR intervals during inspiration.
- 30:15 ratio: The subject was asked to lie supine for 5 min and then to stand up unaided and erect as quickly as possible. During this period continuous lead II ECG was recorded and the point was marked to identify the time of standing. 30:15 ratio was calculated by taking the ratio of maximum R–R interval around 30th beat to minimum R–R interval around 15th beat after standing.

Results

Table 1 depicts the age, height, weight, and BMI of the subjects in different groups. Except for the significantly higher weight and BMI in subjects of group III rest of the parameters were comparable.

Table 2 shows the basal heart rate variability among the different study groups. Average minimum heart rate in the study groups was higher as compared to controls and was statistically significant. The average minimum heart rate in group III was significantly higher than that of group I and II. Average maximum heart rate in control and group I was significantly less than group II and III. Highest values of average minimum and average maximum were observed in group III. The study groups showed a lesser heart rate variability in comparison to controls.

Table 3 shows resting mean blood pressure (after 5 min of lying down) in various groups. In comparison to the control group, systolic BP was observed to be higher in all study groups with group III showing maximum value, which was statistically significant. The resting diastolic BP in the study groups showed no significant difference as compared to that of the control group.

Tables 4 and 5 depict change in SBP and DBP on standing (2 min) after lying down supine for 5 min. A marked individual variation in blood pressure response to standing was observed among subjects of different groups and within the groups also. The average increase in SBP and DBP was maximum in group III. The average increase and decrease in systolic and diastolic blood pressure in the control and study groups was within 10 mmHg.

Table 6 shows change in systolic and diastolic blood pressure on performing sustained handgrip test. Increase in both systolic and diastolic blood pressure was observed in all the groups with the control group showing maximum rise in both systolic and diastolic blood pressure. The average rise in both systolic and diastolic blood pressure in all the groups was within 20 mmHg.

Table 7 shows changes in systolic and diastolic blood pressure on performing cold pressor test in various groups. Increase in both systolic and diastolic blood pressure was observed in all the groups with the control group showing maximum rise in both systolic as well as diastolic blood pressure, although this difference was statistically insignificant.

Table 1: Demographic profile

	Age (mean ± SD)	Height (mean ± SD)	Weight (mean ± SD)	BMI (mean ± SD)
Control	24.90 ± 3.98	1.55 ± 0.04	50.40 ± 6.53	20.98 ± 2.50
Group I	23.90 ± 3.22	1.54 ± 0.04	49.30 ± 8.39	20.69 ± 2.82
Group II	23.47 ± 2.45	1.53 ± 0.03	49.47 ± 7.19	21.20 ± 2.59
Group III	23.53 ± 2.60	1.54 ± 0.05	54.60 ± 5.88**	22.93 ± 2.08**

**$p<0.05$ as compared to other groups

Table 2: Heart rate

Groups	Heart rate (per min)			
	Range	Min (mean ± SD)	Max (mean ± SD)	Variability
Control	50 – 100	64.53 ± 10.74*	81.70 ± 9.25**	17.17
Group I	60 – 109	74.97 ± 10.41	89.50 ± 9.82**	14.53
Group II	57 – 133	83.77 ± 15.62	98.87 ± 16.31	15.1
Group III	52 – 133	84.13 ± 16.10#	99.40 ± 15.02	15.27

*$p<0.05$ as compared to 3 study groups
#$p<0.05$ as compared to other three groups
**$p<0.05$ as compared to group II and III

Table 3: Resting (supine) blood pressure

Groups	Resting (supine) blood pressure (mmHg)	
	SBP (mean ± SD)	DBP (mean ± SD)
Control	106.37 ± 7.28	68.20 ± 6.34
Group I	107.97 ± 7.51	68.83 ± 5.23
Group II	109.47 ± 8.37	65.00 ± 5.58
Group III	112.70 ± 8.50**	68.83 ± 8.71

**p<0.05 as compared to other groups

Table 4: Change in systolic blood pressure on standing after lying down supine for 5 min

Group (n=30) in all	Increase	Decrease
Groups		
Controls		
No. of subjects	17 (56.6%)	13 (43.3%)
Mean change (mmHg)	7.35	6.92
Group I		
No. of subjects	23 (76.6%)	7 (23.3%)
Mean change (mmHg)	5.3	5
Group II		
No. of subjects	21 (70.0%)	9 (30.0%)
Mean change (mmHg)	7.85	9
Group III		
No. of subjects	20 (66.66%)	10 (33.33%)
Mean change (mmHg)	10.1	8.6

Table 5: Change in diastolic blood pressure on standing after lying down supine for 5 min

Group (n=30) in all	Increase	Decrease
Groups		
Controls		
No. of subjects	22 (73.33%)	7 (23.33%)
Mean change (mmHg)	5.63	2.57
Group I		
No. of subjects	20 (66.66%)	8 (26.66%)
Mean change (mmHg)	4.45	2.75
Group II		
No. of subjects	25 (83.3%)	5 (16.66%)
Mean change (mmHg)	6.52	2.4
Group III		
No. of subjects	21 (70.0%)	8 (26.66%)
Mean change (mmHg)	9.76	5.37

The average rise in both systolic and diastolic blood pressure in all the groups was within 20 mmHg.

Table 8 depicts E:I ratio and 30:15 ratio in various groups. The study group showed a decrease in E:I ratio and 30:15 ratio as compared to the control group and this difference was found to be statistically significant.

Discussion

The salient features of the results in the present study revealed a significantly higher resting HR (Table 2), decreased heart rate variability (HRV),lower E:I and 30:15 ratio (Table 8), a higher resting mean SBP (Table 3) in the study groups as compared to those for the control group and an increase in SBP and DBP in response to standing from supine which was maximum in group III (Tables 4 and 5).

In response to handgrip test and cold pressor test the increase in SBP and DBP in all groups was less than that seen in the control group (Tables 6 and 7).

The increased heart rate in the study group seems a good evidence of increased sympathetic or reduced parasympathetic tone in the study group which gets further reinforced by decreased resting HRV and lower E:I and 30:15 ratio. All findings are towards a decreased parasympathetic tone during pregnancy. Gandhi et al 2014 [10]have also reported inhibition of resting parasympathetic activity and an increment of sympathetic modulation during 3rd trimester of pregnancy whereas a generalized reduction of sympathetic tone during pregnancy has been suggested by Ekholm et al.[5] Increased heart rate can also be explained by the general increase in metabolic rate, by about 15% by the end of 3rd trimester of pregnancy under the influence of increased secretion of various hormones like sex hormones (oestrogen and progesterone), thyroxine, and adrenocortical hormones during pregnancy.[11] Some of these hormones directly influence the activity of the SA node (pacemaker) in causing positive chronotropic effect.

The average resting heart rate variability was observed to be less during pregnancy in comparison to non-pregnant healthy controls (Table 2). Similar findings of higher resting heart rate and lesser heart rate variability during pregnancy have been reported by Clark et al, 1989 and Ekhlom et al 1992.[12, 13]

Resting systolic blood pressure and postural challenge test- Resting systolic blood pressure of women in the study group III (3rd trimester of pregnancy) was significantly higher than that for non pregnant women in the control group (Table 3). The increase in systolic blood pressure can also be attributed to increase in cardiac output. Increase in cardiac output during pregnancy has been reported by a number of workers, they attribute this increase in cardiac output to increase in heart rate and stroke volume (due to increased intravascular volume during pregnancy).[2]

Postural challenge test revealed an increase in systolic blood pressure on standing in more number of subjects of the study groups as compared to the controls (Table 4). This effect again suggests over compensation by baroreceptor reflexes accompanied by an increased sympathetic tone. During pregnancy, diminished parasympathetic input to heart may be

Table 6: Sustained handgrip test

Group	Basal		During		Change	
	SBP	DBP	SBP	DBP	SBP	DBP
Control	107.50 ± 8.10	71.97 ± 6.51	126.13 ± 10.10	89.60 ± 7.27	18.63 ± 5.68**	17.63 ± 6.21
Group I	108.93 ± 9.27	71.07 ± 5.63	126.20 ± 9.94	87.13 ± 5.65	17.27 ± 5.11	16.07 ± 4.31
Group II	112.93 ± 8.15	70.07 ± 7.27	129.40 ± 9.51	86.53 ± 6.62	16.47 ± 4.80	16.47 ± 4.69
Group III	120.17 ± 11.19**	75.50 ± 9.36	134.73 ± 12.38**	91.53 ± 8.69	14.57 ± 5.73	16.03 ± 7.06

**p<0.05 as compared to group III

Table 7: Cold pressor test

Group	Basal		During		Change	
	SBP	DBP	SBP	DBP	SBP	DBP
Control	107.80 ± 7.43	71.87 ± 6.17	127.07 ± 9.29	90.00 ± 6.17	19.27 ± 4.74	18.13 ± 6.17
Group I	110.07 ± 7.79	70.53 ± 5.75	127.40 ± 8.73	86.73 ± 5.52	17.33 ± 4.65	16.20 ± 4.71
Group II	113.27 ± 7.97	70.53 ± 6.89	130.87 ± 9.03	85.47 ± 7.33	17.60 ± 5.16	14.8 ± 3.96
Group III	118.73 ± 10.62	75.20 ± 8.80	133.67 ± 10.65	89.97 ± 7.26	14.93 ± 5.27	14.77 ± 4.94

Table 8: Change in E:I ratio and 30:15 ratio

Groups	E:I Ratio	30:15 Ratio
Control	1.43 ± 0.16**	1.38 ± 0.22**
Group I	1.28 ± 0.17	1.25 ± 0.15
Group II	1.30 ± 0.17	1.27 ± 0.16
Group III	1.31 ± 0.13	1.29 ± 0.19

**p<0.05 As compared to study groups

attributed to reduced baroreceptor sensitivity, impaired vagal afferents to brain,and altered efferent signals to the heart.[14]

No significant change in diastolic blood pressure was observed between the study groups and controls, both at rest (Table 3) and in response to standing (Table 5). This indicates that the efferent sympathetic pathway either remains more or less unaffected or gets balanced by vasodilator effect of progesterone during pregnancy.[4] A mild decrease in diastolic blood pressure in group II i.e. 2nd trimester of pregnancy was observed which can be explained by a decrease in peripheral resistance due to vasodilatation caused by increased concentration of progesterone.

Similar decrease in diastolic blood pressure has been reported by Ekholm et al 1992[13] in their study on cardiovascular autonomic reflexes in mid pregnancy as compared to non-pregnant subjects.

In contrast Thomas RE et al.[15] observed significant fall in SBP in response to postural changes during 1st trimester but not during 2nd and 3rd trimester when compared to controls. Panja et al.[16] have reported unaltered postural tachycardia index (PTI) during early stages of pregnancy but a significantly reduced PTI during last trimester of pregnancy.

Handgrip test and Cold pressor test - Present study showed both systolic and diastolic blood pressure response to sustained handgrip test and cold pressor test to be blunted during pregnancy in comparison to the controls (Tables 6 and 7). The lesser pressor response to sustained handgrip test and cold pressor test could be due to higher basal sympathetic tone in the study group subjects. Cardiovascular responses to sustained handgrip test and cold pressor test are mediated by sympathetic stimulation.[17,18] Panja et al[16] in 2013 also observed weaker response during 2nd and 3rd trimester of pregnancy as evident by significant reduced alteration in DBP.

According to Nilekar et al. 2012[19] have reported significantly altered BP response to postural changes and cold pressor test in 1st trimester of pregnancy reflecting higher sympathetic activity and no change in parasympathetic activity.

E:I ratio and 30:15 ratio values of the study groups although within the normal range[20] were significantly lower as compared to those of the control group (Table 8). Ekholm et al. 1994,[14] Panja et al.[16] and Airaksinen et al. 1987[21] in their longitudinal study on pregnant females have reported a similar decrease in E:I ratio as pregnancy progressed. E:I ratio and 30:15 ratio have been used as good indices of vagal activity by many workers,[17,18,20] hence our results strongly suggest a decrease in parasympathetic tone during pregnancy.

In the present study higher resting heart rate, higher resting SBP, and increase in BP with postural change are suggestive of increased sympathetic activity and a decreased heart rate variability and lower E:I, 30:15 ratio are indicative of decrease in vagal tone during pregnancy. Kuo et al. in 2000[22] found biphasic changes in autonomic nervous activity during pregnancy. They reported higher vagal and lower sympathetic activity during first trimester of pregnancy which changed to higher sympathetic and lower vagal activity in 3rd trimester. Hemodynamic changes of pregnancy and aortocaval compression due to progressively enlarging gravid uterus have been suggested to be responsible for biphasic changes in autonomic activity.

Differences in HRV between premenopausal and postmenopausal women pointing to increased parasympathetic activity and involvement of increased estrogen level have been demonstrated.[23,24] Oestrogen receptors in heart, vascular smooth muscle and autonomic brainstem centres are suggested of involvement in regulation of cardiovascular system.[25] Kristiansson et al[26] have also suggested influence of hormones of pregnancy on haemodynamic changes in pregnancy. However, a link between sex hormones and changes in autonomic functions needs to be further investigated.

Pal GK in 2009,[27] suggested that the predictive knowledge of sympathovagal imbalance can be utilized in designing the prevention and management of pregnancy induced hypertension (PIH). In a recent study by Kapoor N in 2011[28] have suggested simple non-invasive tests (hand grip test and cold pressor test) could be used as provocative test in screening women at higher risk of developing pregnancy induced hypertension. Such screening tests require more studies in this area.

Strength and Limitations

In present study autonomic function tests of pregnant women from all the 3 trimesters were compared with those of non-pregnant group. But autonomic changes could not be recorded with progression of pregnancy in the same participant so as to correlate magnitude of autonomic change with progression and outcome of the pregnancy.

Conclusion

Present study has provided evidence of increased sympathetic activity and a decrease in vagal tone during pregnancy by comparing various autonomic function tests conducted on well matched non-pregnant and pregnant women belonging to different trimesters of pregnancy. However, more longitudinal studies to establish norms after correlating autonomic function tests with progression and outcome of pregnancy are warranted.

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