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A study of cardiovascular autonomic function in normal pregnancy

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Abstract: *Objective:* The present study was designed to evaluate the physiological responses to noninvasive cardiovascular autonomic function tests in normal pregnancy and compare them with non- pregnant controls. *Materials and Methods:* The study population comprised of 90 apparently healthy, pregnant women divided equally into three groups based on their period of gestation and 30 otherwise healthy, non-pregnant women as controls. The standard autonomic function tests based on cardiovascular reflexes, including heart rate response tests and blood pressure response tests were performed. *Result:* It was observed that variability of mean between and within all the population groups and controls was significantly different. Multiple comparison analysis revealed a significantly lower Deep Breathing Difference in pregnant subjects, significant difference in Valsalva Ratio in third trimester group, a significantly lower Postural Tachycardia Index only during last trimester and a significantly higher fall in systolic blood pressure on standing only during 1st trimester. A significantly lower alteration in diastolic blood pressure during isometric handgrip in later trimesters and a significant increase in overall cardiovascular autonomic score between and within all groups were also observed. *Conclusion:* The observations serve to corroborate that the cardiovascular indices in pregnant women are significantly altered in comparison to non-pregnant women, thus highlighting the importance of cardiovascular monitoring during pregnancy. The study also helped to reaffirm the efficacy of simple cardiovascular reflex tests in research on pregnancy physiology.

Keywords: Maternal Hemodynamics, Sympathetic Cardiovascular Control, Parasympathetic Cardiovascular Control, Cardiovascular Reflex Tests.

Introduction

Normal pregnancy has been documented to be accompanied by marked alteration in maternal circulation, including an increase in cardiac output by about 45% and a decrease in peripheral vascular resistance, manifested by a progressive fall in blood pressure during second trimester [1]. It has also been noted that blood volume and stroke volume begin to change during first trimester to accommodate the growing fetus [2]. In pregnancy associated changes, the autonomic nervous system plays a fundamental role in adapting the heart and circulation to this dramatic shift in blood volume and increased peripheral demands [3]. An increased heart rate during pregnancy is mediated by the lower level of parasympathetic/vagal discharge [4]. A well controlled interaction between the sympathetic and parasympathetic system is necessary for adapting the cardiovascular hemodynamic changes during normal pregnancy, failure of which may result in pregnancy complication [4]. Thus it becomes imperative to understand the physiological basis of autonomic nervous system control during normal pregnancy in greater detail. Alteration in autonomic cardiovascular control has been implicated to play an important etiological role in certain conditions like pregnancy induced hypertension or insufficient uteroplacental blood flow [5].

A battery of standardized quantitative autonomic function tests using cardiovascular reflexes, which are otherwise simple, non-invasive and reproducible, have been used to assess cardiovascular autonomic function. The important parasympathetic cardiovascular autonomic reflex tests include Valsalva maneuver, heart rate variability during orthostatic test and deep breathing test. The important sympathetic cardiovascular autonomic reflex tests are blood pressure changes during isometric hand grip exercise and orthostatic test [6]. These tests for clinical assessment of autonomic circulatory control in humans have been of great interest for researchers involved in field of cardiovascular physiology in pregnancy. The present study was designed to evaluate the physiological cardiovascular autonomic response to normal pregnancy and comparing these cardiovascular indices with those in non-pregnant women from the same population utilizing simple, noninvasive cardiovascular autonomic function tests.

Material and Methods

The present study was undertaken at the Department of Physiology with collaboration of Department of Gynecology and Obstetrics, Sri Devaraj Urs Medical College and R. L. Jalappa Hospital, Kolar, Karnataka. The study population comprised of 90 apparently healthy, pregnant women selected by standard random sampling procedure from a cohort of subjects attending R. L. Jalappa Hospital for routine antenatal care. These subjects were classed into three groups with 30 subjects in each group based on their period of gestation; viz. Group 1 consisted of 30 subjects in their first trimester of pregnancy, Group 2 in their second and Group 3 in their third.

Inclusion criteria consisted of apparently healthy pregnant women with singleton pregnancy in the age group of 20 to 40 years. All Pregnant women in the age group of less than 20 or greater than 40 years, with multiple pregnancies, gestational diabetes, pre-eclampsia and eclampsia, history of cardiovascular or lung diseases, smokers or on any drugs that might affect autonomic function, e.g. adrenergic receptor stimulants and blockers and those with hemoglobin < 10 gm% were summarily excluded from the study. The Control group comprised of 30 otherwise healthy, non-pregnant women volunteers randomly selected from the students, staff members and relatives of patients. Written informed consent was obtained from all participants of the study after explaining the purpose and procedural details. The study was approved by Institutional Ethics Committee. All the tests were conducted between 11.00 and 13.30 hours. The temperature of the examination room was maintained between 22 to 27°C during the tests. The subjects had been instructed to abstain from coffee, tea, cola e.t.c. for a minimum period of 12 hours before the tests. After thorough examination of the subjects as per proforma, the subjects were asked to relax in supine position for 30 minutes. The resting Heart Rate (HR) was recorded on a standard ECG from lead II and Blood Pressure (BP) was measured. The standard autonomic function tests based on cardiovascular reflexes, including HR response tests and BP response tests were performed after demonstrating the same to the subjects. The test for HR response to deep breathing was performed as per standard procedure described by Piha SJ [6].

Test results were expressed as Deep Breathing Difference (DBD) calculated as the mean of the differences between the maximal and minimal heart rate in 6 respiratory cycles. HR response to Valsalva maneuver was performed as per procedure described by Hirsch JA, et al [7]. The HR changes induced by the Valsalva maneuver were expressed as Valsalva Ratio (VR) and were calculated as the ratio of maximum R-R interval after the maneuver to minimum R-R interval during the maneuver [8]. HR response to standing, expressed as Postural Tachycardia Index (PTI) was performed as per standard procedure described by Ewing DJ, et al [9]. PTI was calculated as the ratio of maximum RR interval around 30^{th} beat to Minimum RR interval around 15^{th} beat.

The test for BP response to standing (Orthostatic test) was performed as per standard procedure after Piha SJ [6]. The fall in systolic blood pressure (SBP) between subject in supine position and at 30 second of standing was measured. BP response to isometric handgrip was measured as per standard procedure described by Piha SJ [6]. The difference in diastolic blood pressure (DBP) was noted in non-exercising arm between subject at rest and at 3 minutes of sustained handgrip was measured [10]. The data collected were statistically analyzed. One way ANOVA and Multiple comparison analyses were performed to compare the cardiovascular indices between the three study groups and controls to calculate whether any significant difference existed between these groups. Further, each subject was assigned a Cardiovascular Autonomic Score (CAS) after classification of each of their test results as normal, borderline and abnormal following the criteria laid down in Table 1 and an overall CAS between 0 and 10 was calculated for each subject.

Table-1: Criteria for Assignment of Cardiovascular Autonomic Score

No.	Tests	Normal (Score 0)	Borderline (Score 1)	Abnormal (Score 2)	References
(A)	**Heart Rate Response Tests**				
1.	Heart Rate Response to Deep Breathing Expressed as Deep Breathing Difference (Beats / Minute)	≥ 15	11 to 14	≤ 10	[19]
2.	Heart Rate Response to Valsalva Maneuver Expressed as Valsalva Ratio	≥ 1.21	1.11 to 1.20	≤ 1.10	[13]
3.	Heart Rate Response to Standing Expressed as Postural Tachycardia Index	≥ 1.04	1.01 to 1.03	≤ 1.00	[9]
(B)	**Blood Pressure Response Tests**				
4.	Blood Pressure Response to Standing (Orthostatic Test) Expressed as Fall in systolic blood pressure (mm Hg)	≤ 10	11 to 29	≥ 30	[20]
5.	Blood Pressure Response to Isometric Handgrip Expressed as Rise in diastolic blood pressure (mm Hg)	≥ 16	11 to 15	≤ 10	[10]

Results

The mean and standard deviation of cardiovascular autonomic test results were calculated. One way ANOVA to compare mean between the different groups of study population and controls was performed and F-distribution and p value calculated. These results are depicted in table 2. It was observed that variability between and within all the population groups and controls was significantly different.

Multiple comparison analysis for individual test results between different groups of study population and controls have been presented in table 3. A significantly lower DBD in pregnant subjects when compared to control group was noted. A significant difference in VR was observed between the control and third trimester group, between 1st trimester group and other trimester groups and between 2nd and 3rd trimester groups. HR response to standing expressed as PTI was observed to be significantly reduced only during last trimester of pregnancy. In the Orthostatic Test, the fall in SBP on standing was found to be significantly higher only during 1st trimester of pregnancy when compared to the controls. A significantly lower alteration in DBP during isometric handgrip was observed in later trimesters when compared to controls. Finally, a significant increase in overall cardiovascular autonomic score (CAS) was observed between all trimester groups and controls and further between each trimester group, increasing consistently with advancing pregnancy to reach its zenith at the 3rd trimester.

Table-2: Mean, Standard Deviation (SD) and one way ANOVA to compare Mean of Cardiovascular Autonomic Test Results between different groups of Study population and Controls

Tests	Controls n = 30		1st Trimester n = 30		2nd Trimester n = 30		3rd Trimester n = 30		Inference
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Heart Rate (HR) Response Tests									
HR Response to Deep Breathing Expressed as Deep Breathing Difference (Beats / Min)	22.53	9.48	13.03	3.43	6.26	4.10	6.50	6.89	F = 42.14 $p < 0.05$*
HR Response to Valsalva Maneuver Expressed as Valsalva Ratio	1.32	0.23	1.29	0.10	1.19	0.15	1.08	0.20	F= 17.27 $p < 0.05$*
HR Response to Standing Expressed as Postural Tachycardia Index	1.13	0.12	1.07	0.10	1.14	0.28	1.01	0.17	F = 7.25 $p < 0.05$*
Blood Pressure (BP) Response Tests									
BP Response to Standing (Orthostatic Test) Expressed as Fall in systolic blood pressure (mm Hg)	5.30	4.91	19.93	7.74	5.66	4.49	7.73	5.13	F = 46.45 $p < 0.05$*
BP Response to Isometric Handgrip Expressed as Rise in diastolic blood pressure (mm Hg)	17.4	4.43	18.20	2.74	3.80	3.49	17.53	2.86	F = 122.3 $p < 0.05$*
Autonomic Score	0.70	1.17	2.36	1.09	4.36	0.61	5.30	1.29	F = 109.6 $p < 0.05$*

* Statistically significant difference at 5 % level. Abbreviations: HR: Heart Rate, BP: Blood PressurE.

Table-3: Multiple Comparison analysis for individual Cardiovascular Autonomic Test Results between different groups of Study population and Controls

	HR Response to Deep Breathing (Deep Breathing Difference)			HR Response to Valsalva Maneuver (Valsalva Ratio)			HR Response to Standing (Postural Tachycardia Index)		
	Control	1st Trimester	2nd Trimester	Control	1st Trimester	2nd Trimester	Control	1st Trimester	2nd Trimester
1st Trimester	$p < 0.05$*			$p > 0.05$			$p > 0.05$		
2nd Trimester	$p < 0.05$*	$p < 0.05$*		$p > 0.05$	$p < 0.05$*		$p > 0.05$	$p > 0.05$	
3rd Trimester	$p < 0.05$*	$p < 0.05$*	$p > 0.05$	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*
	Orthostatic Test (Fall in systolic blood pressure)			**BP Response to Isometric Handgrip (Rise in diastolic blood pressure)**			**Autonomic Score**		
1st Trimester	$p < 0.05$*			$p > 0.05$			$p < 0.05$*		
2nd Trimester	$p > 0.05$	$p < 0.05$*		$p < 0.05$*	$p > 0.05$		$p < 0.05$*	$p < 0.05$*	
3rd Trimester	$p > 0.05$	$p < 0.05$*	$p > 0.05$	$p < 0.05$*	$p > 0.05$	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*

* Statistically significant difference at 5 % level. Abbreviations: HR: Heart Rate, BP: Blood Pressure.

Discussion

In present study, the heart rate response to deep breathing expressed as DBD, a measure of cardiac parasympathetic function was observed to be significantly lower in pregnant subjects when compared to control group and generally followed a decreasing trend with increase in gestation (Tables 2 and 3). This finding was in conformity with observation of Ekholm EMK, et al who have suggested a multifactorial basis for it with involvement at multiple levels of neuraxis including peripheral and central mechanisms [11]. A diminished parasympathetic input to the heart during pregnancy has been attributed to, among others, reduced baroreceptor sensitivity, impaired vagal afferents to brain and altered efferent signals to the heart [12]. A reduction in oscillation of right atrial distension arising from diminished pulsatility of venous return from the growing uterus has been described in pregnant subjects, which may account for the lowering of DBD in pregnancy.

A significant difference in VR was observed between the control and third trimester group, between 1st trimester group and 2nd and 3rd trimester group and finally between 2nd and 3rd trimester groups (table 3). From table 2, it was concluded that VR in pregnancy followed a downward trend through to the end of pregnancy, probably as a consequence of physiologic adaptation to chronic volume overload. These findings corroborated well with those of Souma ML, et al who have reported a higher VR for controls than the mean for every gestational group and a definite downward trend in the VR during later stages [13]. However, a few earlier studies, including one by Eneroth-Grimfors et al have reported unaltered VR during 1st and 3rd trimester registering a significant decrease only in 2nd trimester [14]. The apparent non conformity of these finding with those of present study may be due to the affection of cardiac responses with body position of the subject. While the present study was carried out with the subjects in sitting posture, these studies had been carried out with subjects in semi recumbent position. In contrast to VR showing a generally decreasing trend with advancing gestation, HR response to standing expressed as PTI was observed to remain unaltered during early stages of pregnancy. A significantly reduced PTI was found only during last trimester. Steven LC et al, in their study have noted such blunted heart rate response in primiparous women between 36 to 38 weeks of pregnancy and have suggested that the altered hemodynamic profile brought about by pregnancy may be more profoundly affected in late pregnancy by the effect of gravid uterus on venacaval and aortic blood flow when the subject is supine [15].

In the Orthostatic Test, the fall in SBP on standing was found to be significantly increased during 1st trimester of pregnancy when compared to the controls. A decrease in barorecepteor sensitivity, especially observed in early pregnancy may be attributed to this observed result perhaps signifying an incomplete adaptation of the cardiovascular system to the pregnant state. It has been noted that during second half of pregnancy, the increase in blood volume seemed to improve hemodynamic stability [16]. This has been adequately highlighted in the present study where no significant difference in fall in SBP on standing was observed between controls and 2nd and 3rd trimester groups. Similar findings have been reported by work of other of other researchers. For example, Thomas RE et al, have observed a significant fall in SBP in response to postural changes during 1st trimester but not during 2nd and 3rd trimester when compared to controls [17]. Cardiovascular response to isometric handgrip exercise, primarily mediated by sympathetic stimulation was observed to be weaker during 2nd and 3rd trimester of pregnancy as evidenced by a significantly reduced alteration in DBP in these two groups when compared to controls (Tables 2 and 3). It may be inferred that a smaller increase in vascular resistance in response to isometric exercise may be existent during the second half of pregnancy consequent to a generalized reduction in sympathetic tone during 2nd and 3rd trimester as postulated by Assali, corroborating the result of the present study [18]. Not surprisingly, the significant increase in overall cardiovascular autonomic score (CAS) between all trimester groups and controls and further between each trimester group, increasing consistently with advancing pregnancy to reach its zenith at the 3rd trimester (Tables 2 and 3) may serve to highlight the overall resultant alteration in hemodynamic profile in pregnancy brought about by an interplay of opposing factors, viz. increasing physiologic adaptation to the pregnant state, endeavoring to stabilize hemodynamics in meeting new demands versus the increasingly destabilizing effect of a growing uterus with advancing gestation.

Conclusion

The observations of the present study serve to corroborate that the cardiovascular indices in pregnant women are significantly altered in comparison to non-pregnant women. This finding may be useful in highlighting the importance of cardiovascular monitoring during pregnancy in order to detect abnormalities at an early stage. This is especially important in the context of a developing country like India where early detection of cardiovascular abnormality in pregnancy during routine antenatal visits may prove to be immensely helpful in preventing complications, which, in addition to endangering the lives of mother and baby, prove to be a heavy burden on the health care delivery system. The study also helps to reaffirm the efficacy of simple cardiovascular reflex tests in research on pregnancy physiology and precludes the need of more expensive, complex and invasive procedures requiring specialized facilities and personnel, unavailable in most developing countries, for assessing cardiovascular reflexes during pregnancy.

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