Uncomplicated hyperemesis gravidarum does not alter the course of cardiovascular changes during pregnancy

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Abstract: The purpose of this prospective longitudinal study was to investigate the maternal cardiac haemodynamic and structural changes that occur in pregnancies with uncomplicated hyperemesis gravidarum in a selected Malaysian population. Nine women underwent serial echocardiography beginning at 12 weeks of gestation and throughout pregnancy at monthly intervals. Their echocardiograms were repeated at 6 and 12 weeks following delivery to reflect the pre-pregnancy haemodynamic state. Cardiac output was measured by continuous wave Doppler at the aortic valve. Interventricular septum thickness was determined by M- mode echocardiography and ventricular diastolic function by assessing flow at the mitral valve with Doppler recording. Cardiac output showed an increase of 32.9% at 36 weeks and maintained till 40 weeks of gestation. Heart rate increased from 79 ± 6 to 96 ± 8 beats/min at 36 weeks. Stroke volume increased by 16.4 % at 40 weeks of gestation when compared to the baseline value. Systolic and diastolic blood pressure did not appreciably change but showed a lower reading during the mid-trimester period. Early inflow velocity of left ventricle did not show a rise while peak atrial velocity showed an increasing trend; thus the ratio of early inflow to peak atrial transport showed a declining trend from early pregnancy to term. End diastolic dimension of left ventricle and interventricular septum thickness showed an increased value at term. Uncomplicated hyperemesis gravidarum did not alter the haemodynamic changes throughout pregnancy and concur with established data for normal pregnancy.

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Physiological adaptive changes in the cardiovascular system have been measured since 1915 by various means, including Ficks,[1,2] dye dilution,[3,4] thermodilution,[5] thoracic electrical impedance,[6] radiocardiography[7] and echocardiography using M-Mode[8-11] and Doppler.[12,13] Traditionally cardiac output is said to increase by 40% in pregnancy. However the time course of the increase and contribution of heart rate and stroke volume have been controversial. No Malaysian data on cardiac changes in pregnancy were available at the time of conduct of this study.

Cardiac changes in pregnancy measured by invasive methods (dye dilution and thermodilution) have been cross sectional in nature (which have their inherent problems) unlike noninvasive methods like M-mode echocardiogram and Doppler which allow for longitudinal studies and are acceptable to patients. The same patient can undergo several measurements at different gestational weeks and she can serve as a control during post delivery period.

The aim of this study was to evaluate adaptive changes of the heart during pregnancies in a selected group of patients admitted in the first trimester for uncomplicated hyperemesis gravidarum.

The study was done at the Department of Obstetrics and Gynaecology in Ipoh Hospital from 1.10.1999 to 30.11.2000. The recruitment of the patients was based on convenience sampling of patients consenting to have echocardiography as this investigation is not part of the management protocol in the department. This approach inevitably led to the study being explorative in nature, limited to a small sample and not being able to include a control group. No funding was available.

Consenting non-obese patients with BMI 19-25 kg/m^2 were selected consecutively from cases admitted to the gynaecological ward for uncomplicated hyperemesis gravidarum. Gestational age was confirmed by obstetric ultrasonography.

Selection criteria included patients with hyperemesis gravidarum who did not have disturbances in serum electrolyte levels and ketonuria. They should have complete recovery from symptoms at the end of the first trimester. Hospital stay should not exceed 5 days.

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Only non-obese patients who were having normal, singleton pregnancies with confirmed gestational age were selected. They should also be consenting for the serial echocardiography as per study design.

Patients who refused to participate or who had medical illnesses which could affect the haemodynamic status viz. hypertension, diabetes mellitus, hyperthyroidism and anaemia were excluded. Anemia is defined as women with Hb<11 gm%.

Patients who failed to attend all serial echocardiogram evaluations throughout pregnancy and during the postpartum period were considered drop-outs and not included in the study.

Echocardiography was performed on each subject initially at 12 weeks of gestation, then at monthly intervals throughout pregnancy and at 6 and 12 weeks' post-delivery.

All investigations were performed at the noninvasive cardiac laboratory of Ipoh Hospital and performed by a single cardiac laboratory technician who is an experienced in echocardiograms working in the Department of Medicine. Echocardiograms were performed with Toshiba Corevision SSA-350A (1998). A 25 mHz convex phased array transducer for echocardiography and Doppler with onscreen measurement and 'freezing the image' facilities when necessary were used.

Patient was sitting on a chair for 15 minutes before blood pressure measurement was taken and a mercury sphygmomanometer with a standard sized cuff was used at the left arm. Systolic and diastolic blood pressures were taken at first and fifth Korotkoff sounds.

Echocardiograms and methodology were adopted from the work of Mabie *et al.*[14] The patient then underwent two dimensional, M-mode and Doppler echocardiography in the left lateral recumbent position with the head elevated 15 degrees. Initially the patient was examined with two dimensional parasternal long axis of the heart to measure the aortic diameter. This was followed by M-mode of the left ventricles with long axis of the heart with M-mode cursor bisecting the ventricles just below the tip of the mitral valve leaflets. The apical four chamber view was used for pulsed Doppler for assessment of transmitral flow velocities by placing the sample volume at the tip of open mitral valve. The cardiac measurements viz. cardiac output and fractional shortening (end diastolic dimension – end systolic dimension ÷ end diastolic dimension x 100) were done according to the method described by Mabie *et al.* [14]

Means and standard deviations were used to describe the demographic and haemodynamic data. Epi- info 2000 was used to calculate the means and standard deviations. Forty week values are taken from last echocardiography before delivery. This original study was carried out by the first author while fulfilling a post graduate degree requirement in 1999 where there was no Ethics Committee in the hospital. The study was approved by the Departments of Obstetrics & Gynaecology and Medicine in Ipoh Hospital. Informed consent was obtained from all participants.

Eighteen women fulfilled the criteria for inclusion. However, only nine women were included in the study as the others did not comply with all echocardiographic examinations at the stipulated gestational age including postpartum examinations. All subjects delivered between 39 and 41 weeks.

The subjects' demographic data are shown in Table I, and that of cardiac and haemodynamic parameters in Table 2.

Cardiac output

Figure 1 and Table II showed that cardiac output increased throughout pregnancy representing a 32.9 percent increase in cardiac output above non-pregnant values (6.6 ± 0.6 at 36 and 40 weeks vs 4.9 ± 1.3 at 12 weeks post partum).

Heart rate (HR)

Heart rate began to rise at 16 weeks having increased to 96.3 ± 8 at 36 weeks of gestation. This represents 21.5% increase from non- pregnant values at 12 weeks post partum (82.6 ± 9.6).

Stroke volume and gestational age (SV)

Stroke volume (Figure 3) at 40 weeks was 71 ± 7.9 which was higher than the 'control' (post partum) value 59.2 ± 10.6 ml. This represents 16.4% above non-pregnant values.

Systolic and diastolic blood pressures

Both systolic and diastolic blood pressures (Fig 4) showed a slight decrease in midtrimester before rising back to pre-pregnant values at term.

Body surface area and cardiac output

Increase in body surface area (Figure 5) during pregnancy is associated with a concomitant increase in cardiac output. The changes in both parameters were more pronounced with the rise in body surface area being more significant in the second trimester from 20 weeks of gestation to 32 weeks of pregnancy.

Early inflow velocity and peak atrial transport velocity

Early inflow velocity (Figure 6) which signifies early ventricular filling during diastole did not show an increase compared to peak atrial transport velocity. Peak atrial transport velocity is the measurement for late ventricular filling which coincides with atrial contraction. Peak atrial transport velocity showed a gradual increase throughout the pregnancy, thus the ratio of early inflow to peak atrial transport showed a declining trend from early pregnancy to term.

End diastolic dimension (EDD) and interventricular septum thickness (ST)

End diastolic dimension of the left ventricle is the measurement used to describe the internal diameter of the left ventricular cavity at the end of the diastolic phase and septal thickness and posterior wall thickness is used to calculate the ventricular mass. The posterior wall thickness was not measured in this study and hence we were unable to calculate the left ventricular mass. The graph (Figure 7) showed an increase in both the internal diameter of left ventricle during diastole despite an increase in the interventricular septal thickness compared to non-pregnant values (Figure 7).

Fractional shortening (FS)

Fractional shortening is a widely used index of systolic function of left ventricle. The graph (Figure 8) showed some degree of reduced left ventricular function (but within the normal limit). Normal values for fractional shortening are above 30%. Both fractional shortening and end diastolic dimension showed reduction in the postpartum period.

Our study has demonstrated that there is increase in absolute values of cardiac output, stroke volume, heart rate, flow velocities of the heart through the mitral valve, thickening of the interventricular septum and end diastolic dimension of the left ventricle during pregnancy compared with postpartum values (which presumably are equivalent to pre-pregnant values). Blood pressure essentially remained the same with lower value at mid-trimester and a decrease in fractional shortening. These values cannot fully reflect the cardiac changes in the healthy pregnant Malaysian women population as the numbers of women who were studied were only 9 in number. A larger sample size would be useful.

The increase in cardiac output occurs early in pregnancy before 12 weeks of pregnancy. Robson *et al*[15] showed a significant increase in cardiac output at 5 weeks of gestation which then progressively increased until 24 weeks of pregnancy and maintained until term. We were unable to demonstrate an early increase at 5 weeks of gestation as our subjects were recruited into the study only at 12 weeks of gestation. It appears that cardiac output continues to increase at least until

36 weeks of gestation. This is in agreement with Mabie *et al*[14] who showed an increase until 38 weeks of pregnancy with peak values at 38 weeks. In our study peak values occurred at 36 weeks of pregnancy and maintained until term. Easterling *et al*[12] showed peak values at 34 weeks. The latter reported that in 9 percent of women the cardiac output decreases 1L/min or more. Others have reported a larger percentage of increase in cardiac output, quoting values up to 53 percent.[14] Our study showed an increase of 33 percent. The body surface area of patient studied in our context (Asian) differs considerably compared to Caucasians (1.67 ± 0.2 versus 1.53 ± 0.09).

In our study it was noted that both heart rate and stroke volume increases gradually up to term whereas some studies have reported that stroke volume only increases up to mid-trimester and then plateaus or even decreases at term.[15] Blood pressure did not significantly increase during pregnancy but showed a lower value in mid-trimester.[16] The fall in blood pressure has been attributed to a reduction in systemic vascular resistance. Robson *et al*[15] showed a gradual fall in systemic vascular resistance beginning at 5 weeks.

We have also demonstrated that the increase in cardiac output is in tandem with the increase in maternal body surface area a necessary adaptation for optimum maternal tissue perfusion.

Blood flow to the left ventricle through the mitral valve during diastole is phasic in nature. Rapid filling due to differential pressure gradient between the left atrium and the left ventricle contributes to the major component of volume increase. Atrial contraction only contributes about 15 percent of the volume.[17] The early inflow velocity corresponds to rapid ventricular filling and peak atrial transport velocity corresponds to atrial contraction. Various factors influence the shape of these velocities viz. age, heart rate, preload, after load, systolic function, atrial function and respiration.[16] The results of the flow velocities through the mitral valve in our study are similar to that reported by Mabie *et al.*[14] Early inflow velocity essentially remained the same but peak atrial transport velocity gradually increased throughout pregnancy, hence the ratio of both velocities show a gradual reduction towards term. Possible explanations for this have been noted by Mabie *et al*[14] in that the increased left ventricular preload raised left ventricular end diastolic pressure, requiring an increased force of atrial contraction to complete ventricular filling and the increased wall thickness reduced ventricular compliance necessitating more powerful atrial contraction or a combination of both.

Changes in fractional shortening have been demonstrated. There seems to be a reduction in fractional shortening implicating a reduction in left ventricular systolic function. This needs further exploration considering the small sample size in our study.

Cardiac adaptions in pregnancy bear important implications in terms of fluid management especially in the pregnancies complicated by various medical disorders like severe pre-eclampsia and stenotic valvular heart disease. A thorough knowledge of normal physiological changes goes a long way to accurate fluid therapy and appropriate use of drugs acting on the extracellular fluid compartment.

This study was carried out on patients with uncomplicated hyperemesis gravidarum i.e. the patients did not have any electrolyte imbalance or ketonuria and therefore would mimic normal pregnancies. It is therefore only to be expected that the findings in this study should reflect on cardiac adaptations of normal pregnancy. The lack of a control group is realized. However, considering cardiac changes in pregnant women return to normal six weeks postpartum, performance of echocardiogram in determining cardiac functions at 6 and 12 weeks postpartum in the same cohort obviates the need for a separate control group in this longitudinal study.

Echocardiography has evolved by leaps and bound in recent years with many new techniques and better resolution of the ultrasound machine. This has paved the

way to more accurate assessment and evaluation of cardiac adaptations to pregnancy. One of the new aspects being studied are echocardiographic tissue velocity parameters of longitudinal function.[18,19] It is now possible to study LV mechanics of normal pregnancy using standard and novel morphological and functional echocardiographic parameters while considering LV load and shape.[20] We now know that there no overall changes in LV ejection fraction or in fractional shortening. There is, however an increase in cardiac stroke volume, cardiac output and stroke work with decrease in peripheral vascular resistance as has been known in conventional teaching. The heart tends to be more globular and is associated with eccentric hypertrophy and LV mass.

A comprehensive study by Geoffrey *et al*[21] used a larger cohort of pregnant women (n=97) and non- pregnant women without any cardiovascular disease as a control (n=24) and this study has released extensive data pertaining to normal cardiac adaptations in pregnancy.

The small number of cases (nine) in this longitudinal study is a major limitation in this evaluation. The high drop- out rate was unavoidable. Inter-observer error was minimized by having all echocardiographic evaluations done by the same cardiac laboratory technician.

In conclusion, physiological adaptation of the cardiovascular system in a selected Malaysian pregnant population (with uncomplicated hyperemesis gravidarum) concurs with established data of other workers.

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Table I: Demography of subjects (n=9)

Age (year)	**28.3 ± 6**
Height (metre)	154 ± 0.03
Weight (kg)	53.4 ± 7.2
Body surface area (m^2)	1.53 ± 0.09
Nulliparous	5 (55%)

Table II: Cardiac profile by gestational age and postpartum

	Antepartum								**Postpartum**	
Weeks of Gestation	**12@**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**6**	**12**
Cardiac output (L/min)	5.3 ± 1.3	5.2 ± 1.2	5.4 ± 0.7	5.8 ± 0.9	6.3 ± 1.8	6.3 ± 0.5	6.6 ± 0.6	6.6 ± 0.7	4.9 ± 0.8	4.9 ± 1.3
Heart rate (beats/min)	80.5 ± 8	81.6 ± 6.5	85.6 ± 7.6	92.9 ± 8.6	92.6 ± 4.5	94.3 ± 8.1	96.3 ± 8	92.7 ± 6	77.4 ± 6.7	82.6 ± 9.6
Stroke volume (ml/beat)	59.6 ± 12.4	62.2 ± 10.6	62.8 ± 7.7	66 ± 8.7	64.3 ± 8.3	67 ± 6.3	68.6 ± 8.7	71 ± 7.9	63.6 ± 10.7	59.2 ± 10.6
Systolic blood pressure (mmHg)	115 ± 10	112 ± 7	107 ± 5	106 ± 4	110 ± 4	117 ± 7	115 ± 5	111 ± 8	111 ± 7	110
Diastolic blood pressure (mmHg)	72 ± 5	75 ± 5	69 ± 1	70± 6	72± 5	76 ±5	73 ± 5	71 ± 7	71 ± 3	72 ± 4
Body surface area (m^2)	1.53 ± 0.09	1.49 ± 0.07	1.483 ± 0.06	1.56 ± 0.08	1.66 ± 0.06	1.65 ± 0.06	1.65 ± 0.06	1.67 ± 0.07	1.59 ± 0.08	1.53 ± 0.08
Early inflow velocity (m/sec)	1.04 ± 0.23	0.939 ± 0.17	1.08 ± 0.08	0.98 ± 0.16	0.94 ± 0.12	1.08 ± 0.15	1.06 ± 0.14	0.95 ± 0.07	0.81 ± 0.15	0.87 ± 0.15
Peak atrial transport velocity (m/sec)	0.56 ± 0.10	0.54 ± 0.05	0.62 ± 0.07	0.58 ± 0.05	0.58 ± 0.07	0.6 ± 0.04	0.65± 0.04	0.65 ± 0.03	0.05 ± 0.18	0.53 ± 0.07
Ratio between Early inflow velocity (m/sec) and Peak atrial transport velocity (m/sec)	1.95 ± 0.53	1.72 ± 0.23	1.74 ± 0.14	1.67 ± 0.24	1.61 ± 0.26	1.57± 0.24	1.54 ± 0.24	1.46 ± 0.11	1.51 ± 0.29	1.63 ± 0.29
End diastolic dimension (cm)	4.4 ± 0.4	4.3 ± 0.3	4.4 ± 0.2	4.5 ± 0.3	4.4 ± 0.3	4.5 ± 0.2	4.5 ± 0.2	4.6 ± 0.2	4.5 ± 0.2	4.3 ± 0.3
Inter ventricular septum thickness (cm)	0.7	0.72 ± 0.10	0.73 ± 0.50	0.74 ± 0.10	0.80 ± 0.12	0.85 ± 0.10	0.88 ± 0.09	0.93 ± 0.10	0.78 ± 0.09	0.77± 0.12
Fractional shortening (%)	41 ± 1	42 ± 3	42 ± 2	40 ± 3	39 ± 3	39 ± 3	40 ± 1	40 ± 3	36 ± 3	37 ± 3

High-lighted areas are those showing appreciable changes

Figure 1: Cardiac output and gestational age (n=9)

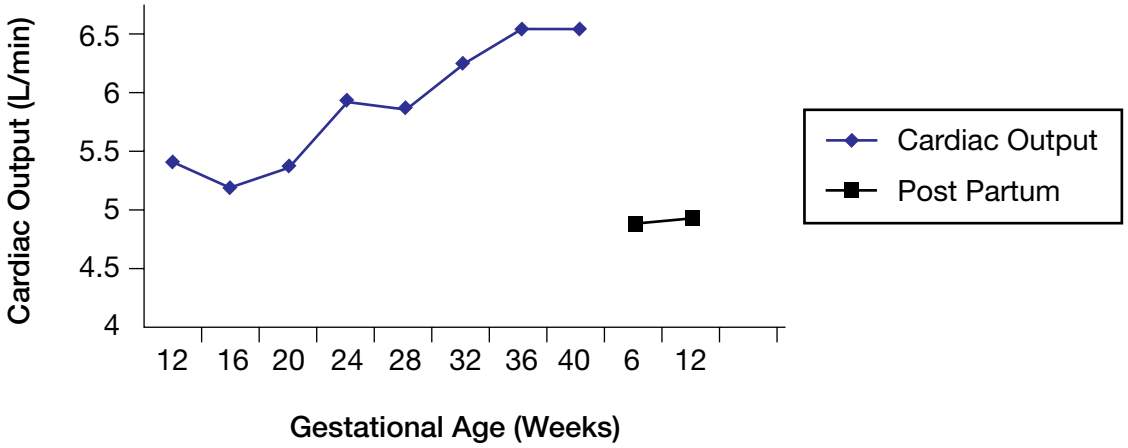


Figure 2: Changes in heart rate and gestational age

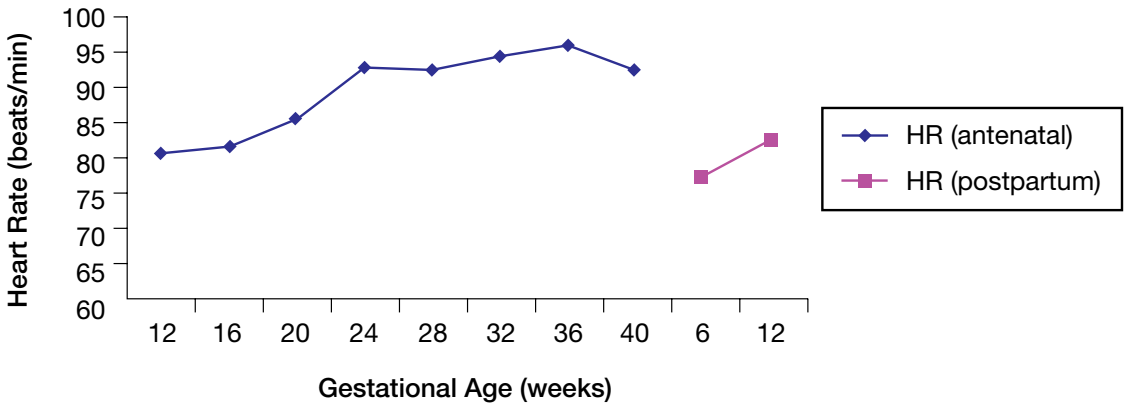


Figure 3: Increase in stroke volume at specific gestational age

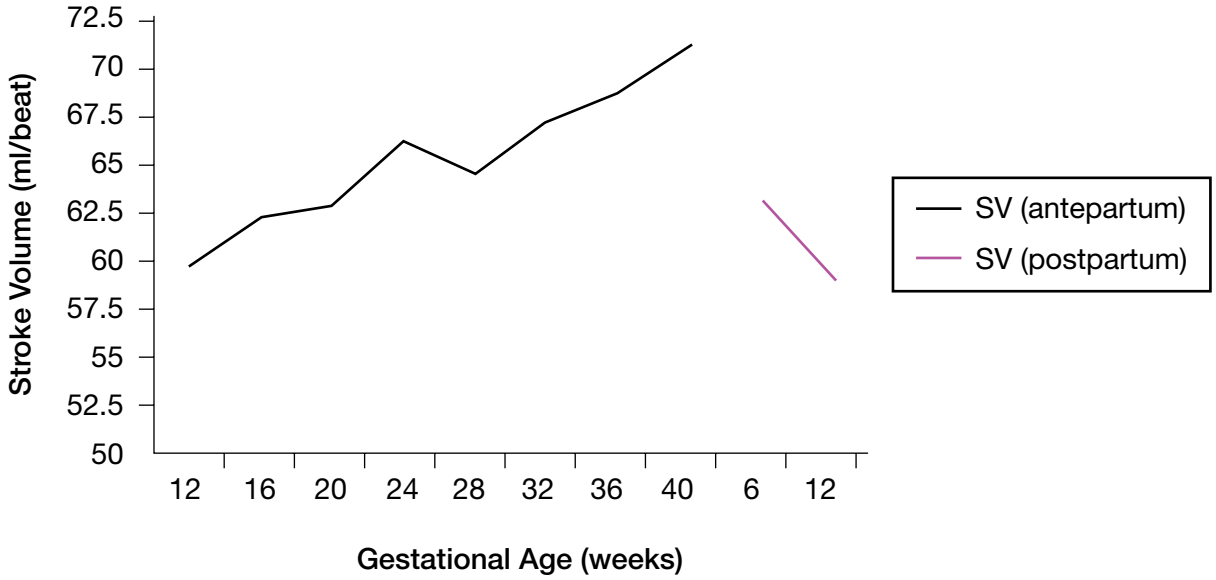
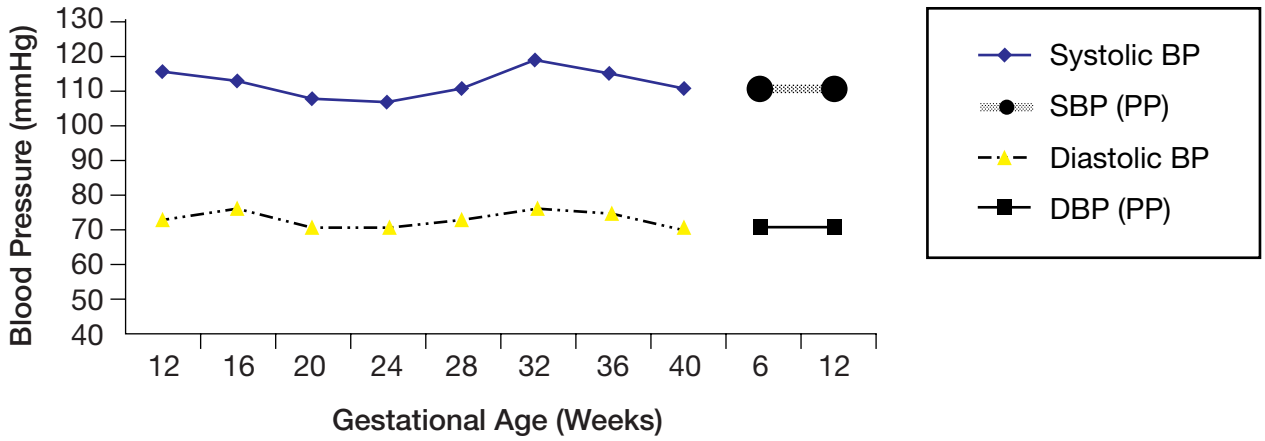


Figure 4: Changes of blood pressure during pregnancy and post partum period

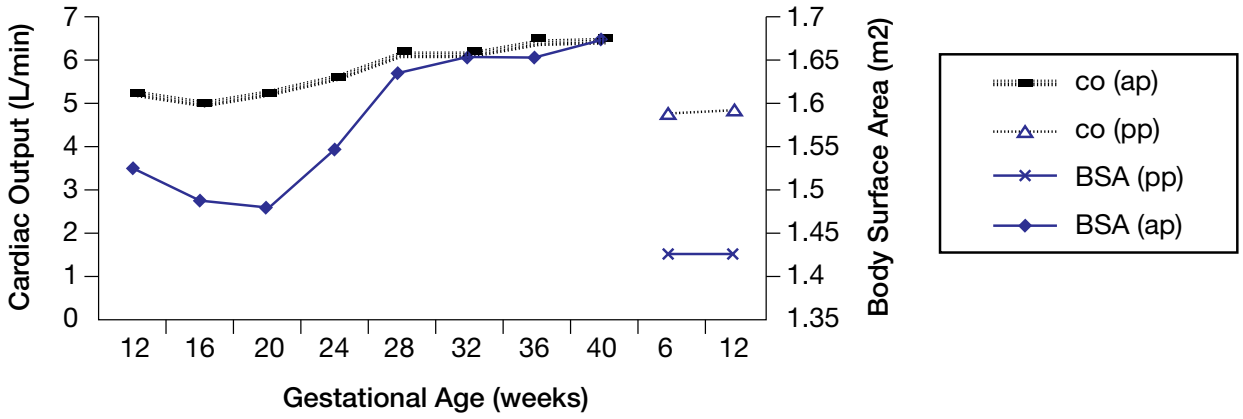


SBP : Systolic Blood Pressure

DBP : Diastolic Blood Pressure

PP : Post Partum

Figure 5: Changes in cardiac output in relation to body surface area

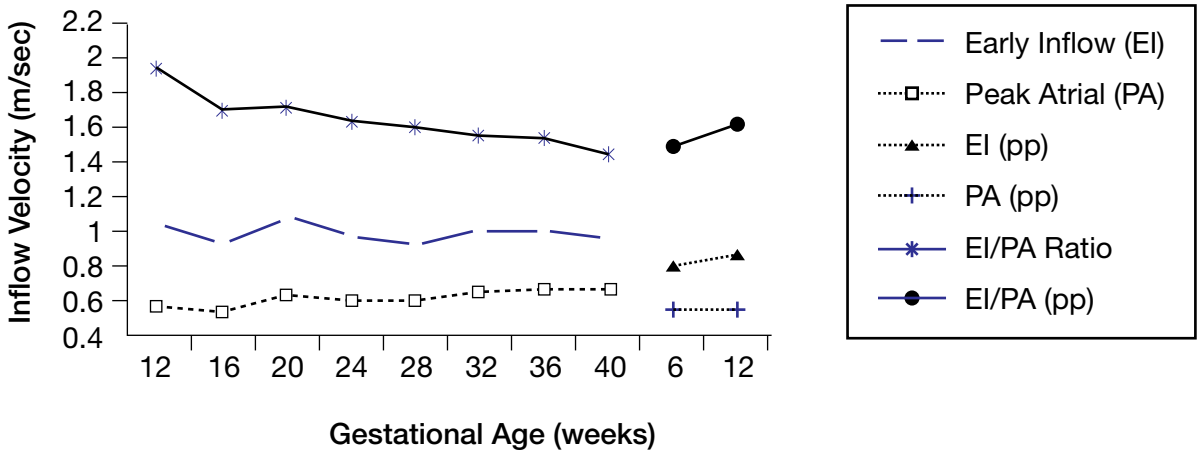


co : Cardiac Output

ap : Ante Partum

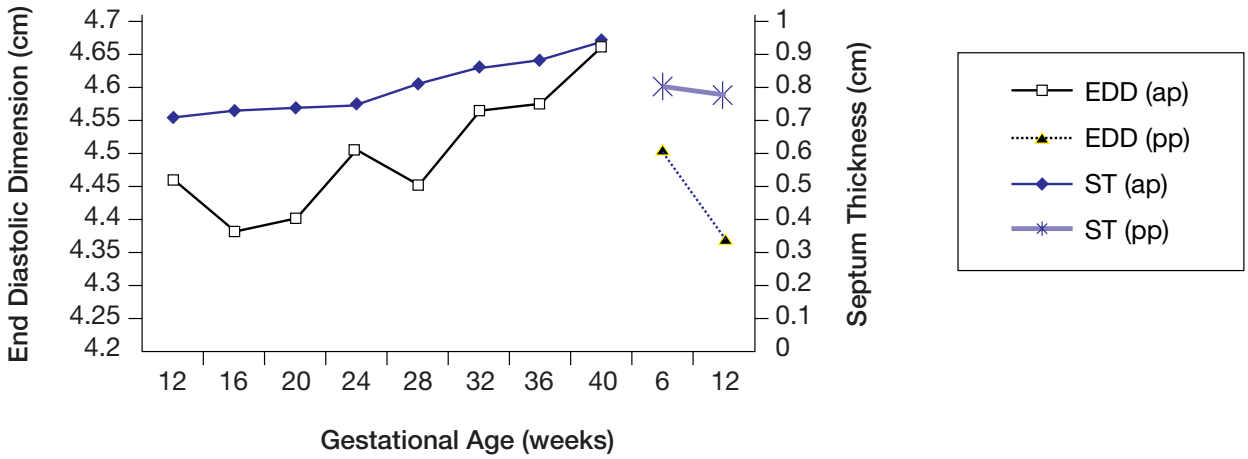
BSA : Body Surface Area

Figure 6: Changes in early inflow velocity and peak atrial transport velocity during pregnancy



pp : Post Partum

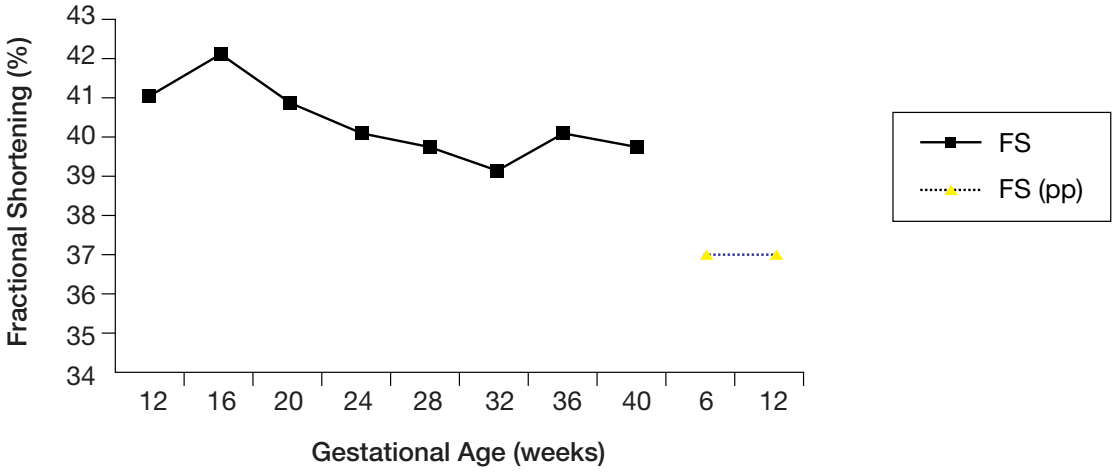
Figure 7: Left ventricular early diastolic dimension and interventricular septum thickness during pregnancy



ap : Ante Partum

pp : Post Partum

Figure 8: Fractional shortening and end diastolic dimension of left ventricle in pregnancy



pp : Post Partum