Second trimester cardiac output and its predictive value for preeclampsia

Talieh Kazerooni, MD, Shahdad Khosropananh, MD.

ABSTRACT

Objective: To predict women at risk of preeclampsia in the second trimester by the assessment of maternal cardiac output (CO).

Methods: Between October 2001 to November 2003, we carried out a cross-sectional, prospective, hospital-base study in Shiraz University of Medical Sciences, Shiraz, Iran. Cardiac output was measured in 102 normotensive women at gestational age 19-25 weeks by Doppler echocardiography. Patients with CO >7.4 L/min were considered high risk group (Group 1) and those with CO ≤7.4 L/min were in Group II. They were followed-up until delivery and the incidence of preeclampsia was determined in both groups.

Result: Twenty percent (6/30) of patient in Group 1, and 1.4% of patients in group II developed preeclampsia (p<0.003). A cut off point of 7.34% L/min was chosen for prediction of preeclampsia that showed 85.7% sensitivity, 74.2% specificity with a negative predictive value of 98% and positive predictive value of 20%.

Conclusion: Cardiac out put is significantly elevated in preclinical state of preeclampsia. Echocardiography is a non-invasive method to evaluate the maternal homodynamic during the second trimester and can help to identify high-risk patient before the development of preeclampsia, thereby it may improve the outcome of pregnancy.

Saudi Med J 2006; Vol. 27 (10): 1526-1529

Pregnancy causes major changes in the maternal circulation, which require necessary adaptation in order to develop normally. When this adaptation failed to occur, the consequence is hypertensive disorder including preeclampsia.[1,2] Preeclampsia is a multisystem disorder, peculiar to and frequent in human pregnancy. It remains a leading cause of maternal and neonatal mortality and morbidity and affecting 7-10% of pregnancies.[3,4] It involves a marked and generalized vasoconstriction, secondary to endothelial dysfunction. In these cases, the hemodynamic situation is different from that of the normal pregnancy and characterized by high cardiac output (CO) in a preclinical phase of disease.[4-6] Some longitudinal studies clearly demonstrated the existence of a hyperdynamic circulatory state during the latent phase of preeclampsia. In this situation, a significantly elevated cardiac output in presence of a normal or low total peripheral resistance is present early in pregnancy and is further exaggerated during the latent phase.[6] In order to measure hemodynamic status in pregnancy, non-invasive techniques have been validated such as Doppler ultrasonography, echocardiography, and thoracic electrical impedance.[1,7] Combinations of echocardiography and Doppler ultrasound provide a unique non-invasive method that is simple, quick and cause no discomfort for the patient. These physiologic changes in women

From the Department of Obstetrics and Gynecology, (Kazerooni), and the Cardiology Section, Department of Internal Medicine (Khosropananh), Shiraz University of Medical Science, Medical School, Shiraz, *Iran*.

Received 19th February 2006. Accepted for publication in final form 28th June 2006.

Address correspondence and reprint request to: Dr. Talieh Kazerooni, No. 313 Nouavaran Ave, Farzanegan Street, PO Box 71948-95897, Shiraz, *Iran*. Tel. +98 (711) 6262680. Fax. +98 (711) 6288427.

with preeclampsia can be detected as early as the first and second trimester.[8] The aim of this study was to evaluate the CO in second trimester of pregnancy and its predictive value for preeclampsia.

Methods. Between October 2001 to November 2003, a cross sectional, prospective, university hospital base study was carried out to measure the CO of 102 normotensive pregnant women at 19-25 weeks of gestation (gestation was confirmed by ultrasound examination). Written inform consent was obtained before inclusion, and approval was obtained from the Hospital and University Ethics Committee. Inclusion criteria were: primigravida, age <35 years, no history of renal or cardiac disease or hypertension. Exclusion criteria were chronic hypertension, chronic illness or long term use of medication, history of any collagen vascular disease and twin pregnancy. Hemodynamic measurement was carried out in the left lateral recumbent position after at least 5 minutes of rest, for all patients between 19-25 weeks of pregnancy. They were monitored by using Doppler echocardiography performed by a single observer. The employed method for measurement of ventricular volume was Simpson's rule, in which the endocardium was traced during systole and diastole in apical 4-chamber view and were automatically subdivided in to a series of disc by the echocardiography. The volume of each disc was calculated as disc area (IIr2) multiplied by the height of each disc. The volume of each separate disc was then summed to provide the volume of the ventricles during systole and diastole. By subtracting the ventricular volume during systole from that of the diastole, the ejection volume was calculated. Cardiac output was calculated by multiplying the ejection fraction volume by the heart rate. The other method used was measuring the CO using the continuity equation based on Doppler determination of volumetric flow. Flow through the tubular object can be calculated as area times mean velocity (integrated flow velocity). This phasic flow times the heart rate equals the cardiac output (CO = Area x integrated flow velocity x heart rate). Then the average of both methods was calculated and considered as CO of the patient. Blood pressure was measured using a mercury sphygmomanometer according to the recommendation of the American National High Blood Pressure Education Working Group before echocardiography. The mean arterial pressure (MAP) calculated by using the following formula: MAP = [2(diastolic blood pressure) + (systolic blood pressure)] / 3, and total peripheral resistance (TPR), calculated by using the following formula: TPR = 80 (MAP)/CO depending to the level of CO subjects were divided into 2 groups: patients with CO >7.4 L/min were considered high risk (group I) and those with CO ≤7.4L/min were in group II. All pregnant women had prenatal care visit in the prenatal clinics until delivery. At each visit the blood pressure was recorded in the sitting position and first and fifth Korotkoff sounds were used to determine the systolic and diastolic component. Intrapartum blood pressure was recorded and urine was checked for protein if indicated. Preeclampsia was defined as an absolute blood pressure of at least 140/90 mm Hg on at least 2 occasions, 6 hours apart after 20 weeks of gestation with significant proteinuria (at least 1+ by dipstick). They were followed-up until delivery and the incidence of preeclampsia was measured in both groups. The incidence of preeclampsia was compared between low risk and high-risk groups by chi-square test. The receiver operator curve analytic technique was used to determine the best cut off value for prediction of preeclampsia. The sensitivity, specificity, positive and negative predictive values were calculated according to this cut-off point. Data were expressed as mean ± SEM; $p<0.05$ was considered statistically significant. All statistical procedures were performed using SPSS software (Statistical package for the Social Sciences, version 10.0; SPSS Inc., USA).

Results. Two patient delivered preterm (28, 32 weeks) and they were excluded. In 100 patients, the mean CO was 6.5±1.8 L/min and the mean gestational age was 21.8± 2.2 weeks at the time of CO measurement. Mean maternal age, gestational age at the time of echocardiography and birth weight of fetus was not significantly different in both groups. However, the mean of CO, heart rate, stroke volume, systemic vascular resistance and maximum systolic and diastolic pressure during delivery was significantly different between the 2 groups ($p<0.005$). About 45% of asymptomatic pregnant women had mild mitral valve prolapse (MVP). Six out of thirty pregnant women in group I and one out of seventy gravid patients in group II developed preeclampsia ($p<0.003$). There were no any perinatal mortality and morbidity in each group. Only 2 cases of premature delivery which excluded from the study. Hemodynamic measurements of both groups are shown in **Table 1**. By receiver operator curve, a cut of point of 7.3 L/min was chosen for prediction of preeclampsia. Sensitivity at this point was 85%, specificity 74.2%, negative predictive value 98% and positive predictive value 20% (**Figure 1**). It means that 85% of nulliparous women with CO >7.3 L/min in second trimester have risk to develop preeclampsia during the course of pregnancy.

Table 1 - Clinical and hemodynamic measurement of both experimental groups.

Clinical and hemodynamic measurement	Group 1 (CO >7.41 L/min) N = 30	Group II (CO ≤7.41 L/min) N = 70	*P* value
Maternal age (years)	23.2 ± 4.3	23.9 ± 4.2	NS
Gestational age at the time of echo (week)	21.6 ± 1.9	21.9 ± 2.3	NS
Cardiac out put (L/min)	8.8 ± 1.3	5.6 ± 0.9	0.0001
Heart rate (beat/min)	107.3 ± 13.5	93 ± 1.1	0.0001
Stroke volume (ml/min)	82.1 ± 11.7	60.8 ± 10.5	0.0001
Arterial pressure (mm Hg)	87.3 ± 8.1	81.9 ± 6.7	0.002
Systemic vascular resistance (dyne.sec.cm^{-5})	801.5 ± 101	1193 ± 213.7	0.0001
Gestational age at delivery (weeks)	38.5 ± 1.1	38.9 ± 1	NS
Birth weight (g)	3076.3 ± 353.5	3128 ± 345.2	NS
Maximum systolic BP during delivery (mm Hg)	125.6 ± 13.5	117.4 ± 11.6	0.006
Max Diastolic BP during delivery(mm Hg)	80 ± 108	74.7 ± 6.5	NS

P value of ≤0.005 were considered significant, BP - blood pressure, NS - not significant, CO - cardiac output.

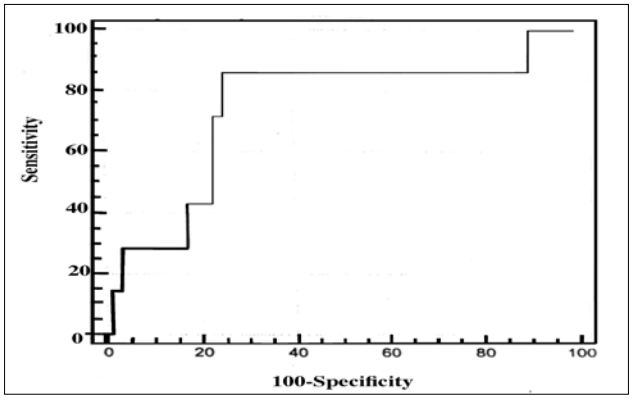

Figure 1 - Receiver operator curves for cardiac output. Cut-off level was set at 7.34 L/min.

Table 2 - Demographic data of experimental groups.

Demographic data	Mean ± SD
Maternal age (year)	23.7 ± 4.2
Gestational age at the time of Echo (week)	21.8 ± 2.2
Cardiac out put (L/min)	6.5 ± 1.8
Heart rate (beat/min)	97.3 ± 13.5
Stroke volume (ml/min)	67.2 ± 14.6
Mean arterial pressure (mm Hg)	83.5 ± 7.5
Systemic vascular resistance (dyne.sec.cm^{-5})	1075.5 ± 256.4
Gestational age at delivery (week)	38.8 ± 1
Birth weight (g)	3112.3 ± 346.7
Maximum systolic blood pressure (mm Hg)	119.9 ± 12.7
Maximum diastolic blood pressure (mm Hg)	76.3 ± 8.3

Discussion. The cardiovascular system undergoes significant changes in association of preeclampsia, which ultimately leads to classic low cardiac out put, and systematic vascular resistant state.[9] Although most of the studies reported that higher CO and lower vascular resistance in early pregnancy suggesting an increase plasma volume,[2,5,6,10,11] 2 other studies observed evidence for a diminished plasma volume.[12,13] In our study, we used echocardiography to measure CO. Easterling et al,[10] also have demonstrated that this technique is an accurate method for measuring CO during pregnancy. They also showed that nulliparous women with a CO >7.4 L/min in the second trimester were twice as likely to experience preeclampsia.[5] In comparison to our study, both cut off points were too close (7.34 L/min versus 7.4 L/min) and it means that this point may be considered as a critical point for measurement of CO in early pregnancy. In the preclinical phase of preeclampsia, when the blood pressure is still normal, a generalized fall in vascular tone by systemic vasorelaxation causes an increase in blood volume, heart rate and cardiac output.[3] Knowledge of the existing circulatory state should lead to a more rational use of antihypertensive therapies, appropriately tailored to the hemodynamic profile. Easterling et al,[5] conducted an intervention study to determine whether reducing the abnormally elevated CO would decrease the rate of preeclamsia.[14] For this reason, they used atenolol 100 mg daily or placebo. Treatment with atenolol was associated with the development of preeclampsia in 3.8% compared with 18% in those treated with placebo, suggesting that a hyperdynamic circulation contributes to the pathogenesis of preeclampsia. The

circulatory cross-over found in preeclampsia might also indicate increase in prenatal morbidity. Our results imply that the timing of this cross-over is the important factor in this respect because the earlier it occurs, the greater the need for preterm delivery. Although the current study showed that in those patients who become preeclamptic, there is a higher rate of low birth weight and premature delivery, but these differences were not statistically significant (**Table 2**). Butters et al[15] reported that 67% of babies weighted less than the 10th percentile at birth after mothers were treated empirically with atenolol for chronic hypertension. In contrast, Easterling et al, hypothesized that selection of appropriate patients for treatment with atenolol, particularly those with elevated CO, resulted in the reduced rate of small for gestational age of fetuses in their studies.[14] Blood pressure and plasma volume regulation is an intricate system with strong auto regulating mechanisms attempting to maintain homeostasis. Knowledge of the early pregnancy maladaptation and the role of pre-existing hypertension is limited. Antihypertensive drugs are still the mainstay in the management of preeclampsia. However, the blood pressure cut off value for starting the treatment is still controversial. In addition, the preferred type of medication and its effect on maternal plasma volume expansion cannot be concluded from our study or the other available literature. More randomized study with clinical endpoint is suggested.

References

1. San-Frutos LM, Fernandez R, Almagro J, Barbancho C, Salazar F, Perez-Medina T, et al. Measure of hemodynamic patterns by thoracic electrical bioimpedance in normal pregnancy and in preeclampsia. ***Obstet Gynecol Repro Bio*** 2005; 121: 149-153.
2. Rosso P, Donoso E, Bram S, Espinoza R, Fernandez C, Salas SP. Maternal homodynamic adjustment in idiopathic fetal growth retardation. ***Gynecol Obstet Invest*** 1993; 35: 162-165.
3. Ganzevoorrt W, Rep A, Bonsel GJ, de Vrises JI, Wolf H. Plasma volume and blood pressure regulation in hypertensive pregnancy. ***J Hypertens*** 2004; 22: 1235-1242.
4. Carr DB, McDonald GB, Brateng D, Desia M, Thach CT, Esterling TR. The relation between hemodynamics and inflammatory activation in women at risk for preeclampsia. ***Am J Obstet Gynecol*** 2001: 98: 1109-1116.
5. Easterling T, Benedetti T, Schmucker B, Millard S. Maternal hemodynamic in normal and preeclamptic pregnancies: A longitudinal study. ***Obstet Gynecol*** 1990; 76: 1061-1069.
6. Bosio PM, Mckenna PJ, Conroy P, O'Hherlihy R. Maternal central hemodynamics in hypertensive disorders of pregnancy: A longitudinal study. ***Obstet Gynecol*** 1999; 94: 978-984.
7. Van Open C, Stigter RH, Bruinse HW. Cardiac output in normal pregnancy: a critical review. ***Obstet Gynecol*** 1996; 87: 310-318.
8. Look Wood C, Peter J. Increase plasma level of EDT cellular fibrinogen precede the clinical sign of preeclampsia. ***Am J Obstet Gynecol*** 1990; 162: 357-362.
9. Hibard JU, Shroff SG, Lang Rm. Cardiovascular changes in pregnancy. ***Seminar Nephrol*** 2004; 24: 580-587.
10. Easterling T, Watts D, Schmucker B, Benedetti T. Measurement of cardiac out put during pregnancy: validation of Doppler technique and clinical observation in preeclampsia. ***Obstet Gynecol*** 1987; 69: 845-850.
11. Brown MA, Zammit VC, Mitar DM. Extracellular fluid volume in pregnancy-induced hypertension. ***J Hypertens*** 1992; 10: 61-68.
12. Duvekot JJ, Cheriex EC, Pieters FA, Peeters LL. Severely impaired fetal growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. ***Acta Obstet Gynecol Scand*** 1995; 74: 693-697.
13. Spaanderman ME, Aardnburg R, Ekharat TH, van Eyndhoven HW, van der Heijden OW, van Eyck J, et al. Non-pregnant circulatory volume status predicts subsequent pregnancy outcome in normotensive thrombophilic formerly preeclamptic women. ***Eur J Obstet Gynecol Reprod Biol*** 2001; 95: 218-222.
14. Easterling T, Barteng D, Schmucker B, Brown Z, Maillard S. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before onset of hypertension. ***Obstet Gynecol*** 1999; 93: 725-733.
15. Butters L, Kennedy S, Rubin P. Atenolol in essential hypertension during pregnancy. ***BMJ*** 1990; 301: 587-589.