ROLE OF DUCTUS VENOSUS DOPPLER IN PREDICTION OF FETAL CARDIAC DYSFUNCTION IN PREECLAMPSIA

By
Mostafa M.Zaitoun; Anwar E. Ismail; Dahlia O. ELHaieg And Bassem M. Talaat
Obstetrics and Gynecology Department
Faculty of Medicine, Zagazig University

ABSTRACT

Background: Venous Doppler changes generally accompany further metabolic deterioration of the fetus and are a result of declining forward cardiac function and abnormal organ autoregulation. **Objectives:** The aim of this study was to determine the correlation between ductus venosus (DV) Doppler velocimetry and fetal cardiac troponin T (cTnT) as a biochemical marker of fetal cardiac dysfunction in preeclamptic patient. **Subjects and methods:** A prospective study to 120 preeclamptic women admitted to the Obstetrics and Gynecology department, Zagazig University Hospitals, from May 2008 through November 2010. Patients recruited in this study were further divided according to their Doppler study within 24 hours before delivery into 3 groups; group of normal arterial and venous Doppler indices, group of abnormal arterial flow but normal ductus venosus flow and group of abnormal arterial flow and abnormal ductus venosus flow. Immediately after delivery, umbilical artery blood samples were obtained for the measurement of Ph and cTnT levels. Statistical analysis included one way analysis of variance (ANOVA) test with LSD posthoc multiple 2-group comparisons. Comparisons of quantitative variables within each group was done using Mann Whitney test for independent samples. For comparing categorical data, Chi square ($\chi 2$) test was performed. **Results:** In group of abnormal arterial flow and abnormal ductus venosus flow, Cord cardiac troponin T (cTnT) concentrations at birth were >0.05 ng/ml in 22 (55%) cases, a proportion significantly higher than that observed in groups of normal arterial and venous Doppler indices and of abnormal arterial flow but normal ductus venosus flow (12.5% and 22.5% respectively; $p < 0.01$). **Conclusion:** Ductus venosus pulsatility index of veins (DV PIV) was significantly related to high cord troponin (cTnT) concentrations at delivery. Abnormal DV flow represents severe cardiac compromise, with increased systemic venous pressure, and arise in right ventricular afterload, demonstrated by myocardial damage and elevated fetal cTnT.

Keywords: Troponin T, ductus venosus, pulsatility index of veins

INTRODUCTION

Venous Doppler changes generally accompany further metabolic deterioration of the fetus and are a result of declining forward cardiac function and abnormal organ autoregulation. Increasing venous Doppler indices are the hallmark of advancing circulatory deterioration since they document the inability of the heart to accommodate venous return. The venous flow velocity waveform is triphasic, and therefore more complex than the arterial waveform. It consists of systolic and diastolic peaks (the S- and D-wave) that are generated by the descent of the AV-ring during ventricular systole and passive diastolic ventricular filling, respectively. The sudden increase in right atrial pressure with atrial contraction in late diastole causes a variable amount of reverse flow producing a second trough after the D wave (the a-wave). In extreme cases atrial pressure waves may be transmitted all the way back into the free umbilical vein resulting in pulsatile flow. At this stage ductus venosus shunting away from the liver may compromise hepatic perfusion to a degree that interferes with organ function. Steep elevation in blood lactate and transaminases, as well as sudden compensatory hepatic artery vasodilatation as a secondary source of blood supply to the liver have been reported under such conditions. When the increased metabolic demands of cardiac work cannot be met myocardial dysfunction super-venes[(1)].

Abnormalities in the umbilical artery and in the central and cerebral arterial fetal circulation can persist for weeks while venous flow may show a tendency to deteriorate, but still remain in the normal range**.** Venous Doppler changes appear

therefore at a late stage in the process of fetal deterioration. A pathological venous flow (increased PIV, absent/reverse flow during the a-wave) is typical of severe early FGR (before 30–32 weeks) and may appear 2-to-1 week prior to the appearance of abnormal fetal heart rate traces which may prompt fetal delivery[2].

Troponin T is one of the three subunits (troponin T, I and C) of the troponin complex. This regulatory protein interacts with actin and myosin to determine cardiac muscle contraction. The relative amount of the adult cTnT isoform increases significantly around the time of birth. A rabbit model study showed that this increase is more prominent in the left than in the right ventricles and is influenced by adrenergic stimulation and stress in the cardiovascular system during development[3].

Fetuses with increased cTnT levels (cTnT > 0.05 ng/ml) and severe placental insufficiency showed signs of increased venous pressure. These fetuses were delivered earlier than those with normal umbilical artery Doppler. Placental dysfunction predisposes the fetus to progressive deterioration of acid–base balance and irreversible impairment of organ function, mainly the central nervous system and heart. The antepartum quantification of this fetal involvement is fundamental for the optimal timing of delivery before the occurrence of fetal myocardial cell injury[3].

The aim of the present study was to investigate the association between changes in ductus venosus PIV and myocardial cell injury in compromised fetuses with elevated cord cTnT in preeclamptic patient.

SUBJECTS AND METHODS

120 preeclamptic women were evaluated from May 2008 through November 2010, all of them had gestational proteinuric hypertension developed antenatally diagnosed according to American College of Obstetricians and Gynecologists guidelines[4], they fulfilled the inclusion criteria which were singleton pregnancy, gestational age on admission ranging from 28 to 38 weeks of gestation determined by the date of the last menstrual period and/or early second trimester ultrasonographic examination and absence of fetal congenital malformations.

Women with complications as vaginal bleeding, preterm premature rupture of membranes (PPROM), diabetes or multiple pregnancies were excluded.

In addition, patients were recruited according to the results of arterial (umbilical and middle cerebral arteries) and venous (ductus venosus) Doppler velocimetry in to 3 groups. 40 preeclamptic patients with normal arterial and venous Doppler flow (group 1), 40 preeclamptic patients with abnormal arterial flow but with normal venous flow (group 2) and 40 preeclamptic patients with abnormal arterial flow and abnormal ductus venous flow (group 3).

All women were subjected to complete history taking, clinical examination, routine laboratory investigations as CBC, liver, kidney function, coagulation profile and urine analysis.

Routine ultrasound examinations was done to all patients included fetal viability, fetal weight and growth (intrauterine growth restriction (IUGR) was defined as an estimated fetal weight less than 10^{th} centile or poor fetal growth on serial ultrasound), amniotic fluid volume (oligohydramnios was defined as amniotic fluid index (AFI) less than 5 cm. This index is the sum of the vertical amniotic fluid pocket depths in the 4 abdominal quadrants)[5].

Doppler study of the feto-placental circulation was done to all patients included the measurement of umbilical artery pulsatility index (PI). The presence of absent or reversed end diastolic blood flow was recorded, middle cerebral artery PI, ductus venosus pulsatility index for vein (PIV). The presence of absent or reversed a wave was recorded.

Ultrasonographic examinations and Doppler blood flow study were performed using Voluson730 Pro V unit (GE healthcare, Zipf, Austria) equipped with a broad band multifrequency convex probe 3.5/7MHz. . The high pass filter was set at the minimum. The size of the sample volume was adapted to the vessel diameter. Doppler measurements of three consecutive and symmetrical waves were recorded in the absence of fetal breathing and activity and uterine contractions and at a heart rate of 120–160 bpm. The angle of insonation was always kept below 30 degree for arteries and was always set at 0◦for DV measurements.

The umbilical artery blood velocity waveforms were recorded from loops of umbilical cord free, the fetal middle cerebral artery (MCA) was identified in the following manner: the circle of Willis was located in the fetal head at the level of the cerebral peduncles using color Doppler mode. The MCA was observed passing anteriorly to the peduncles, close to the greater wing of the sphenoid bone, with the angle of insonation being close to zero. The sample volume was placed approximately 1 cm from the beginning of the vessel from the circle of Willis.

The DV was identified using color Doppler imaging in a transverse or midsagittal section of the fetal abdomen. The sample volume was placed in the narrowest isthmic portion, to record the highest blood velocities and to control the insonation angle.

The pulsatility index (PI) of the umbilical and middle cerebral arteries and pulsatility index for veins (PIV) of the ductus venosus were calculated. The mean interobserver variability of UA, and MCA PI calculations was from 3.9% to 6.0% (95% CI, 2.5 to 6.5) The mean interobserver variability of DV, calculations was 4.8% (95% CI, 1.9 to 7.5).

Abnormal arterial Doppler flow was defined according to **Arduini and Rizzo**[6] as umbilical artery PI above the 95th percentile for gestational age. Centralization which is a middle cerebral artery PI below the 5th percentile for gestational age or as the presence of cerebral/umbilical PI ratio < 1 abnormal venous Doppler flow was defined as Ductus venosus PIV above the 95th percentile according to **Kessler et al.**[7].

Immediately after delivery, a sample of maternal cubital vein and umbilical artery blood samples were collected for the measurement of pH and cTnT. Serum cTnT concentration was measured with commercially available enzyme- linked immunosorbent assay kits (Enzyme-test Troponin T, Roche 623 Diagnostics, Germany) as described by the manufacturer.

Comparisons of quantitative variables within each group was done using Mann Whitney test for independent samples. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between the different variables was done using Pearson moment correlation equation for linear data. Receiver operator characteristic (ROC) analysis was done to determine the optimum cutoff value for DVPI in predicting positive cord troponin. Accuracy was represented by sensitivity and specificity. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

Comparing the clinical characteristics between the three groups, no significant differences were found regarding age and parity. All deliveries were by Caesarean section. Gestational age at delivery showed no significant differences between the three groups (34.65±2.27, 34.70±2.33, 33.95±1.58

weeks; respectively). On the other hand, Cases with abnormal arterial and venous Doppler(group3) results had significantly lower mean birth weight in grams (1377±42) than groups of normal arterial and venous Doppler flow and group of abnormal arterial but normal flow in ductus venosus (2177±619, 1887±63; p< 0.001). The difference in the mean birth weight between groups 1 and 2 was also significant (p<0.001). The frequency of IUGR was significantly higher in groups 3 and 2 compared with that in group 1 (p<0.01); whereas, the difference between groups 2 and 3 was not significant (table 1).

The difference in the mean cord blood ph were highly significant between the three groups. In group 3, the mean cord blood ph was significantly lower (7.17±0.05) (table 1).

Frequency of oligohydramnios were significantly higher in groups 3 and 2 in comparison to group 1; however, there was no significant difference between groups 2 and 3 (table 1).

In group 3, Cord cardiac troponin T (cTnT) concentrations at birth were >0.05 ng/ml in 22 (55%) cases, a proportion significantly higher than that observed in groups 1 and 2(12.5% and 22.5% respectively; p < 0.01 (table 2).

To examine the correlation between the studied Doppler parameters and gestational age, the study groups were combined (n = 120). No statistically significant correlations were found between gestational age and Doppler indices (umbilical PI, MCA PI and ductus venosus PIV) (table 3).

The mean values of ductus venosus PIV were also significantly higher in group 3 than in both groups 1 and 2 p<0.001. In group 3, among the 40 cases with abnormally high DV PIV 21 cases (52.5%) showed reversed a wave. Comparing Doppler parameters between the three groups, the frequency of absent or reversed end diastolic flow in the umbilical artery was significantly higher in groups 2 and 3 than in group 1 p<0.001, but there were no significant difference between groups 3 and 2 (table 4).

Lastly, out of the 120 studied cases 36 (43%) neonates had an elevated cord troponin T level (>0.05ng/ml). When patients were regrouped according to the presence/absence of positive cord troponin T, there were no significant differences regarding maternal age, parity, gestational age at delivery however, the frequency of IUGR and oligohydramnios were significant between the 2 groups. Neonates with positive cord cTnT level were more associated with lower cord blood Ph. The mean values of umbilical artery PI, ductus venosus PIV as well as the frequency of centralization, abnormal ductus venosus flow, AREDF in the umbilical artery, reversed a wave in the ductus venosus were significantly higher in those with positive cord cTnT than those without (P<0.001). Middle cerebral artery PI mean values were significantly lower in babies with positive Troponin T P<0.001 (table 5).

Table (1): Comparison of demographics and perinatal outcome parameters among pre-eclamptic women with various Doppler findings.

	Group1 normal Doppler N=40	Group 2 Abnormal arterial Doppler With normal DV N=40	Group 3 Abnormal arterial Doppler With abnormal DV N=40	***P*** value
Age (years,mean± SD)	24.73 ± 5.61	25.30 ±5.00	26.15±5.41	*NS
Parity (mean± SD)	2± 1.32	2.33±1.35	1.90±1.24	*NS
Gestational age at delivery (weeks, mean± SD)	34.65±2.27	34.70±2.33	33.95±1.58	*NS
Non-reactive CTG n(%)	0(0%)	13 (32.5%)	14(35%)	†<0.001
Fetal weight (grams, mean± SD)	2,177.25±619	1,878.75±63	1,376.50±42	*<0.001
IUGR n (%)	1 (2.5%)	16 (40%)	21 (52.5%)	†<0.001
Cord pH	7.236 ±0.069	7.20±0.053	7.17 ±0.049	*<0.001
Positive cord cTnT n (%)	5 (12.5%)	9 (22.5%)	22 (55%)	*<0.001

IUGR= intrauterine growth restriction. NS= nonsignificant. *P value determined by analysis of variance. † P value determined by Chi square

Table (2): Comparison of cord cTnT results among preeclamptic women with various Doppler finding

	Group1 Normal Doppler *(n*=40)	**Group 2** Abnormal arterial Doppler With normal DV *(n*=40)	**Group 3** Abnormal arterial Doppler With abnormal DV *(n*=40)	***P*** value
Positive cord cTnT (%)	5 (12.5%)	9 (22.5%)	22 (55%)*‡	<0.001

cTnT, cardiac troponinT, DV, ductus venosus; †p<0.01 comparing groups 2 & 1; *p<0.01 comparing groups 3 & 1; ‡p<0.01 comparing groups 3 & 2

Table (3): Correlation between gestational age and umbilical PI, middle cerebral artery PI and ductus venosus PIV

	Gestational age	
	r	**p**
Umbilical artery PI	-0.131	0.153
Middle cerebral artery PI	0.047	0.611
Ductus venosus PIV	-0.041	0.655

PI, pulsatility index; PIV, pulsatility index of veins

Table (4): Comparison of Doppler parameters among preeclamptic women with various Doppler findings:

	Group1 Normal Doppler *(n*=40)	**Group 2** Abnormal arterial Doppler With normal DV *(n*=40)	**Group 3** Abnormal arterial Doppler With abnormal DV *(n*=40)	***P*** value
Umbilical artery PI	1.09 ± 0.24	1.90 ±0.23†	1.96 ± 0.15*	<0.001
Middle cerebral artery PI	1.82 ± 0.33	1.17± 0.42†	1.00 ± 0.28*ǂ	<0.001
Ductus venosus PIV	0.50 ± 0.10	0.46 ± 0.06	1.15 ± 0.44*ǂ	<0.001
Centralization	0(0%)	20(50%)†	32(80%)*ǂ	<0.01
AREDF	0(0%)	20 (50%)†	26(65%)*	<0.001

DV, ductus venosus; AREDF: absent/reversed end diastolic flow in the umbilical artery; PI, pulsatility index; PIV, pulsatility index of veins † P<0.01 between 1&2 *p<0.01 between 1&3; ǂp,0.01 between 2&3

Table (5): Comparison of clinical characteristics and Doppler parameters among preeclamptic women according to cord Troponin T results

	Negative cord cTnT n=84	**Positive cord** cTnT n=36	***P* value**
Age (years,mean± SD)	24.93 ± 5	26.5 ± 5.5	NS[a]
Parity (mean± SD)	2.07 ± 1.18	2.08 ± 1.57	NS[a]
Gestational age at delivery (weeks, mean± SD)	34.5 ± 2.14	34.2 ± 2.1	NS[a]
Cord PH (mean±SD)	7.21 ± 0.06	7.18 ± 0.05	0.026[a]
Umbilical artery PI (mean ± SD)	1.55 ± 0.46	1.87 ± 0.34	<0.001[a]
Middle cerebral artery PI (mean ± SD)	1.44 ± 0.50	1.08± 0.3	<0.001[a]
Ductus venosus PIV (mean ± SD)	0.68± 0.49	1.54 ± 1.06	<0.001[a]
Abnormal ductus venosus n (%)	18 (21%)	22 (61%)	<0.001[b]
Centralization n (%)	27 (32.1%)	25 (69.4%)	<0.001[b]
AREDF n (%)	21 (45.7%)	25 (54.3%)	<0.001[b]
Reversed a wave n (%)	6 (7.1%)	15 (41.7%)	<0.001[b]

AREDF, absent or reversed end diastolic flow; PI, pulsatility index; PIV, pulsatility index of veins; cTnT, cardiac troponin T; [a] p value determined by student T- test; [b] p value determined by chi square

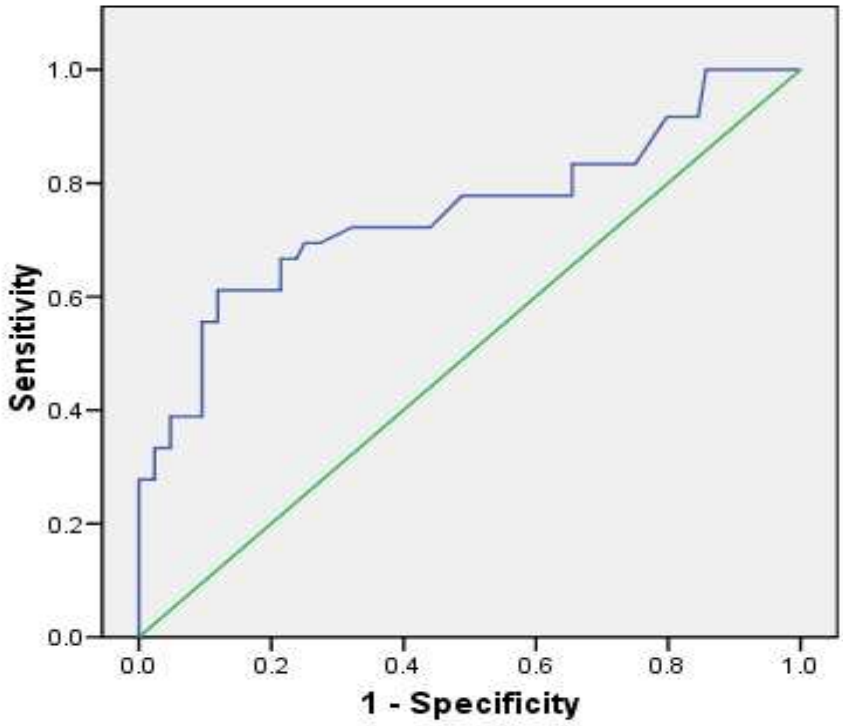

Figure (1): ROC curve showing prediction of positive cardiac troponin T at birth by using ductus venosus pulsatility index of veins

DISCUSSION

In the current study, attempt was made to find the relationship between the elevated ductus venosus pulsatility index and fetal cardiac dysfunction in pre eclamptic patient by testing cord cTnT.

We found that ductus venosus Doppler was a good predictor of fetal outcome as it was found that the frequency of oligohydramnios was significantly higher in groups 3(group of abnormal arterial and venous Doppler) in comparison to group 1 (group of normal arterial and venous Doppler). According to **Hecher et al.[2],** ductus venosus does not change before non stress test all the time; but the majority of the authors as **Ferrazzi et al.[8]; Romero et al.[9] and Baschat[10]** describe the ductus venosus Doppler velocimetry as indicating changes before modifications in other biophysical tests At present, the ductus venosus seems to be one of the best vessels to monitor in compromised fetuses, helping to decide when to deliver.

A significant difference in mean newborn weight was also observed in the study of **Alves et al.[11]** between the group of abnormal ductus venosus Doppler with reversed a wave and group of abnormal ductus venosus Doppler with continuous foreward flow.

Cardiac troponin T (cTn T) is biochemical markers of myocardial injury in humans are commonly used diagnostic and prognostic tools in the evaluation of patients with acute myocardial injury associated with ischemic damage due to infarction[12].

Herndon et al.[13] reported that, in normal uncomplicated pregnancies, neonatal troponin T concentrations showed no clinically significant increase, but levels were increased when complications were associated with abnormal fetal umbilical venous return (pulsations in the umbilical vein or abnormal ductus venosus Doppler waveform).

In our study, Cord cardiac troponin T (cTnT) concentrations at birth were >0.05 ng/ml in 22 (55%) cases in group 3, a proportion significantly higher than that observed in groups 1 and 2(12.5% and 22.5% respectively; $p < 0.01$), 15 cases of

group 3 (37.5%) had reversed a wave and positive (cTnT) in cord blood, in general reversed a wave in the ductus venosus were significantly higher in those with positive cord cTnT than those without (P<0.001). These results were in agreement with **Nomoura et al.**[3], who showed elevated cord Troponin T in the presence or absence end diastolic flow in umbilical artery and increase ductus venosus pulsatility index.

Mäkikallio et al.[14] reported that Pulsatility in human fetal systemic veins correlated significantly with cTnT and cardiac secretion of atrial natruretic factor (ANP). Fetuses with myocardial damage demonstrate increased systemic venous pressure, a change in the distribution of cardiac output toward the left ventricle, and a rise in right ventricular afterload.

Alexandre et al.[15] found that centralization and birth acidemia are associated with detectable cardiac troponin I (cTnI) in cord blood supporting the possibility of myocardial ischemia in these fetuses, they used troponin I as the marker of cardiac injury because this protein is not expressed in fetal skeletal muscle they found abnormal Doppler velocimetry (centralization) and birth acidemia were associated with detectable cTnI in umbilical cord blood, suggesting the possibility of myocardial ischemia in these fetuses.

Finally in our study analysis of the ROC curve indicated that ductus venosus PIV was a good predictor of positive cord troponin T (cTnT) at birth, with an AUC of 0.749 (95% CI, 0.642–0.856; P < 0.001; figure 1).

Predictive performance of positive cord troponin T using ductus venosus pulsatility index of veins at 1.04 as a cut off value, showed sensitivity 66.1% ,specificity 88.1 % , positive predictive value 68.7% and negative predictive value 84%.

REFERENCES

1- **Detti L, Segata M and Mari G:** Doppler Ultrasound in Obstetrics and Gynecology. 2nd Edition, chapter 14, Springer Link 2005; 199-209.
2- **Hecher K:** Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet. Gynecol. 2001; 18: 564– 570.
3- **Nomura RMY, Fabio Roberto Cabar, Verbenia Nunes Costa, et al.:** Cardiac troponin T as a biochemical marker of cardiac dysfunction and ductus venosus Doppler velocimetry. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2009; 6683: 271-275.
4- **ACOG practice bulletin:** International Journal of Gynecology & Obstetrics. 2002; 77: 67-75
5- **Chauhan SP, Doherty DD, Magann EF, et al.:** Amniotic fluid index vs. single deepest pocket technique during modified biophysical profile: a randomized clinical trial. Am J Obstet Gynecol 2004;191: 661–7.
6- **Arduini D. and Rizzo G:** Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. Perinat Med. 1990; 18: 165-172.
7- **Kiserud T, Ebbing C, Kessler J, et al.:** Fetal cardiac output, distribution to the placenta and impact of placental compromise. Ultrasound Obstet Gynecol .2006; 28: 126–136.
8- **Ferrazzi E, Bozzo M, Rigano S, et al.:** Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 2002; 19: 140–146.
9- **Romero R, Kalache KD, Kadar N:** Timing the delivery of the preterm severely growth-restricted fetus: venous Doppler, cardiotocography or biophysical profile? Ultrasound Obstet Gynecol 2002; 19: 118–121.
10- **Baschat AA, Gembruch U, Weiner CP, et al.:** Qualitative venous Doppler waveform analysis improves prediction of critical perinatal outcomes in premature growth-restricted fetuses. Ultrasound Obstet. Gynecol 2003; 22: 240–245.
11- **Alves SKA, Francisco RPV, Miyadahira S, et al.:** Ductus venosus Doppler and postnatal outcomes in fetuses with absent or reversed end-diastolic flow in the umbilical arteries. European Journal of

Obstetrics & Gynecology and Reproductive Biology 2008; 141; 100:103.

12- **Adamcova M. and Pelouch V:** Isoforms of troponin in normal and diseased myocardium. Physiol Res. 1999; 48:235–47.

13- **Herndon WE, Kittleson MD. and Sandrson K.** Cardiac troponin in hypertrophic cardiomyopathy. J Vet Intern Med. 2002; 16:558–564.

14- **Mäkikallio K, Vuolteenaho O, Jouppila P, et al.:** Ultrasonographic and Biochemical Markers of Human Fetal Cardiac Dysfunction in Placental Insufficiency. Circulation 2002;105:2058-2063.

15- **Alexandre SM, D'Almeida V, Guinsburg R, et al.:** Cord blood cardiac troponin I, fetal Doppler velocimetry, and acid base status at birth. International Journal of Gynecology and Obstetrics 2008; 100:136–140.